e-ISSN:2602-2079

Volume 5
Issue 7
2021

JOURNAL of Surgery and Medicine

International Medical Journal

Journal of Surgery and Medicine

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J Surg Med. 2021;5(7):657-660.
DOI: 10.28982/josam.950736

Research article

Journal of Surgery and Medicine
e-ISSN=2602-2079

Retrospective analysis of isolated renal hydatid cysts: A single-center study

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Ethics Committee Approval
Harran Universıty Clinical Studies Ethics Committee (Decision No.HRU/21.11.04). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 July 8

Abstract

Background/Aim: Hydatid disease is a parasitic infection caused by Echinococcus granulosus larvae settling in organs through blood and lymph circulation. Hydatid cysts are often observed in the liver and lungs, and isolated renal involvement is extremely rare. In this study, we aimed to evaluate patients who were diagnosed with an isolated renal hydatid cyst and treated in our clinic.

Methods: In this case series, the data of patients with renal hydatid cysts, who presented to our clinic between January 2010 and April 2021, were retrospectively reviewed. Only patients with an isolated renal hydatid cyst were included in the study. Demographic data, clinical findings, laboratory findings, indirect hemagglutination test results, radiological findings, treatment methods, complications and follow-up processes of the patients were evaluated.

Results: Eighteen patients (11 males and 7 females) were included in the study. The mean age and cyst diameter of the patients were 29.6 years and 9.2 cm, respectively. Reasons for hospital admission included flank pain (38.9%), palpable mass (22.2%), incidental (16.6%), abdominal pain (11.1%), nausea (5.5%) and hematuria (5.5%). Seropositivity in the indirect hemagglutination test was detected in was detected in 61.1%. Fourteen and four of the patients underwent cystectomy and nephrectomy, respectively. No major postoperative complications were observed in any of the patients. The mean follow-up period was 27 months, during which no local and renal recurrence were observed.

Conclusion: Although hydatid cysts are most observed in the liver and lungs, they may also be observed in other organs, especially the kidney. The primary treatment for a renal hydatid cyst should be kidney-sparing surgery. Additionally, albendazole treatment is should be recommended pre- and post-operatively to reduce the risk of inoculation and recurrence.

Keywords: Echinococcus granulosus, Hydatid cyst, Kidney, Cystectomy, Nephrectomy

How to cite: Demir M, Şengel A, Yağmur İ, Pelit ES, Katı B, Tunçekin A, Çiftçi H. Retrospective analysis of isolated renal hydatid cysts: A single-center study. J Surg Med. 2021;5(7):657-660.

Introduction

Hydatid disease is a parasitic infection transmitted by oral ingestion of Echinococcus granulosus eggs. Dogs are the definitive hosts of the parasite, and sheep and cattle are the intermediate hosts. Humans may also be intermediate hosts [1]. The disease is endemic in the Mediterranean Basin, including Turkey, and some parts of Eastern Europe, South America, the Middle East, Australia and South Africa [2]. Liver, lung and kidney involvement occurs in 70%, 25% and 2%–4% of the patients, respectively. As most parasites are retained by hepatic and pulmonary filters during circulation, isolated renal involvement is extremely rare (1.9%) [3, 4]. Renal involvement is usually in the form of a single cyst in the renal cortex. Clinical signs vary depending on the size, location and extension of the cyst. As the growth of the cyst takes years, patients may remain asymptomatic for long periods. Sometimes, patients may present with symptoms of flank pain, hematuria, hydatiduria or abdominal mass [5, 6]. In addition, they may be mistaken as tumors because they can mimic cystic kidney tumors clinically and radiologically [7]. In this study, we aimed to evaluate the rare cases of isolated renal hydatid cysts (HCs).

Materials and methods

For this study, the hospital records of patients who were treated for renal HCs between January 2010 and April 2021 were retrospectively reviewed after approval was obtained from Harran University Clinical Studies Ethics Committee (Decision No.HRU/21.11.04). All procedures in this study were conducted in accordance with the guidelines of Helsinki Declaration. All patients with isolated renal HC were included in the study. Patients' age, gender, reason for hospital admission, physical examination findings, serum creatinine levels, complete blood count, urinalysis, indirect hemagglutination test (IHA) results, cyst localization, cyst size, treatment methods, hospital stay, surgical complications and follow-up findings were analyzed. Abdominal ultrasonography (US), abdominal computed tomography (CT) (Figure 1) and IHA test results aided in the diagnosis of HCs. An IHA test result of ≥1/160 was considered positive. Patients underwent open or laparoscopic cystectomy or nephrectomy based on the cyst size and location as well as kidney function. Albendazole (10mg/kg/day) was initiated 3 weeks before the operation in all patients who were scheduled for surgery with a preliminary diagnosis of HC. Postoperative albendazole treatment was continued for 3 months in patients who underwent cystectomy and discontinued in those who underwent nephrectomy. Preoperative retrograde pyelography was performed in patients with a large cyst presenting with colic pain, and whether the cyst opened up to the collecting system was investigated. Povidone-iodine gauze pads were placed on the surrounding tissues to prevent intraoperative spread in patients who underwent cystectomy. After the cyst content was aspirated, hypertonic sodium chloride, a scolicidal agent, was injected into the cyst. After 10 min, the cyst was opened, daughter vesicles and germinative membrane were removed and cyst wall was excised (Figure 2). Nephrectomy was performed in patients who could not be conclusively diagnosed as having either malignancy or HCs by radiological and clinical data and in patients with non-functional kidneys. A non-functioning kidney was diagnosed using Tc-99m dimercaptosuccinic acid (DMSA) scintigraphy. Postoperative complications were classified according to the Clavien classification. The patients were followed up with an abdominal ultrasound (US) in the first and third months postoperatively. Subsequently, the patients were followed up every 6 months.

Statistical analysis

Mean, lowest, highest, frequency and ratio values were included in descriptive statistics. SPSS 27.0 software was used in the analysis.

Figure 1: Abdominal CT; 124x112 mm hydatid cyst located in the left kidney upper pole

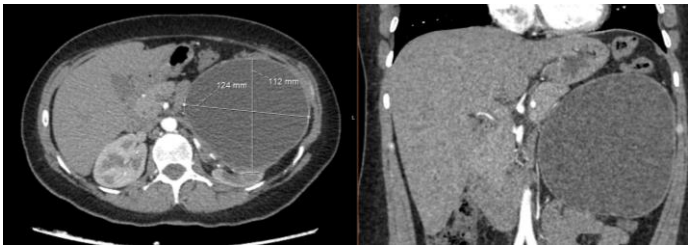
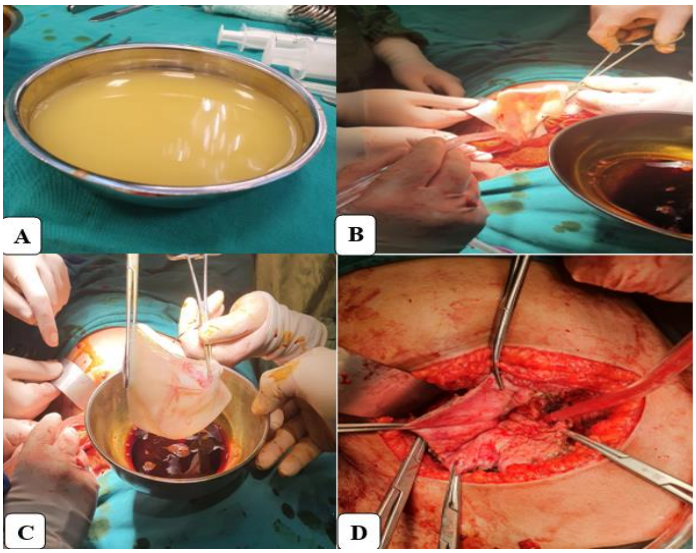


Figure 2: Intraoperative cystectomy images: A; aspirated cyst content, B and C; removal of germinative membrane, D; after cystectomy



Results

Among the 18 patients included in the study, 11 were male and 7 were female. The mean age and cyst diameter of the patients were 29.6 years and 9.2 cm, respectively (Table 1).

Table 1: Characteristics and clinical findings of the patients

		Mean (Min-Max) n (%)
Age (year)		29.6 (6-58)
Cyst diameter (cm)		9.2 (5-16)
Gender	Male	7 (38.9%)
	Female	11 (61.1%)
Side	Right	9 (50.0%)
	Left	9 (50.0%)
Symptoms	Flank pain	7 (38.9%)
	Palpable mass	4 (22.2%)
	Abdominal pain	2 (11.1%)
	Sickness	1 (5.5%)
	Hematuria	1 (5.5%)
	İncidental	3 (16.6%)
Indirect hemagglutination test	Positive	11 (61.1%)
	Negative	7 (38.9%)
Surgical complication	Yes	3 (16.6%)
	No	15 (83.4%)
Duration of hospitalization (days)		5.1 (3-8)
Duration of follow-up (months)		27 (6-60)

The reasons for admission to the hospital included flank pain (38.9%), palpable mass (22.2%), incidental (16.6%), abdominal pain (11.1%), nausea (5.5%) and hematuria (5.5%).

Seropositivity was detected in 61.1% of the patients in the IHA test (Table 1).

Cyst excision was performed in 14 of the patients with an isolated renal HC. A total of 4 patients underwent nephrectomy as 2 patients had non-functional kidneys and 2 were suspected to have malignancies (Table 2). Retrograde pyelography was performed in 4 patients with large cysts, and the connection of the cyst with the collecting system was evaluated (Table 2). There was no opening to the collecting system in these patients. The postoperative complication rate was 16.6%, and no major complications were observed in any of the patients. Three of the patients were found to have postoperative fever, wound infection and transient creatinine elevation, each. The complications were Grade 1 according to the Clavien classification.

Table 2: Cyst localization and treatment methods

		n	%
Cyst location	Upper Pole	8	44.4%
	Middle Pole	6	33.3%
	Lower Pole	4	22.2%
Treatment	Open cystectomy	13	72.2%
	Laparoscopic cystectomy	1	5.5%
	Open nephrectomy	2	11.1%
	Laparoscopic nephrectomy	2	11.1%
Retrograde pyelography	Yes	4	22.2%
	No	14	77.8%

The mean hospital stay and follow-up was 5.1 days and 27 months, respectively (Table 1). During the follow-up period, no recurrence was observed in any patient, whereas a new cyst was detected in the ovary of one patient.

Discussion

Although the kidney is the most frequently involved organ in the urogenital system, renal involvement is observed in only 2%–4% of all HC cases. More than half of those with kidney involvement simultaneously have cysts in other organs, and an isolated renal HC is very rare [3, 4, 8]. Although renal involvement is unilateral in 85% of the patients, it is bilateral in 15% [3]. A renal HC can cause serious complications, such as vascular compression, cyst infection, shock, sepsis and death [9]. A renal HC is difficult to diagnose. The cyst gradually grows and remains asymptomatic for a long time. Hence, it is usually diagnosed in adults, with an average age at diagnosis of 30 years. The most common complaint is flank pain due to cyst compression. In enlarged cysts, the reason for hospital admission may be a palpable mass in the abdomen [3, 4, 10]. In our study, the most common reason for admission was flank pain (38.8%), followed by palpable mass (22.2%), abdominal pain (11.1%), nausea (5.5%), and hematuria (5.5%). There were no clinical symptoms in 16.6% of the patients, and incidental cysts were detected. These findings were consistent with literature.

Although hydatiduria is a pathognomonic finding for an HC, it is very rare. The opening of the cyst to the collecting system occurs when the scolexes pass into the urine. Hydatiduriais is usually associated with renal colic [9, 10]. There are different incidences of hydatiduria in literature; a study by Horchani et al. reported it to be 28% [11] and a study by Göğüş et al. reported it as 5% [4]. Hydaturia was not observed in any of the patients in our study.

There is no laboratory finding that can aid in making a definitive diagnosis of a renal HC. Although IHA and enzyme-linked immunosorbent assay used in the diagnosis are the most sensitive tests, they may provide false positive or negative results. Positive serological tests confirm the diagnosis, whereas negative ones do not rule it out [12]. In a study conducted by Efesoy et al. [6] in isolated renal HC patients, the rate of IHA positivity was 71.4%, and a study conducted by Rexiati et al. [10] stated that the positivity rate of serological tests was 74%. In our study, the IHA positivity rate was 61.1%.

Although imaging plays an important role in diagnosis, there is no specific finding that may aid in making a definitive diagnosis [10]. On US, kidney HCs can be seen as unilocular, multiseptal or calcified cysts, and daughter vesicles can be detected [13]. CT has the highest specificity and sensitivity among imaging methods. Multiple internal septations in the cyst and hypodense areas of daughter vesicles compared with the fluid in the cyst (rosette pattern), calcification in the cyst wall and increased density of the germinative membrane after intravenous contrast agent injection can be detected on CT [13, 14]. US and CT were used as imaging modalities in the diagnosis of renal HCs in all cases in our study.

Renal HC management options include medical treatment, percutaneous intervention and surgical treatments. Mebendazole and albendazole are used in medical treatment. Although these drugs reduce the size of the cyst, they have a low rate of effectiveness. In addition, serious side effects of these drugs, such as hepatotoxicity, allergic reaction, leukopenia and alopecia may be observed. There is not enough data on the effectiveness of medical treatment in renal HC cases [15]. Hence, medical treatment before and after surgical intervention, instead of as primary treatment, is advocated to prevent disease spread [16]. Thus, albendazole 10–15 mg/kg/day administration 1–4 weeks before surgery and its continuation for 1–3 months after the procedure is recommended [4, 17]. We do not recommend medical treatment as primary treatment in our clinic, but we recommend it perioperatively to reduce the risk of recurrence and need for a potential transplant.

The primary treatment for renal HC is surgical removal of the cyst. Here, the aim is to remove the cyst without contaminating the patient. Cystectomy and total or partial nephrectomy are among the surgical options. Anaphylactic shock and death due to allergic reactions may occur in case of HC rupture [18, 19]. Therefore, irrespective of which surgical technique is followed, the surgery should be performed with utmost care. Evacuating the cyst contents and washing the cyst with a scolicidal (hypertonic sodium chloride, 0.5% silver nitrate, 2% formalin and 1% iodine) solution before cystectomy reduces the risk of allergic reaction and implantation [20]. Hence, we used hypertonic sodium chloride as a scolicidal in all patients who underwent cystectomy. We did not observe an allergic reaction intraoperatively in any of our patients.

Renal-sparing surgery should be the first line of treatment in patients with an isolated renal HC. However, nephrectomy is recommended in dysfunctional kidneys, large cysts thought to be associated with the collecting system and cysts suspected to be tumors [3, 4, 21]. Today, kidney loss, the rate of which is 25%, has been reduced due to factors such as an increase in the rate of incidental diagnosis and the ease of access to health services [22]. In the literature, nephrectomy was performed in 13 patients in a series of 20 patients according to a

study published in 2003, whereas it was performed in 1 patient in another series of 30 patients, as reported in 2014 [4, 10]. In our series consisting of 18 patients, 14 kidneys were preserved, 2 patients had non-functional kidneys, and 2 patients underwent nephrectomy due to suspected malignancy. There is no study in literature reporting local recurrence. In our study, which had a mean follow-up period of 27 months, no local recurrence was observed in any patient; however, a new cyst was detected in the ovary of one patient.

Conclusion

Although the HCs are commonly observed in the liver and lungs, they may also occur in other organs, especially the kidney. Isolated renal involvement, although rare, has been observed. In areas where hydatid disease is endemic, HCs should be considered as a diagnosis in patients with renal cysts, even if serological tests are negative. The primary treatment in a renal HC should be kidney-sparing surgery. Nephrectomy should be performed in cases of large cysts opening into the collecting system, non-functioning kidneys and suspected malignancy. To reduce the risk of recurrence and inoculation, albendazole treatment should be recommended before and after surgery.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):661-664.
DOI: 10.28982/josam.932472

Research article

Journal of Surgery and Medicine
e-ISSN=2602-2079

Comparison of EZ blocker and left double-lumen endotracheal tube for one lung ventilation in minimally invasive cardiac surgery

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Ethics Committee Approval
Ethics committee approval was obtained from Ankara University School of Medicine, AUTFKAEK 2021/127
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 July 10

Abstract

Background/Aim: Effective lung isolation is required in minimally invasive cardiac surgery. Double lumen tubes (DLT) are most preferred for this type of operation, and data on the use of EZ blockers in cardiac surgery are limited. We aimed to compare the efficiency of the double lumen tube and EZ blockers in minimally invasive cardiac surgery with cardiopulmonary bypass performed through a right mini thoracotomy.

Methods: A total of 89 patients who underwent minimally invasive cardiac surgery through right mini thoracotomy with cardiopulmonary bypass between January 1 and December 31, 2020, were included in this single-center, retrospective case control study. The group in which double lumen tubes were used for lung isolation (n = 58) was compared with that in which EZ blockers (n = 31) were used in terms of placement time, repositioning rate, lung collapse quality score, and postoperative sore throat and hoarseness.

Results: The time needed to place the devices in the correct position was shorter in the DLT group (3.2 (2.7) min vs 4.6 (2.4) min, P=0.02). No significant difference was found between the prevalence of at least one repositioning and lung collapse quality scores (P=0.42, P=0.21). VAS scores for sore throat were lower and hoarseness was less encountered in the EZ blocker group (21.2 (8.8) vs 49.4 (7.6), P=0.01, 16.1% vs 48.2%, P=0.01, respectively).

Conclusion: Although the EZ blocker has a longer placement time, it provides lung isolation as effective as DLT. Less sore throat and hoarseness show that EZ blocker is an important alternative for this type of surgery.

Keywords: Minimally invasive cardiac surgery, Lung isolation, bronchial blocker, Double-lumen tube

How to cite: Bermede O. Comparison of EZ blocker and left double-lumen endotracheal tube for one lung ventilation in minimally invasive cardiac surgery. J Surg Med. 2021;5(7):661-664.

Introduction

Minimally invasive cardiac surgery (MICS), which is performed through a mini thoracotomy, has gained popularity in recent years. Minimal trauma, less postoperative pain, shorter hospital stays, and rapid recovery are among the most important advantages of this method [1, 2]. However, the small incision restricts the surgeon's vision and manipulations. One of the most important ways of reducing these restrictions is providing an effective lung isolation.

Double lumen tube (DLT) is the most used product for lung isolation, because of its easy accessibility, and low risk of malposition. Also, DLT allows continuous positive airway pressure to the deflated lung [3]. Bronchial blockers (BB) are different types of devices placed inside the endotracheal tube which provide effective lung isolation [4]. Although there are many types, the use of the EZ blocker (Teleflex Life Sciences Ltd., Athlone, Ireland), a Y-shaped BB, has increased due to its easy insertion and stability.

The superiority of these products to each other are still controversial. DLTs are easier to settle and cause lung deflation in a shorter time, whereas BBs cause less sore throat and hoarseness [5]. There is no clear information on the use of these products for MICS.

In this context, this study primarily aimed to compare the efficiency of DLT with an EZ blocker in MICS with cardiopulmonary bypass (CPB) performed through a right mini thoracotomy and evaluate the postoperative patient complaints.

Materials and methods

After the institutional ethics committee approval (Ankara University School of Medicine, AUTFKAEK 2021/127) was received and written inform consents were provided by the participants, patients who underwent nonemergent MICS with CPB through a right mini thoracotomy between January and December 2020 were approached for the study, retrospectively. Patients with an anticipated difficult airway, and prior thoracic radiotherapy were excluded. The groups in which DLT or EZ blockers were used for lung isolation were compared.

In the DLT group, a 35F, 37F or 39F left-sided double lumen endotracheal tube (Mallinckrodt Medical Ltd, Athlone, Ireland) was inserted according to the physical characteristics of the patients under video laryngoscopy and positioned using a fiberoptic bronchoscope. In the EZ blocker group, patients were intubated with a single-lumen endotracheal tube (internal diameter of 7.5 to 8.5 mm), and then the EZ blocker (Teleflex Life Sciences Ltd., Athlone, Ireland) (Figure 1) was inserted through the tube in the presence of a fiberoptic bronchoscope and anchored securely on the carina (Figure 2). After the surgery began, the right channel of the tube was clamped and opened to the atmosphere in the DLT group. In the EZ blocker group, after the lungs were completely deflated, the cuff in the right main bronchus was inflated and ventilation continued. During OLV, the peak pressure of the mechanical ventilator was set to remain below 25 cmH_2O and the $EtCO_2$, between 35-45 mmHg.

Placement time starting with laryngoscopy until the end of the control bronchoscopy, prevalence of at least one repositioning during surgery or one lung ventilation, quality of lung collapse scores (1: no collapse, 2: partial collapse or 3: total collapse), duration of anesthesia, one lung ventilation (OLV), and surgery were recorded for both groups.

In the DLT group, the tube was replaced with a single lumen endotracheal tube at the end of the surgery. In the EZ blocker group, the blocker was removed from the tube and the patient was transferred to the intensive care unit. Visual analog scale (VAS) scores from 0 to 100 mm (0 = no pain and 100 = the worst pain imaginable) for sore throat and the presence of hoarseness were recorded after the patients were extubated in the intensive care unit.

Figure 1: EZ blocker

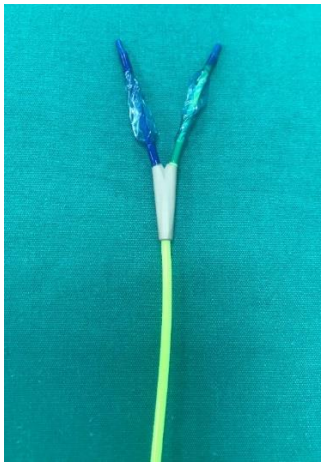
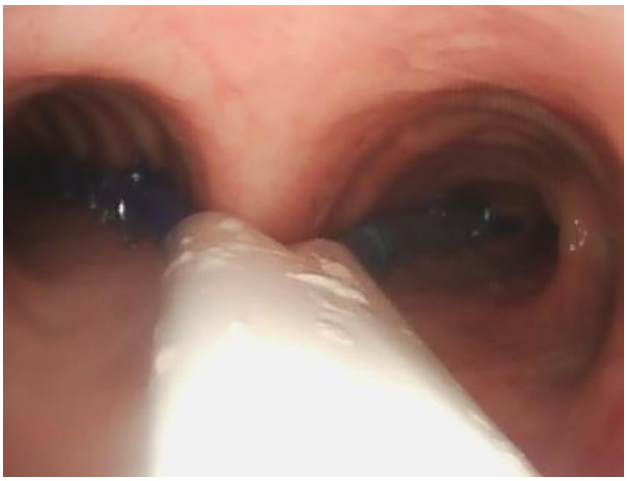


Figure 2: EZ blocker anchored on the carina



Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS, Version 15.0, Chicago, IL.). The data were presented as mean (SD) or median, as needed. Demographic and surgical parameters between groups and placement times were analyzed with the student-t test. Categorical variables, shown as frequencies and percentages, were evaluated with the Chi-square test. Surgical satisfaction and the quality of lung collapse were assessed with the Mann-Whitney U Test. *P*-values ≤0.05 were considered statistically significant.

Results

A total of 89 patients, 58 in Group DLT and 31 in Group EZ blocker, were included in the study. The two groups were similar in terms of age, gender, body mass index, types of surgeries, duration of anesthesia, OLV, and surgery ($P>0.05$ for all) (Table 1). The time required to place the devices in the

correct position was shorter in the DLT group [3.2 (2.7) min vs 4.6 (2.4) min, *P*=0.02). No significant difference was found between the prevalence of at least one repositioning and lung collapse quality scores (*P*=0.42; *P*=0.21). However, VAS scores for sore throat were lower, and hoarseness was less encountered in the EZ blocker group (21.2 (8.8) vs 49.4 (7.6), *P*=0.01, 16.1 % vs 48.2 %, *P*=0.01, respectively) (Table 2).

Table 1: Demographic features of the patients and surgical data

	DLT (n:58)	EZ Blocker (n:31)	*P*-value
Age, y, mean (SD)	63.2 (11.3)	59.4 (12.5)	0.45
Sex (M/F)	31/27	17/14	0.37
Body mass index, kg/m^2, mean (SD)	26.4 (5.1)	25.9 (4.9)	0.52
Types of surgery, n (%)			
ASD closure	5 (8.6)	3 (9.6)	
Mitral valve surgery	22 (37.9)	13 (41.9)	
Aortic valve surgery	14 (24.1)	7 (22.5)	
Multiple valve surgery	12 (20.6)	5 (16.1)	
Intracardiac mass	5 (8.6)	3 (9.6)	
Duration of anesthesia (min), mean (SD)	252 (46)	261 (51)	0.26
Duration of OLV (min), mean (SD)	58 (16)	55 (19)	0.61
Duration of surgery (min), mean (SD)	221 (31)	224 (26)	0.57

DLT: Double Lumen Tube, ASD: Atrial Septal Defect, OLV: One Lung Ventilation

Table 2: Comparison of devices and postoperative complaints of the patients

	DLT (n:58)	EZ Blocker (n:31)	*P*-value
Placement time (min), mean (SD)	3.2 (2.7)	4.6 (2.4)	0.02
Prevalence of at least one repositioning [n (%)]	14 (24.1)	8 (25.8)	0.42
Lung collapse quality scores, mean (SD)	2.91 (0.41)	2.83 (0.37)	0.21
VAS scores for sore throat, mean (SD)	49.4 (7.6)	21.2 (8.8)	0.01
Hoarseness [n (%)]	28 (48.2)	5 (16.1)	0.01

DLT: double lumen tube, VAS: visual analog scale

Discussion

As there is no significant difference between lung collapse scores, EZ blockers can be used as effectively as DLT in MICS with CPB performed through a right mini thoracotomy. However, placement may take a little longer. Sore throat and hoarseness after extubation were less encountered when EZ blocker was used during this type of surgery.

Minimally invasive cardiac surgery has become widespread in recent years due to their advantages. In addition to its surgical features, it also requires varying anesthesia techniques such as lung isolation, venous cannulation, and monitoring. DLTs are more frequently used for lung isolation because they are easily accessible and inexpensive, but EZ blocker is also an alternative. Ruetzler et al. reported that although the time for intubation is longer, the EZ blocker is an efficient and easy-to-use device and can be used as an alternative to DLT [6]. In our study, the placement of the EZ blocker took longer. Considering that patients are transported to the intensive care unit while intubated after MICS, the lack of a need for tube replacement in patients who received the EZ blocker may compensate for this loss. Lu et al. stated that there was no significant difference between placement time in cases where lung isolation was performed for right video-assisted thoracoscopic surgery (VATS) [7]. However, the necessity of bronchoscopic control may be a limiting factor for EZ blockers.

One of the major problems during single lung ventilation is device malposition, which be caused by poor fixation, and the position of the patient. Morris et al. found no difference in terms of repositioning in patients who underwent left thoracic surgery, while the repositioning rate in the right sided cases was higher in the EZ blocker group [8]. Lu et al. could not detect any malposition difference in right VATS [7]. This difference may be due to patient positions. In our study, the repositioning needs were similar between the two groups. Unlike thoracic surgery, we were able to position the patients with an inflatable pillow under the right thorax while in supine position.

It is critical for the surgeon to have good surgical vision during MICS. To facilitate this, the lung on that side must be deflated sufficiently. Grocott et al. did not find a difference in surgeon satisfaction when they compared DLT with a different bronchial blocker during port access cardiac surgery [9]. Since bronchial blockers have a thinner lumen, lung deflation times may be longer. In addition, proximal misplacement off the right upper lobe may cause insufficient lung deflation [10]. Yoo et al. stated that in cases where spontaneous collapse was achieved with BB, the surgical exposure was not equivalent to that with DLT. However, they reported no difference between BB use with the disconnection technique and DLT [11]. According to Cheng et al., there was no difference between BB with the disconnection technique and DLT in patients who underwent VATS [12]. In our study, we did not find any difference between the disconnection technique that we use in our routine practice and DLT in terms of lung collapse quality scores.

Besides all these, devices used for OLV may cause airway damage and consequently, sore throat and hoarseness. In many studies, tracheal hematoma, hyperemia, or bronchial hematoma were reported after DLT placement [13, 14]. The replacement of DLT with a single lumen tube after MICS can be considered to increase the possibility of added airway damage. Mourisse et al. reported that the group in which the EZ blocker was used for lung isolation had less sore throat on postoperative day 1 compared to the group in which DLT was used [15]. Zhong et al. found that both sore throat and hoarseness were less common when BBs were used [16]. Similarly, in our study, sore throat and hoarseness were significantly less common when EZ blocker was used.

This study has some limitations. First, due to the retrospective nature of the study, there was no randomization. Second, the fact that different specialists used these devices may have caused individual differences. Third, the difference in complication rates and pain scores after discharge were not evaluated. Prospective, randomized, double-blind, multicenter studies are needed to make these data clearer in this type of surgery.

Conclusion

Although the placement time is longer, the EZ blocker provides just as effective lung isolation as DLT in MICS with CPB performed through a right mini thoracotomy. The tube does not need to be replaced at the end of the surgery, and it causes less sore throat and hoarseness in the postoperative period.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):665-669.
DOI: 10.28982/josam.793016

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of patients with multiple sclerosis and sleep disorders

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Ethics Committee Approval
Approval for the study was granted by the Medical Research Ethics Committee of Kahramanmaraş Sütçü Imam University Medical Faculty (Decision no:01, Dated: 08.11.2017). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 July 10

Abstract

Background/Aim: Sleep disorders are often reported by MS patients and various studies have shown sleep disorders to be more widespread in MS patients than in healthy control groups. However, despite the high frequency, they are often overlooked. This study aimed to determine the characteristics of fatigue and daytime sleepiness in MS patients, the underlying factors, and their relationship for testing the reliability of subjective scales and establishing when patients presenting with these symptoms should be referred to a sleep specialist.

Methods: The patients enrolled in this cohort study were aged >18 years, had a confirmed diagnosis of relapsing remitting MS, were in the remission phase, had not taken steroids within the last 3 months, and had complaints of fatigue, daytime sleepiness, and sleep disorders. Patients with EDSS score <3 were admitted to the sleep laboratory for 2 days to perform 1 night of polysomnography (PSG) and a 5-nap multiple sleep latency test (MSLT) the following day. The results were evaluated with regards to the clinical scales.

Results: A total of 41 patients were evaluated. Excessive daytime sleepiness was found in 14 (34.1%), and sleep quality was poor in 28 (68.29%). According to the PSG-MSLT, a sleep disorder was found in 37 patients (90.24%). A diagnosis of hypersomnolence was made in 23 (56.1%) patients, and two (4.88%) were categorized as type 2.

Conclusion: It is necessary for every clinician involved in MS treatment to correctly diagnose and treat fatigue, excessive daytime sleepiness, and other sleep disorders, which increase the disability of disease. When the high prevalence of these types of disorders and the fact that they are multifactorial are taken into consideration, the timing of the referral of these patients to a sleep specialist and the implementation of objective tests become more important.

Keywords: Multiple sclerosis, Sleep disorders, Polysomnography

How to cite: Bavli S, İnanc Y, Tuncel D. Evaluation of patients with multiple sclerosis and sleep disorders. J Surg Med. 2021;5(7):665-669.

Introduction

Multiple Sclerosis (MS) is a chronic disease of the central nervous system (CNS) characterized by loss of motor and sensory function, resulting from immune-mediated inflammation, demyelination and subsequent axonal damage. Approximately 2.2 million people are affected worldwide, and the prevalence is expected to increase. It is more common in women compared to men. MS is a frequent cause of nontraumatic neurological disability in young adults. The neurological symptoms can be various and heterogeneous, while fatigue and sleep disorders, even though extremely frequent, are often underestimated and underdiagnosed. Comorbid conditions are common in MS and may contribute to disability. Many patients with MS report sleep disorders, more often than in the general population. Poor sleep quality in MS has been associated with negative outcomes, such as decreased quality of life, exacerbation rate and disease severity, and with other comorbidities such as fatigue, depression, anxiety, and pain [1].

This study aimed to determine the characteristics of fatigue and daytime sleepiness in MS patients, the underlying factors and their relationship for testing the reliability of subjective scales and establishing when patients presenting with these symptoms should be referred to a sleep specialist.

Materials and methods

This cohort study was conducted between 09.11.2017 and 01.11.2018. The patients enrolled in the study were aged >18 years, had a confirmed diagnosis of relapsing remitting MS (RRMS), were in the remission phase, had not taken steroids within the last 3 months, and had complaints of fatigue, daytime sleepiness, and sleep disorders.

Patients were excluded from the study if they were aged < 18 years, had any other disease which could be confused with MS (systemic lupus erythematosus, CNS vasculitis), were in the attack phase of RRMS, had experienced an attack within the last 3 months, had received steroid treatment within the last 3 months, had been diagnosed with sleep disorders because of other systemic diseases, especially respiratory, had been diagnosed with a psychiatric disorder such as depression or anxiety disorder before the MS diagnosis, had taken various treatments for a sleep disorder before the MS diagnosis, or were using drugs which have a direct effect on sleep such as benzodiazepines, modafinil or melatonin during the evaluation or in the recent past.

Approval for the study was granted by the Medical Research Ethics Committee of Kahramanmaraş Sütçü Imam University Medical Faculty (Decision no:01, Dated: 08.11.2017). The study was conducted per the Declaration of Helsinki. In the neurological evaluation, the neurologist applied the Expanded Disability Status Scale (EDSS) of Kurtze, and neuro-imaging methods were used. Those who presented with complaints of fatigue and sleep disorders, and those with an EDSS score <3 were admitted to the sleep laboratory for 2 days for 1 night of polysomnography (PSG) and a 5-nap multiple sleep latency test (MSLT) performed the following day. The results were evaluated with the clinical scales and demographic data. A total of 41 patients aged >18 years who met these criteria were included in the study.

The age, gender, marital status, smoking status, comorbidities, nocturia, drugs used, duration of disease, body mass index (BMI), EDSS score, Epworth Sleepiness Scale (ESS), Fatigue Severity Scale (FSS), Hospital Anxiety Depression Scale scores (HAD-A, HAD-D), the presence of restless legs syndrome, widespread body pain scores according to the Visual Analog Scale (VAS), the Pittsburgh Sleep Quality Index (PSQI) score, and the data obtained from the PSG and 5-nap MSLT the following day were recorded for each patient. The patient scores obtained from the subjective scales were examined with respect to their relationship with each other and the diagnoses made with objective tests.

All patients provided written informed consent for participation in the study.

Statistical analysis

Data obtained in the study were statistically analyzed using Jamovi and JASP (Jamovi project (2018) version 0.9.6.9) and JASP Team (2019) version 0.10.2 software. Descriptive statistics were presented as mean (standard deviation) (SD), median, minimum, and maximum values and interquartile range for continuous variables according to distribution. Categorical variables were given as number (n) and percentage (%). Conformity of numerical variables to normal distribution was assessed with the Kolmogorov-Smirnov test. In the comparison of two independent groups, the Mann Whitney U-test was used for numerical variables not showing normal distribution. In the comparison of differences between categorical variables, the Pearson Chi-square test and Fisher's Exact test were used in 2x2 tables and RxC tables, respectively. The Spearman Rho correlation coefficient was used to examine the correlations between numerical variables. A value of $P<0.05$ was considered statistically significant.

Results

A total of 41 patients, comprising 30 (73.17%) females and 11 (26.83%) males, who were followed up in the Neurology Outpatient Clinic of Sütçü Imam University Medical Faculty Hospital were evaluated. The mean and median EDSS scores of the patients were 1 (range: 1-2.5) and 1.2 (0.4), respectively. Twenty-seven patients (65.85%) received injection treatment and fifteen patients (31.71%) were administered oral treatment. Among the patients receiving injections, interferon-ß was used in 25 (Table 1).

Table 1: Demographic and clinical data of the patients

	n (%) / mean (SD)	Median [Min - Max]
Gender		
Male	11 (26.83)	
Female	30 (73.17)	
EDSS	1.2 (0.4)	1 [1 - 2.5]
Treatment		
Injection treatment	27 (65.85)	
Oral	13 (31.71)	
Age (years)	35 (9)	34 [18 - 53]
Marital status		
Single	10 (24.39)	
Married	31 (75.61)	
Disease duration (years)	5.3 (3.04)	5 [1 - 13]
Smoker	12 (29.27)	
Body mass index	25.2 (4.59)	25.63 [17.3 - 36.05]

According to the HAD-A scale, 20 (48.8%) patients had anxiety, and according to the HAD-D scale, 24 (58.5%) had depression. The mean VAS score for widespread body pain was

4.73 (3.1). According to the FSS, fatigue was found in 30 (73.2%) patients.

According to the ESS, excessive daytime sleepiness was found in 14 (34.1%) patients. Based on PSQI, sleep quality was poor in 28 (68.29%) patients. Based on PSG-MSLT, there was a sleep disorder in 37 patients (90.24%), categorized as type 2 due to a medical condition, including obstructive sleep apnea syndrome (OSAS), hypersomnolence, restless legs syndrome (RLS), periodic limb movement disorder (PLMD). A diagnosis of hypersomnolence was made in 23 (56.1%) patients, and 2 patients (4.88%) had hypersomnolence type 2.

Following PSG, OSAS was found in 26 (63.41%) patients. The mean and median Apnea-Hypopnea Index (AHI) scores were 9, and 6 (range, 1-39), respectively. According to the AHI scores, OSAS was mild in 20 (48.78%), moderate in 4 (9.75%) and severe in 2 (4.87%) patients. Of the 26 patients diagnosed with OSAS, 6 (23.07%) were obese. The 2 patients diagnosed with severe OSAS were admitted to the sleep laboratory a second time and started on n-CPAP treatment. Two (4.87%) patients had central type apnea in addition to OSAS. A moderate, significant linear correlation was found between the PSQI scores and the HAD-A and HAD-D scores ($P<0.001$, $P=0.014$) (Table 2).

Table 2: Descriptive statistics of various data

	n (%) / mean (SD)	Median [Min - Max]
ESS	8 (6)	7 [0 - 23]
FSS	45 (17)	50 [9 - 63]
HAD-A	10 (4)	9 [0 - 21]
HAD-D	8 (5)	8 [1 - 20]
VAS	4.7 (3.1)	4.5 [0 - 10]
RLS	5 (12.2)	
OSAS	26 (63.41)	
AHI	9 (9)	6 [1 - 39]
Hypersomnolence	23 (56.1)	
Narcolepsy	2 (4.88)	
PLMD	12 (29.3)	
PLMI	16 (35)	0 [0 - 188]
Sleep Efficacy (%)	86.17 (10.72)	87 [52.6 - 99]
PSQI	8 (4)	8 [1 - 15]
PSQI sleep quality		
Good	13 (31.71)	
Poor	28 (68.29)	
Obesity	6 (14.63)	
Sleep latency (mins)	22.7 (27.3)	11.5 [1 - 109]
N1 (%)	2.59 (2.62)	2 [0.3 - 17]
N2 (%)	52.5 (9.64)	52.2 [28.6 - 71.3]
N3 (%)	29.45 (6.74)	28.6 [14.5 - 45.8]
REM (%)	15.76 (7.33)	16.8 [1.8 - 34.7]
First REM Latency	147.1 (90.5)	116.5 [46 - 376]
MSLT sleep latency	8.2 (4.5)	7.7 [0.8 - 17.5]
SOREM	1 (1)	0 [0 - 4]
Interferon Beta Treatment		
Using	25 (61.0)	
Not using	16 (39.0)	

Considering the effects of injection on quality of life and sleep disturbance, some clinical parameters were compared according to Interferon-ß use. The median sleep latency values in the MSLT significantly differed between those using and not using interferon beta ($P=0.048$) (Table 3).

Table 3: Comparisons of various clinical and objective parameters according to the treatment used

	Interferon Beta Treatment		
	Using (n=25)	Not using (n=16)	*P*-value
OSAS (%)	15 (60.0)	11 (68.8)	0.814
RLS (%)	2 (8.0)	3 (18.8)	0.362
Hypersomnolence (%)	16 (64.0)	7 (43.8)	0.341
ESS (median [IQR])	8.0 [4.0 - 12.0]	6.5 [4.2 - 8.8]	0.376
FSS (median [IQR])	50.0 [31.0 - 61.0]	45.5 [33.2 - 57.8]	0.355
HAD-A (median [IQR])	9.0 [6.0 - 14.0]	9.5 [7.0 - 12.2]	0.861
HAD-D (median [IQR])	8.0 [4.0 - 9.0]	7.5 [5.8 - 11.0]	0.397
PLMI (median [IQR])	0.0 [0.0 - 16.0]	2.0 [0.0 - 18.0]	0.652
PSQI (median [IQR])	8.0 [5.0 - 11.0]	7.0 [4.0 - 12.0]	0.957
MSLT sleep latency (median [IQR])	6.1 [3.9 - 10.6]	9.1 [6.7 - 13.8]	0.048
Sleep latency - mins (median [IQR])	10.0 [4.0 - 32.0]	12.5 [4.9 - 35.0]	0.678
N1 (median [IQR])	1.7 [1.3 - 2.4]	2.5 [1.6 - 3.0]	0.177
N2 (median [IQR])	51.2 [46.3 - 56.1]	54.0 [46.8 - 60.1]	0.530
N3 (median [IQR])	28.6 [26.0 - 31.5]	28.2 [24.8 - 32.3]	0.820
REM (median [IQR])	17.0 [9.3 - 21.1]	15.2 [9.9 - 20.6]	0.602
First REM Latency (median [IQR])	105.0 [84.0 - 171.5]	140.2 [88.8 - 190.1]	0.593
Minimum O2 Saturation (median [IQR])	92.0 [90.0 - 93.0]	92.0 [91.0 - 93.2]	0.580
SOREM (median [IQR])	0.0 [0.0 - 0.0]	0.0 [0.0 - 1.0]	0.693

Discussion

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and neurodegenerative disease of the central nervous system. It is a heterogenous, multifactorial, immune-mediated disease caused by complex genetic-environmental interactions with the demyelination occurring in the white and grey matters of the brain and the spinal cord, and axonal damage. In addition to the disease itself primarily leading to disability, secondary factors such as fatigue, excessive daytime sleepiness, anxiety, depression, sleep disorders and pain also increase disability and affect the daily activities of the patient.

Due to many factors which contribute to their existing disability, several MS patients find themselves not being able to complete their academic life or being fired from work as a person who quickly tires and cannot resist sleep. When motor and sensory symptoms develop, although the majority of patients understand that they have suffered an attack and present to a physician, they may not be able to easily express complaints such as excessive daytime sleepiness or not pay enough importance, since it is overshadowed by other major symptoms. In addition, patients may mistakenly use the two distinct but closely related and intertwined concepts of fatigue and daytime sleepiness interchangeably.

Fatigue is defined subjectively as a decrease in mental and physical energy leading to difficulty in performing routine daily activities, which is noticed by the patient or their caregiver [2]. The patient feels exhausted, fatigued, burnt-out, and listless. The social and professional life of the patient can be affected. It can be evaluated subjectively with some scales but there is no test with proven reliability and validity for objective evaluation. In subjective evaluations, the Fatigue Severity Scale (FSS), which has a critical cutoff of ≥36 points, is used. Fatigue has been reported in 50-80% of MS patients [3]. Approximately 55% of MS patients report that fatigue is one of the worst symptoms [4] and 40% of patients state that it is the complaint that disables them most [5]. There are many studies in the literature which evaluate the frequency of fatigue and the reasons, and the rates found in most of these studies are similar.

In this study, we only included ambulatory RRMS patients who presented to the outpatient clinic with complaints of fatigue, excessive daytime sleepiness, and poor sleep and those who had an EDSS score of <3, and a relatively short duration of disease. When these inclusion criteria are considered, it can be

assumed that the effects of factors such as spasticity, pain, disability, anxiety and depression on sleep and fatigue are relatively low. According to the FSS, fatigue was found in 30 (73.2%) of the 41 patients.

In a study by Veauthier et al. [6] assessing which MS patients with fatigue should be referred to a sleep specialist, the optimal cutoff for PSQI was 5 points, and sensitivity was higher in those with positivity in the PQSI and fatigue scales. It was emphasized that each patient with fatigue should be evaluated carefully in terms of sleep disorders, and patients with a PQSI score >5 and Modified Fatigue Impact Scale (MFIS) score of >34 should certainly be referred to a sleep specialist and PSG should be used. In that study, only PSG was used to objectively evaluate sleep disorders, while in our current study, we used both the nocturnal PSG and the 5-nap MSLT performed the following day, along with the FSS, which evaluates fatigue.

In our patients, the sensitivity of the PSQI to sleep disorders, and whether there was accompanying fatigue were similar with the literature. In the analysis of the PSG-MSLT data of the patients with fatigue, an underlying sleep disorder was found in 86.6%. If a patient presented with other symptoms and fatigue was found in subjective scales, the patient was referred to a sleep specialist. It is recommended to perform MSLT the following day in addition to PSG.

Sleepiness is different from fatigue. When it is necessary to remain awake during the day, fatigue is the difficulty in remaining awake, feeling the need to sleep and not being able to prevent falling asleep. The ESS is used for subjective evaluation, and the critical cutoff value is >10. In objective evaluations, the maintaining awakeness test or MSLT are used. Therefore, the physician must differentiate these two concepts, for which the diagnosis and treatment are different [7]. Evaluation with differentiation of these two concepts will be beneficial in understanding the underlying biological mechanisms of these pathologies.

Merkelbach et al. [8] reported that 20% of MS patients had pathological sleepiness. According to the ESS scores in the current study, excessive daytime sleepiness was found in only 14 (34.1%) patients. According to the PSG-MSLT, a diagnosis of hypersomnolence was made in 23 (56.1%) patients. Two (4.88%) patients had narcolepsy. According to the objective data, there was pathological sleepiness in a total of 25 (60.9%) patients. When examined in this respect, if excessive daytime sleepiness in patients with symptoms is evaluated with a single subjective scale, those with non-pathological scores are considered normal and the objective tests are not applied, approximately half of the patients could be missed. Therefore, the ESS alone is not sufficient in the evaluation of excessive daytime sleepiness, and it is necessary for patients with this complaint to undergo PSG and more importantly, the MSLT the following day.

In the PSQI, which is a subjective scale for sleep quality, the cutoff value was >5, and sleep quality was poor in 28 (68.29%) patients. Thirty-seven (90.24%) patients were diagnosed with a sleep disorder according to the PSG-MSLT results. The rate in PSQI is of good guidance in the evaluation of sleep quality in MS patients, irrespective of whether they have fatigue.

Several studies in recent years have shown that sleep disorders contribute to fatigue and excessive daytime sleepiness, which can be intertwined with fatigue. There are many publications in the literature related to the reasons for MS fatigue and associated conditions. However, there are no systematic studies which evaluate fatigue and its frequency in MS patients. In 2017, Popp et al. [7] conducted a systematic review by screening all the studies in literature which used the ESS evaluation scale. A total of 48 original articles were examined. There was a correlation between the ESS and FSS in 19 studies. The results of the current study do not support this information as we found no correlation between the two (P=0.256).

Popp et al. [7] found 9 PSG studies and 2 actigraphy studies which objectively evaluated sleep disorders in MS patients. While most studies emphasized the clinical importance of fatigue in MS patients, excessive daytime sleepiness was less frequent and of a lower severity. In this study, we stressed the importance of fatigue, consistent with the literature. However, the lower frequency of excessive daytime sleepiness in the literature can be attributed to the use of subjective scales only, such as the ESS. In the current study, while the rate was 34.1% according to the ESS, the actual rate of pathological sleepiness was 60.9% according to the PSG and MSLT data. Therefore, it must be emphasized again that subjective scales are not sufficient in the evaluation of excessive daytime sleepiness. Generally, fatigue and excessive daytime sleepiness have been associated with respiratory disorders and PLMD. In an earlier study, it was concluded that while fatigue without accompanying excessive daytime sleepiness was frequent, excessive daytime sleepiness without fatigue was uncommon. Consistent with this finding, in our study, the most common underlying reasons were respiratory disorders and PLMD.

In an actigraphy study by Mendozzi et al. [9] conducted to examine the effect of long-term treatment of Interferon beta on sleep quality and fatigue, 42 ambulatory RRMS patients were monitored for at least 7 nights. Sleep quality was evaluated every day through actigraphy. The data were compared by grouping the patients as those did not receive immunomodulator treatment, those using glatiramer acetate, those using Interferon beta 3 days a week, and those using Interferon beta 1 day a week. There was a 5% decrease in sleep efficacy in two-thirds of the nights when Interferon beta injection was made, and sleep efficacy was lower in patients using glatiramer acetate compared to those not using the drug. It was emphasized that these types of side-effects on sleep should be taken into consideration when planning long-term treatment. In the current study, the scores obtained from the subjective scales, the diagnoses of sleep disorders obtained and the PSG-MSLT data were compared by separating the patients as those using and not using Interferon-ß, and a significant difference was found between the median MSLT sleep latency values only. It would be useful for physicians treating MS to know the effects of the treatments on sleep.

In a study by Shahrbanian et al. [10] that compared 79 and 110 MS patients with and without pain, respectively, the prevalence of pain among MS patients was 42%. The presence of pain and the pain severity were the factors most related to disability in MS. Fatigue was also one of the main factors contributing to pain. Moreover, a relationship was found between

pain and higher rates of depression and anxiety, sleep problems and impaired cognition. In our study, the mean VAS score of the patients was 4.7 (0.31). This may be attributed to the fact that spasticity and disability have not yet developed, as the study sample included a selected group of RRMS patients with EDSS scores of <3.

There are studies in literature which report that RLS is seen in 32.7% of MS patients, and in the primary progressive form of MS, this rate increases and leads to higher disability scores [11]. Predictive factors for RLS in MS patients are advanced age, a long duration of disease, primary progressive form, higher disability score, and shaking the legs before sleeping. RLS symptoms related to MS are more severe compared to RLS with no association with MS [12]. In the current study, RLS was found in 5 patients (12.2%).

In a PSG study, Ferini-Stramb et al. [13] showed a higher prevalence of PLMD in MS patients compared with a control group (36% vs. 8%). These movements can partially explain the disrupted sleep among individuals with PLMD, but anatomically, a specific region or neurophysiological mechanisms are still not fully known. In the current study, PLMD was found in 12 (29.3%) patients.

In their review, Marrieve et al. [14] reported that OSAS prevalence ranged between 7.14%-58.1%. While central sleep apnea is seen in <1% of the normal population, in some studies, it is reported to range between 0-8% in MS, especially in those with brain stem involvement [15]. In the current study, OSAS was found in 26 (63.41%) patients, 2 of which (4.88%) had mixed type with a combination with central apnea.

The prevalence of narcolepsy in the general population is approximately 4-5 per 10,000, or 0.047% [16]. Although its prevalence in MS patients is still not clearly known, in their systematic review, Marrieve et al. [14] reported the prevalence of narcolepsy in MS patients as varying between 0-1.6%. In the current study, a type 2 diagnosis was made because of a medical condition in 2 (4.88%) patients.

Our study has some limitations. The low number of cases and the use of single-center data may impede the generalizability of the results.

Conclusion

It is necessary for every clinician treating MS and its components to correctly diagnose and treat fatigue, excessive daytime sleepiness, and other sleep disorders, which increase the disability of disease. When the high prevalence of these disorders and their multifactorial nature are taken into consideration, however reliable subjective scales are, the timing of referral of these types of patients to a sleep specialist and the implementation of objective tests become more important.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):670-675.
DOI: 10.28982/josam.922612

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of serum oxytocin levels in patients with depression, generalized anxiety disorder, panic disorder, and social anxiety disorder: A case-control study

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Ethics Committee Approval
Abant İzzet Baysal University School of Medicine Ethics Board with the Decision No. 2013/22-105 on 02.06.2014.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 July 12

Abstract

Background/Aim: Oxytocin, an endogenous anti-stress, antidepressant, and anxiolytic hormone, is reported to increase in stressful situations to reduce the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and amygdala for coping with stress and improving social functioning. This study aimed to compare serum oxytocin levels of patients with depression, generalized anxiety disorder (GAD), panic disorder (PD), and social anxiety disorder (SAD) with that of healthy controls.
Methods: The study included 50 patients (25 male, 25 female) with major depression, 26 patients (9 male, 17 female) with GAD, 31 patients (14 male, 17 female) with SAD, and 40 patients (17 male, 23 female) with PD and 30 healthy volunteers. Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Rating Scale (HARS), Perceived Stress Scale (PSS), and Anxiety Sensitivity Index-3 (ASI-3) were applied to all groups. In addition, Generalized Anxiety Disorder-7 (GAD-7), Panic Disorder Severity Scale (PDSS), and Liebowitz Social Phobia Scale were applied to patients with GAD, panic disorder, and social anxiety disorder, respectively. Serum oxytocin levels were measured by ELISA.
Results: Serum oxytocin levels of patients with depression were significantly lower, and those of patients with generalized anxiety disorder, social anxiety disorder, and panic disorder with agoraphobia were significantly higher compared to the control group (2.46 (2.8) vs. 2.86 (0.72), P=0.004, 11.49 (11.35) vs. 2.86 (0.72), P=0.001, 10.67 (11.32) vs. 2.86 (0.72), P=0.001, and 6.97 (5.01) vs. 2.86 (0.72), P=0.001, respectively).
Conclusion: Lower oxytocin levels in depressed patients and higher oxytocin levels in patients with GAD, and PD with agoraphobia suggest that oxytocin has a role in psychiatric disorders. Further studies are needed to better understand the relationship between depression, anxiety disorders, oxytocin, and the underlying mechanisms.

Keywords: Oxytocin, Depression, Generalized anxiety, Social anxiety, Panic disorder

How to cite: Tuman TC, Yıldırım O, Tufan AE. Evaluation of serum oxytocin levels in patients with depression, generalized anxiety disorder, panic disorder, and social anxiety disorder: A case-control study. J Surg Med. 2021;5(7):670-675.

Introduction

Oxytocin is a peptide hormone that is known to have a role in birth, breastfeeding, maternal behavior, attachment, and social behaviors [1, 2]. Several studies are conducted on animals to investigate the roles of oxytocin in birth, breastfeeding, reduction of aggression, social behaviors, attachment between the mother and the baby, and partners [1]. Human studies report that oxytocin enhances the sense of attachment, facilitates human interaction, and may have a therapeutic potential in psychiatric patients with social function disorders. Oxytocin is considered a prosocial neuropeptide [2, 3]. It reduces anxiety due to social stress by suppressing cortisol release and amygdala activity [4, 5]. In addition to regulating the reward of the attachment, it makes coping with stress easier. Mother-baby attachment is crucial among mammals and oxytocin enables the emotional functions of this attachment to be regulated during adulthood. Oxytocin suppresses the hypothalamic-pituitary-adrenal (HPA) axis induced by stress [6]. In animal studies, oxytocin was released into the bloodstream and cerebrospinal fluid after stress exposure [7].

Oxytocin has been investigated in various psychiatric disorders due to its potential impacts on psychopathology. The oxytocin system is also affected by early life experiences [8]. A study found out that exposure to emotional abuse was associated with low oxytocin in the cerebrospinal fluid in women [9]. Oxytocin is believed to influence the regulation of stress response, mood, and anxiety disorders by reducing the adrenocorticotropic hormone (ACTH) and basal cortisol levels [10, 11]. It has been reported that there is more variability in the pulsatile release of oxytocin in depressed women compared to non-depressed women [12]. In a study conducted with patients with unipolar and bipolar depression, the oxytocin levels were lower than controls both before and after treatment with antidepressants and ECT [13]. Turan et al. [14] suggested that oxytocin levels were higher both before and after treatment in bipolar disorder patients compared to healthy controls; therefore, oxytocin may be a trait marker for bipolar disorder. In another study, plasma oxytocin levels were lower in schizophrenia patients compared to healthy controls, and oxytocin levels in schizophrenia patients were associated with impairment in metacognitive functions [15].

Taking into consideration the role of the oxytocin in coping with stress, its anxiolytic effects, that it regulates the amygdala response to the social stimuli, reduces anxiety and HPA axis response, we thought that serum oxytocin levels may differ in patients with depression, generalized anxiety disorder (GAD), social anxiety disorder (SAD), panic disorder (PD) and panic disorder with agoraphobia [16]. This study aimed to comparatively investigate the serum oxytocin levels in patients with depression, GAD, SAD, PD, panic disorder with agoraphobia, and healthy controls.

Materials and methods

Participants

A total of 177 participants aged between 18 and 65 years were included in this study, as follows: Fifty patients (25 male, 25 female) with major depression, 26 patients (9 male, 17 female) with GAD, 31 patients (14 male, 17 female) with SAD and 40 patients (17 male, 23 female) with PD according to DSM 5 criteria and a healthy control group of 30 (13 male, 17 female) individuals who visited the Psychiatry outpatient clinic of Abant İzzet Baysal University Faculty of Medicine. The patients were not using any psychiatric medications.

Patients who had undergone electroconvulsive therapy within the last six months, patients who had used psychotropic medications within the last month, patients with dementia, schizophrenia, mental retardation, autism, and other comorbid psychiatric disorders such as substance abuse or addiction other than smoking, a history of head trauma, neurological diseases, a known metabolic or endocrine disorders, menstrual irregularities, confirmed pregnancy or patients on contraceptive or hormone therapy were excluded from the study. A total of 30 (13 male, 17 female) healthy individuals who voluntarily participated in the study were also included. The control group had the same age range as the patient groups and no psychiatric, neurologic, endocrine, and metabolic disorders. Exclusion criteria for the control group were the same as the patient group.

This study was supported by Abant İzzet Baysal University Scientific Research Projects Committee (Project No: 2015.08.35.828), approved by the Abant İzzet Baysal University School of Medicine Ethics Board with the Decision No. 2013/22-105 on 02.06.2014, and conducted per the Helsinki Declaration.

Measurements

All patients were diagnosed according to DSM-5 [17]. After the participant filled out the sociodemographic data form, Hamilton Depression Rating Scale (HAM-D) was applied to evaluate the severity of depression. Hamilton Anxiety Rating Scale was used to evaluate the severity of anxiety. Generalized Anxiety Disorder 7-item (GAD-7), Panic Disorder Severity Scale (PDSS), Liebowitz Social Phobia Scale were applied to patients with GAD, PD, and SAD, respectively. The Anxiety Sensitivity Index-3 (ASI-3) and Perceived Stress Scale (PSS-14) were both applied to all groups. To measure the oxytocin serum levels, 10 milliliters of blood samples were collected from the patients and the control group between 08.00 AM and 09.00 AM into the standard vacuumed tube and centrifuged for 15 minutes at 1600 rpm at the biochemistry lab within the first 30 minutes after collection. The serum samples were stored at -70°C until the biochemical analysis.

Hamilton Depression Rating Scale (HDRS): It is an interviewer-filled scale developed by Hamilton to evaluate the severity of depression in patients diagnosed with depression. [18]. There are subgroups such as depressive temperament, suicide, loss of work and activities, retardation, agitation, gastrointestinal symptoms, general somatic symptoms, hypochondriac symptoms, insight, appetite and weight loss, insomnia, and anxiety. Its Turkish validity and reliability study was conducted by Akdemir et al. The internal consistency coefficient of the scale was 0.75 [19].

Hamilton Anxiety Rating Scale (HARS): This scale, developed by Hamilton, was prepared to determine the level of anxiety and symptom distribution in individuals and measure the change in severity. It consists of 14 items that question both mental and physical symptoms [20]. The presence and severity of the items on the scale are evaluated by the interviewer. Its

Turkish validity and reliability study was conducted by Yazıcı et al. [21].

Generalized Anxiety Disorder 7-item test (GAD-7): Developed in 2006 by Spitzer et al. to detect symptoms of common anxiety disorder in primary care, the scale consists of 7 items that individuals will answer based on their self-reports [22]. It is a four-point Likert-type scale, graded between 0 (none) and 3 (almost every day). The higher the scores, the higher the level of anxiety disorder symptoms. The Turkish adaptation and validity-reliability study of the scale were performed by Konkan et al. and the internal consistency coefficient was 0.85 [23].

Panic Disorder Severity Scale (PDSS): As a seven-item, semi-structured scale scored by the physician, PDSS provides a grading of panic frequency, anticipation anxiety, avoidance of physical sensations, and impairment in work and social functionality [24]. Each of these symptoms is graded by the interviewer between 0 and 4. The total score ranges between 0-28. Its Turkish validity, reliability, and standardization study were performed by Monkul et al. The internal consistency coefficient of the scale was 0.92 [25].

Liebowitz Social Phobia Scale (LSPS): The validity and reliability study of the scale, developed by Liebowitz (1987), was conducted by Heimberg et al. [26]. There are a total of 24 items on the scale. LSAS was developed to evaluate situations in which individuals with social phobia exhibit fear and/or avoidance behavior. The Turkish validity and reliability studies of the Liebowitz Social Anxiety Scale were conducted by Soykan, Özgüven, and Gençöz in 2003 [27].

Anxiety Sensitivity Index-3 (ASI-3): The ASI measures anxiety sensitivity, or fear of anxiety-related emotions. A new version of the ASI, the ASI-3, consists of 18 items [28]. It evaluates the three most cantilevered AS domains: Social, cognitive, and physical. The score that could be obtained from the scale ranges between 0 and 72. Mantar et al. demonstrated the validity and reliability of the Turkish version of the ASI-3. The internal consistency coefficient of the scale was 0.93 [29].

Perceived Stress Scale (PSS-14): The PSS-14 is designed to assess an individual's perceived stress. The total score from the scale ranges from 0 to 56 [30]. Its Turkish validity and reliability study was conducted by Eskin et al. [31] and the internal consistency coefficient was 0.84.

Biochemical analysis

Serum samples were analyzed via ELISA (Sunrise Basic Tecan, Tecan Austria GmbH) device at Erciyes University School of Medicine Central Biochemistry Laboratory. Serum oxytocin level was measured via enzyme-linked immune-sorbent assay (ELISA) (Phoenix Human Oxytocin ELISA Kit) kit (Measurement range: 0- 100 ng/ml, Sensitivity: 0.09 ng/ml). The optic density values were transformed into serum concentration values via an absorbance/concentration curve that draws a reverse sigmoidal shape shown on the QC data plate, as per the prospectus of the oxytocin kit.

Statistical analysis

The normality of the distribution of continuous variables was evaluated by the Shapiro-Wilk test. The Mann-Whitney U test was used to compare non-normally distributed numerical data between two groups. Chi-square test and Bonferroni correction were used for categorical variables. Mean (SD), median and interquartile ranges were given as descriptive statistics. Statistical analysis was performed with SPSS for Windows version 24.0 and a *P*-value <0.05 was considered statistically significant.

Results

No significant difference was found between the depression, panic disorder, panic disorder with agoraphobia groups in terms of age. The generalized anxiety group was older, and the social phobia group was younger than the control group. The groups significantly differed in terms of marital status and education level ($P<0.001$, for all), and were similar in terms of gender, daily smoking, and family history of psychiatric illness ($P=0.910$, $P=0.503$, $P=0.900$, respectively) (Table 1).

Serum oxytocin levels of patients with depression were significantly lower, and those of patients with generalized anxiety disorder, social anxiety disorder, and panic disorder with agoraphobia were significantly higher compared to the control group (2.46 (2.8) vs. 2.86 (0.72), $P=0.004$, 11.49 (11.35) vs. 2.86 (0.72), $P=0.001$, 10.67 (11.32) vs. 2.86 (0.72), $P=0.001$, and 6.97 (5.01) vs. 2.86 (0.72), $P=0.001$, respectively). Patients with panic disorders without agoraphobia had insignificantly higher serum oxytocin levels compared to the control group ($P=0.147$).

Table 1: Comparison of demographic data and family history of psychiatric diseases of all study participants

	Depression (n=50)	Panic disorder (n=20)	Gen. Anxiety dis. (n=25)	Social phobia (n=20)	Panic dis. + Agoraphobia (n=20)	Control (n=30)	*P*-value
Age (Mean (SD))	28.4 (5.88)	27.9(6.29)	32.08(6.74)	24.55(4.19)	28.55 (6.03)	28.4(5.15)	0.001[1]
Gender							0.910
Female	25(50%)	12 (60%)	16 (64%)	17(54.8%)	11 (55%)	17 (56.7%)	
Male	25(50%)	8 (40%)	9 (36 %)	14 (45.2%)	9 (45%)	13(43.3%)	
Marital status							0.001*
Married	23 (46%)	7 (35%)	17 (68%)	4 (12.9%)	8 (40%)	5 (16.7%)	
Widow	0 (0%)	0 (0%)	0 (0 %)	1 (3.2%)	0 (0%)	5 (16.7%)	
Divorced	4 (8%)	3 (15%)	0 (0%)	2 (6.5%)	1 (5%)	0 (0%)	
Single	23 (46)	10 (50%)	8 (32%)	24(77.4%)	11 (55%)	20(66.7%)	
Education status							0.001*
Primary school	2 (4%)	0 (0%)	0 (0%)	1 (3.2%)	4 (20%)	0 (0%)	
High school	25 (50%)	12 (60%)	12 (48%)	4 (12.9%)	10 (50%)	6 (20%)	
Higher education	23 (46%)	8 (40%)	13 (52%)	26 (83.9%)	6 (30%)	24 (80%)	
Smoking							0.503
No	27 (54%)	14 (70%)	19 (76%)	24(77.4%)	14 (70%)	20(66.7%)	
1-10 cigarettes	17 (34 %)	5 (25%)	5 (20%)	5 (16.1%)	5 (25%)	4 (13.3%)	
10-20 cigarettes	5 (10%)	1 (5%)	1 (4%)	2 (6.5%)	1 (5%)	6 (20%)	
20> cigarettes	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Family history of psychiatric disease							0.900
Yes	10 (20%)	2 (10%)	3 (12%)	5 (16.1%)	3 (15%)	4 (13.3%)	
No	40 (80%)	18 (90%)	22 (88%)	26(83.9%)	17 (85%)	26(86.7%)	

* Significant at $P<0.05$, Chi-square test, [1] Significant at $P<0.05$, Kruskal-Wallis test

The mean scores of psychological scales applied to patients with depression and the control group are presented in Table 2. The mean panic disorder severity scale scores of panic disorder patients without and with agoraphobia were 11.4 (3.7) and 14.75 (4.72), respectively (Tables 3 and 4). Panic disorder severity and anxiety sensitivity were significantly higher in panic disorder patients with agoraphobia than in those without (P=0.018 and P=0.016, respectively) (Table 5).

Table 2: Comparison of oxytocin levels and scale scores between depressed patients and healthy controls

	Depression (n=50)	Control (n=30)	*P*-value
Oxytocin	2.46 (2.8)	2.86 (0.72)	0.004*
Hamilton anxiety scale	13.6 (6.33)	1.73 (2.21)	0.001*
Hamilton depression scale	24.82 (5.45)	0.73 (1.53)	0.001*
Anxiety sensitivity index	23.44 (14.97)	13.8 (6.26)	0.010*
Perceived stress scale	24.32 (12.25)	14.5 (8.22)	0.001*

* Significant at P<0.05, Mann-Whitney U test

Table 3: Comparison of oxytocin levels and scale scores between panic disorder patients and healthy controls

	Panic disorder (n=20)	Control (n=30)	*P*-value
Oxytocin	2.98 (2.21)	2.86 (0.72)	0.147
Hamilton anxiety scale	25.15 (5.91)	1.73 (2.21)	0.001*
Hamilton depression scale	7.7 (4.54)	0.73 (1.53)	0.001*
Anxiety sensitivity index	29.65 (6.52)	13.8 (6.26)	0.001*
Perceived stress scale	34.35 (5.16)	14.5 (8.22)	0.001*
Panic disorder severity scale	11.4 (3.7)		

* Significant at P<0.05, Mann-Whitney U test

Table 4: Comparison of oxytocin levels and scale scores between panic disorder patients with agoraphobia and healthy controls

	Panic disorder with agoraphobia (n=20)	Control (n=30)	*P*-value
Oxytocin	6.97 (5.01)	2.86 (0.72)	0.001*
Hamilton anxiety scale	28.15 (6.01)	1.73 (2.21)	0.001*
Hamilton depression scale	10.75 (5.13)	0.73 (1.53)	0.001*
Anxiety sensitivity index	35.55 (7.85)	13.8 (6.26)	0.001*
Perceived stress scale	37.6 (6.15)	14.5 (8.22)	0.001*
Panic disorder severity scale	14.75 (4.72)		

* Significant at P<0.05, Mann-Whitney U test

Table 5: Comparison of oxytocin levels and scale scores between panic disorder patients with and without agoraphobia

	Panic disorder with agoraphobia (n=20)	Panic disorder without agoraphobia (n=20)	*P*-value
Oxytocin	6.97 (5.01)	2.98 (2.21)	0.01*
Hamilton anxiety scale	28.15 (6.01)	25.15 (5.91)	0.09
Hamilton depression scale	10.75 (5.13)	7.7 (4.54)	0.05
Anxiety sensitivity index	35.55 (7.85)	29.65 (6.52)	0.016*
Perceived stress scale	37.6 (6.15)	34.35 (5.16)	0.06
Panic disorder severity scale	14.75 (4.72)	11.4 (3.7)	0.018*

* Significant at P<0.05, Mann-Whitney U test

The mean Generalized Anxiety Disorder-7 scale score of patients with GAD was 13.08 (2.29), and the mean total Liebowitz social anxiety scale score of patients with SAD was 102.81 (13.81). The comparison of the scores of these patient groups with the control group is presented in Tables 6 and 7.

Among depressed patients, the serum oxytocin levels, and HAM-A, ADI-3 and PSS scores were significantly correlated (r=0.647, P<0.001; r=0.734, P=0.001; r=0.760, P=0.001, respectively). There was no significant correlation between oxytocin levels and HAM-D scores (P>0.05). In GAD patients, serum oxytocin levels and HAM-D scores were significantly negatively correlated (r=-0.427, P=0.033), while there was no correlation with GAD-7, HAM-A, ADI-3, and PSS scores. In those with panic disorders with and without agoraphobia, serum oxytocin levels and PSS, HAM-D, HAM-A, ADI-3, and PSS scores were not correlated (P>0.05 for all). There was no significant correlation between oxytocin levels and LSPS social anxiety, LSPS avoidance, and LSPS total scores, HAM-D, HAM-A, ADI-3, and PSS scores in patients with social phobia (P>0.05) (Tables 8 and 9).

Table 6: Comparison of oxytocin levels and scale scores between generalized anxiety disorder patients and healthy controls

	Generalized Anxiety Disorder (n=25)	Control (n=30)	*P*-value
Oxytocin	11.49 (11.35)	2.86 (0.72)	0.001*
Hamilton anxiety scale	25.64 (6.62)	1.73 (2.21)	0.001*
Hamilton depression scale	12.16 (3.1)	0.73 (1.53)	0.001*
Generalized anxiety disorder scale	13.08 (2.29)	1.87 (2.01)	0.001*
Anxiety sensitivity index	42.96 (8.76)	13.8 (6.26)	0.001*
Perceived stress scale	35.92 (6.69)	14.5 (8.22)	0.001*

Table 7: Comparison of oxytocin levels and scale scores between patients with social phobia and healthy controls

	Social Phobia (n=20)	Control (n=30)	*P*-value
Oxytocin	10.67 (11.32)	2.86 (0.72)	0.001*
Hamilton anxiety scale	15.84 (4.65)	1.73 (2.21)	0.001*
Hamilton depression scale	7.42 (3.39)	0.73 (1.53)	0.001*
Liebowitz social phobia- anxiety	52.39 (6.81)	34.83 (9.54)	0.001*
Liebowitz social phobia-avoidance	50.42 (7.14)	34.27 (8.35)	0.001*
Liebowitz social phobia-Total	102.81 (13.81)	69.1 (17.55)	0.001*
Anxiety sensitivity index	28.84 (6.7)	13.8 (6.26)	0.001*
Perceived stress scale	35.58 (8.94)	14.5 (8.22)	0.001*

* Significant at P<0.05, Mann-Whitney U test

Table 8: Correlations between oxytocin levels and HAM-A, HAM-D, PSS, ADI-3, PDSS, LSPS, GAD-7 scores in patient groups

		Panic disorder Oxytocin	GAD Oxytocin	Depression Oxytocin	Panic disorder with agoraphobia Oxytocin	Social phobia Oxytocin
HAM-A	r	0.172	0.183	0.647**	0.024	0.252
	P	0.467	0.381	0.000	0.920	0.171
	n	20	25	50	20	31
HAM-D	r	0.285	-0.427*	0.093	0.164	0.064
	P	0.224	0.033	0.520	0.490	0.731
	n	20	25	50	20	31
PDSS	r	-0.362			-0.234	
	P	0.117			0.321	
	n	20			20	
GAD-7	r		-0.069			
	P		0.744			
	n		25			
ADI-3	r	-0.044	-0.019	0.734**	0.253	0.189
	P	0.855	0.930	0.001	0.282	0.307
	n	20	25	50	20	31
PSS	r	0.143	0.264	0.760**	-0.174	0.287
	P	0.549	0.203	0.001	0.463	0.117
	n	20	25	50	20	31

r: Spearman Rank Correlation Coefficient, * Significant at P<0.05, ** Significant at P<0.01

Table 9: Correlations between oxytocin levels and LSPS scores in patients with social phobia

		Social phobia Oxytocin
LSPS-anxiety	r	0.189
	P	0.309
	n	31
LSPS-avoidance	r	0.213
	P	0.250
	n	31
LSPS-total	r	0.197
	P	0.289
	n	31

Discussion

In this study, we first aimed to compare serum oxytocin levels in patients with depression and healthy controls and investigate the relationship between oxytocin levels and depression severity, anxiety severity, perceived stress, and anxiety sensitivity. Second, we aimed to compare serum oxytocin levels in patients with generalized anxiety disorder, social anxiety disorder, panic disorder, and panic disorder with agoraphobia and healthy controls. We found decreased serum oxytocin levels among patients with depression, and increased oxytocin levels in panic disorder patients with agoraphobia, SAD, and GAD. In patients with PD with agoraphobia, oxytocin levels were significantly higher than in PD patients without agoraphobia. Oxytocin regulates stress response by regulating the HPA axis, which plays a key role in depression and anxiety disorders [16].

Oxytocin is secreted via psychosocial stimuli and stimulates social attachment and social recognition [32]. It also suppresses HPA activity induced by stress and reduces anxiety. The nerve fibers containing oxytocin reaching out to the amygdala, hippocampus, and lateral septum, which are centers related to the emotional regulation and stress adaptation, from parvicellular cells reveals the importance of oxytocin in depression pathophysiology [5]. In a study by Frasch et al. [33], in which they compared twelve patients with major depression and twelve control group individuals in terms of nocturnal oxytocin level, nocturnal oxytocin level was significantly lower in patients with major depression.

Lower plasma oxytocin levels were detected in 14 fibromyalgia patients with comorbid depression compared to 25 female fibromyalgia patients without depression and 30 healthy controls; oxytocin levels were negatively correlated with daily depression, pain, and stress scores [34]. In another study, serum oxytocin levels were lower in 40 patients hospitalized due to unipolar and bipolar depression compared to the control group. Antidepressant treatment did not alter oxytocin levels [35]. Likewise, a negative correlation was reported between oxytocin levels and HAM-D scores in patients with depression [36]. Mean saliva oxytocin level was lower in women with chronic depression [37]. Contradictory results are available in the literature. A study conducted by Van Londen et. al. [38] on 52 patients with major depression and 37 healthy controls found no difference between plasma oxytocin levels. Parker et al. [33] stated that nocturnal oxytocin peak was evident in patients with depression following plasma oxytocin measurement from 6 pm to 9 am, and their oxytocin levels were higher than those of the control group. The differences in the results might be associated with the limited sample size, differences in patient selection, heterogeneous patient groups (unipolar depression, bipolar depression, fibromyalgia, etc.), unmatched patients with regards to age, gender, BMI and menopause periods, the inclusion of patients taking psychotropic medications, disregard of the attachment type and childhood trauma, the differences in blood sample collection time, conduction of a cross-sectional evaluation with a single measurement and anxiety symptoms accompanying depression.

In animal depression models, oxytocin shows anxiolytic and stress-reducing effects similar to antidepressants [39]. Reduction in oxytocin might contribute to the HPA axis irregularity because oxytocin suppresses HPA axis activity induced by stress [4]. Serotonergic and noradrenergic pathways have known roles in the development of depression. Oxytocin fibers cause serotonin secretion by stimulating the raphe nuclei directly. Reduction in oxytocin levels might affect serotonin secretion and lead to depression [36]. Norepinephrine, which has a prominent role in depression pathophysiology, is one of the regulators of oxytocin secretion. Norepinephrine fibers facilitate oxytocin secretion from the hypothalamus and hippocampal oxytocin enhances mRNA expression and plasma oxytocin levels [40]. When oxytocin receptors are blocked, the amount of norepinephrine secreted as a response to stress is reduced. There is a close interaction between oxytocin and the dopamine system, which modulates mother-baby attachment, attachment between partners, social cognition, sexual behavior, and reward systems. For example, oxytocin receptors are intense in the mesocorticolimbic pathways which contain PFK, and in the nucleus accumbens. Dopamine also affects the oxytocin receptor expression in the amygdala [41]. Oxytocin activates the MAP kinase pathway and hippocampal neural plasticity by enhancing CREB phosphorylation, induces BDNF expression, and weakens hippocampal shrinkage induced by glucocorticoids or stress. It is thought that activation of this pathway is how oxytocin shows its antidepressant effect [42]. Oxytocin also weakens proinflammatory cytokine response by diminishing the HPA axis response to stress in depression and limits the depressive symptoms [43].

Oxytocin has been widely investigated in anxiety disorders, as well [44, 45]. In our study, serum oxytocin levels in patients with GAD, SAD, and panic disorder with agoraphobia were significantly higher than the control subjects. Interestingly, oxytocin levels in patients with panic disorder with agoraphobia were significantly higher than the panic disorder patients without agoraphobia. A study conducted with 24 patients with generalized SAD found no difference in oxytocin levels when compared with healthy controls and reported that high social anxiety scores were associated with high oxytocin levels [44]. Yet another study stated that oxytocin levels which were similar to the control group initially, were lower when compared with healthy controls after the completion of the trust game task with the partner [45]. Oxytocin reduces anxiety and stress by activating GABAergic interneurons in the amygdala. In a study in which brain activities of the SAD patients were examined via fMRI by showing emotional faces to them, amygdala hyperactivity, found in SAD patients, normalized following a single dose of intranasal oxytocin. However, no changes occurred in the subjective anxiety symptoms reported by the patients [46]. Stressful stimuli increase oxytocin levels directly by stimulating the oxytocin synergic fibers in the amygdala.

There may be several reasons why oxytocin levels are high in patients with anxiety disorders. Oxytocin is an endogenous anti-stress neuropeptide and has a role in stress response [47]. Increased stress exposure and anxiety levels in patients with anxiety disorders may have contributed to the high oxytocin levels. Also, HPA activity induced by stress stimulates oxytocin release and increases oxytocin levels [7]. Similarly, in our study, perceived stress level and anxiety sensitivity were significantly higher in patients with GAD, SAD, PD, and panic disorder with agoraphobia than in healthy controls. Anticipation anxiety, avoidance behaviors, and chronic stress arising out of avoidance might have triggered the oxytocin secretion in patients with anxiety disorders. There is a reciprocal interaction between oxytocin and CRH. CRH stimulates ACTH and oxytocin secretion. It was reported that oxytocin secretion is reduced in anxiety-related behaviors in rats that received CRH-1 receptor antagonists, and CRH receptor stimulation was required for oxytocin secretion [48]. Oxytocin suppresses the HPA axis, reduces saliva cortisol levels, and suppresses amygdala activity. In lactating rats with high oxytocin levels, stress response declined considerably [49]. In the mice with deleted oxytocin genes, corticosterone response to psychogenic stressors increased remarkably [50]. While oxytocin secretion, which increases following acute stress in rats, is normalized after 24 hours, in

chronic stress exposure, oxytocin level cannot be normalized [51]. Exposure to chronic stress of patients with GAD, SAD, and patients with agoraphobia might account for the non-normalization of the oxytocin levels increased with stress. In parallel with the literature, in our study when all groups were analyzed together, oxytocin level was positively correlated with perceived stress.

Another cause of high oxytocin levels in anxiety disorder patients might be the change in oxytocin receptor function following chronic stress exposure. Deletion of the oxytocin gene increases anxiety in rodents [52]. Chronic stressors reduce the mRNA expression of oxytocin receptors; accordingly, oxytocin levels are elevated to compensate [53]. Perhaps increased oxytocin levels in anxiety disorders may be a part of the compensatory physiological mechanism to suppress the hyperactivity of the HPA axis.

Limitations

Our study had some limitations. First, it was a cross-sectional study, so a causality relationship could not be established. Second, the sample size was small. Third, anxiety sensitivity and perceived stress levels were evaluated with self-report scales. Therefore, the results may have been affected by participants' bias. Also, the fact that all patients and controls are from the hospital population may have caused selection bias. Fourth, serum oxytocin levels may not reflect central oxytocin levels. Fifth, childhood trauma, attachment styles, genetic variations in oxytocin receptors that may affect oxytocin levels were not evaluated [54]. Sixth, oxytocin secretion changed situationally and during the daytime, but we measured serum oxytocin levels once and cortisol levels that affect oxytocin were not measured.

Conclusion

Oxytocin is an important marker for depression and anxiety disorders. Prospective studies with large samples, including childhood traumas and attachment styles, are warranted to determine the role of oxytocin in the pathophysiology of depression and anxiety disorders.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):676-678.
DOI: 10.28982/josam.936595

Research article

Journal of Surgery and Medicine
e-ISSN=2602-2079

Investigation of ultrasonic chronic total occlusion system on a rabbit model

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Abstract

Background/Aim: Advanced treatment options are needed in chronic total occlusion (CTO), which is a special subgroup of peripheral artery disease. Endothelial damage remains a problem in the endovascular treatment of peripheral artery CTO. In our study, this subgroup was examined with an ultrasonic total occlusion system for vascular endothelial damage on an animal model.
Methods: We used twenty-four rabbits divided equally into three groups, created chronic total occlusion in the common iliac artery by applying a bioabsorbable polymer sponge, and waited four weeks for CTO formation. After four weeks, the samples obtained from the groups were examined histologically.
Results: Significantly less endothelial damage was detected in the ultrasonic total occlusion system group compared to the directional atherectomy group ($P<0.05$).
Conclusion: Ultrasonic atherectomy minimizes thrombus load and causes minimal endothelial damage. These findings show that the ultrasonic atherectomy method can be successfully used in CTO treatment.

Keywords: Peripheral artery, Ultrasonic chronic total occlusion system, Animal model, Endothelial injury

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Ethics Committee Approval
The ethics approval was obtained from Sivas Cumhuriyet University Animal Experiments Local Ethics Committee with the decision numbered 65202830-050.04.04-331.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Financial Disclosure
This study was supported by TÜBİTAK 1507 program with project number 7190674.

Published
2021 July 12

How to cite: Kasimzade F, Ada F, Karataş Ö. Investigation of ultrasonic chronic total occlusion system on a rabbit model. J Surg Med. 2021;5(7):676-678.

Introduction

Treatment of chronic total occlusion in patients with infrainguinal peripheral artery disease is particularly challenging for vascular surgery specialists. Surgical revascularization is the gold standard for CTO therapy; however, endovascular treatments have become the first choice, primarily due to the patients' advanced age and increased comorbidities. In addition, many patients prefer endovascular treatment due to its low cost, shorter hospital stay, and low procedural morbidity [1].

Treatment procedures in segmental subtotal occlusions are relatively more precise and promising, while in CTOs, they are more ambiguous. CTOs reduce both the quality of life and daily activities of the patients and cause economic and social dependence with increased amputation rates [2].

The patients with CTO are negatively affected by many variables, from the anesthesia management to the factors included in surgical procedures. For this reason, minimally invasive methods, which have become more promising, are being used more frequently in this patient group. In our study, we compared the ultrasonic induced system with directional atherectomy in terms of endothelial damage for CTO treatment on an animal model.

Materials and methods

The ethics committee approval for our study was obtained with the decision numbered 65202830-050.04.04-331 from Sivas Cumhuriyet University Animal Experiments Local Ethics Committee. The study was conducted on three groups of eight rabbits each (New Zealand white rabbit, 6-8 months old, males weighing 3.2-3.5kg, females weighing 2.75-3kg). The rabbits were housed in equally sized cages and at a constant temperature of twenty degrees, in a laboratory environment capable of receiving twelve hours of night and twelve hours of daylight. Standard rabbit food was used in all rabbits and their water was changed every other day. Ninety milligrams per kilogram (mg/kg) subcutaneous ketamine and 3 mg/kg intraperitoneal xylazine were administered to the animals for anesthesia before surgical procedures.

Group 1 (Control group): The animals in this group did not undergo any procedures. After four weeks, samples were obtained from the iliac artery after sacrification.

Group 2: CTO was created in the iliac artery and a directional atherectomy was performed. After four weeks, samples were obtained from the iliac artery after sacrification.

Group 3: CTO was created in the iliac artery and atherectomy was performed with ultrasonic chronic total occlusion system. After four weeks, samples were obtained from the iliac artery after sacrification.

The CTO model was created in Groups 2 and 3, as previously described by Suzuki et al. [3, 4]: A Bioabsorbable polymer sponge was surgically placed in the right common iliac artery to create total occlusion. At the end of four weeks, the right common iliac arteries of the rabbits were explored distal to the lesion under sterile conditions and general anesthesia. The ultrasonic atherectomy system (Metrical Medical Devices, Turkey) and directional atherectomy system (HawkOne Directional Atherectomy System, Medtronic, USA) were used in the relevant groups. Surgical procedures were performed under general anesthesia and following ethical rules. The iliac arteries of the animals were explored and an atherectomy was performed so that both the atherectomy catheters were visible and manually felt. The samples obtained after sacrification of the animals were evaluated histopathologically and the results were compared among the three groups.

Histopathological method

After the animals were sacrificed, common iliac artery tissues were fixed in 10% neutral formalin solution. Tissues were embedded in paraffin blocks after a routine alcohol-xylol procedure. The 5 µ-thick sections placed on poly L-lysine coated slides were stained with hematoxylin-eosin. The size of the thrombotic mass was evaluated under a light microscope, and the damage to the endothelium was assessed as shown in Table 1.

Table 1: Histological scoring system

Histopathological Score	
Thrombus in the entire lumen (3)	Damage to the entire endothelium (3)
Thrombus in half of the lumen (2)	Damage to half of the endothelium (2)
Thrombus in a quarter of the lumen (1)	Damage to the quarter of the endothelium (1)
No thrombus (0)	No damage (0)

Statistical analysis

The data were analyzed with the SPSS 20.00 program (StataCorp LP, College Station, TX, USA). The significance of the difference between the groups was assessed by the Kruskal Wallis test. The group that created the difference was further examined with the Mann-Whitney U test. *P*-values <0.05 were considered statistically significant.

Results

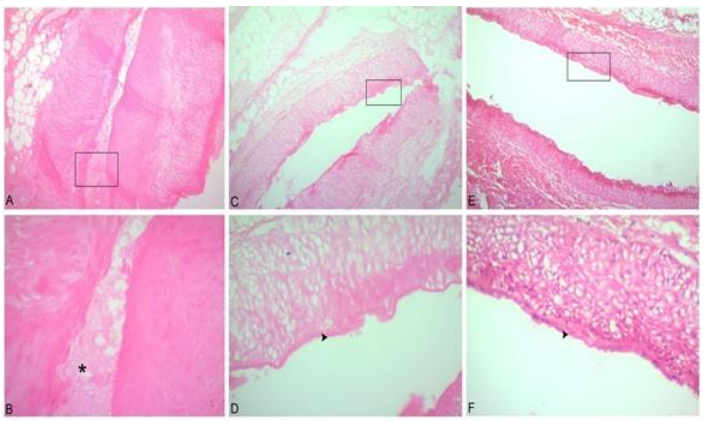
Common iliac artery samples significantly differed between the groups in terms of thrombosis and endothelial damage (P=0.03) (Table 2). The difference between the groups was analyzed by a post-hoc test. There was a mild thrombotic mass in the lumen of the vessels in the ultrasonic atherectomy group (P=0.03). In the directional atherectomy group, there were severe degenerative changes in the vascular endothelium. There was no thrombotic mass in the control group. Endothelial damage was severe in the directional atherectomy group compared to the other groups (Figure 1).

Table 2: Histopathological evaluation results

Groups	Thrombosis	Endothelial Damage
Group 1 (Control group), mean (SD)	0.16(0.40)[b]	1.33(0.51)[b]
Group 2 (directional atherectomy group) mean (SD)	1.16(0.40)[a]	2.16(0.40)[a]
Group 3 (Ultrasonic atherectomy group) mean (SD)	0.33(0.51)[c]	1.96(0.40)[c]
Statistical Significance	(P=0.03)	(P=0.03)

a: Significant difference between Groups 1 and 2, b: Significant difference between Groups 1 and 3, c: Significant difference between Groups 2 and 3, p<0.05 for all.

Figure 1: A and B: Mild thrombotic mass (□, *). (x10, x40. Common iliac artery. H-E) (Ultrasonic atherectomy group), C and D: Severe degenerated vascular endothelium (□, arrowhead) (directional atherectomy group), E and F: Slightly degenerated vascular endothelium (□, arrowhead) (Control group).



Discussion

The main purpose of treatment in CTOs is to provide blood supply to the distal part of the occluded segment. Therefore, the gold standard treatment method today is surgical revascularization. However, the current patient population is usually made up of the elderly and the added disease burden is high [5].

Treatment of CTO in patients with infrainguinal peripheral artery disease remains particularly challenging for vascular surgery specialists. Although surgical revascularization continues as the gold standard in CTO treatment, endovascular treatment methods have often become a priority due to the advanced age of the patients and increased comorbidities [6]. In addition, low cost, shorter hospital stays, and less procedural morbidity puts endovascular treatment in the foreground [1].

Balloon angioplasty alone has been shown to have a 5-year patency rate in the treatment of coronary artery CTO [7]. In the endovascular treatment of peripheral artery CTO, the chance of passing the lesion can often be low. Most of the time, this rate is between 40-60%, but various studies report over 90% success [8, 9].

While the treatment procedures in segmental subtotal occlusions are relatively more precise and promising, they are more ambiguous in CTOs. CTOs hinder the quality of life and daily activities of the patients, also causing economic and social dependence with increased amputation rates [2].

The elderly patient group with increased comorbidities is adversely affected by many factors, both related to anesthesia and surgical procedures. For this reason, minimally invasive methods are currently used more frequently in this patient group with satisfactory results. The atherectomy methods involved in the treatment of CTO due to peripheral artery disease include directional atherectomy, radiofrequency atherectomy, and intravascular ultrasound-guided atherectomy [10-12]. Each of these methods is applicable with different techniques [13-17]. As it is possible to pass through the atherosclerotic plaque that causes CTO directly, some devices allow recanalization with reentry by subintimal advancement [6, 13-19]. In our study, we observed that ultrasonic atherectomy was superior to directional atherectomy, resulting in less endothelial damage and thrombotic burden. Minimum endothelial damage helps prevent a recurrence, and the smallest thrombus burden is an indicator of positive response in the acute phase. The difficulty of long-term follow-up in animal experiments and the inability to create one-to-one human models necessitate long-term clinical studies. No studies have compared various atherectomy methods in terms of vascular endothelial damage in the literature. The absence of endothelial damage is essential for the effectiveness of treatment, long-term preservation of patency, and prevention of recurrence. With this study, important findings were obtained in comparing the endothelial damage between directional atherectomy and ultrasonic CTO systems. The minimum endothelial damage and thrombus load in ultrasonic atherectomy devices stand out as an advantage.

Limitations

There are several limitations to our study. First, only two of the atherectomy methods were compared. Second, conducting an animal experiment limited the chance of a long-term follow-up.

Conclusion

We observed that ultrasonic atherectomy minimizes thrombus load and endothelial damage. These findings show that the ultrasonic atherectomy method can be successfully used in CTO treatment.

Acknowledgments

We would like to thank Prof. Dr. Mustafa Özkaraca for his support during the examination of the samples.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):679-682.
DOI: 10.28982/josam.953641

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of changes in corneal endothelial morphology during the progression of pterygium by specular microscopy

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Ethics Committee Approval
Ethics committee approval was obtained from the Ethics Committee of our hospital (2017-KAEK-189_2021.03.10_02).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Published
2021 July 19

Abstract

Background/Aim: Corneal endothelial morphology may be corrupted due to pterygium progression. To the best of our knowledge, no study in the literature investigates this. We aimed to evaluate corneal endothelial morphology using specular microscopy (SM) in patients with pterygium.
Methods: In this case-control study**,** we included thirty-three Type 1 pterygium, thirty-one Type 2 pterygium, thirty Type 3 pterygium patients, and thirty healthy controls. The corneal endothelia of all patients were evaluated by SM, and cell density (CD), hexagonal cell ratio (HEX), corneal thickness (CT), and coefficient of variation (CV) were noted.
Results: While there was no significant difference in corneal thickness (P=0.480) and coefficient of variation (P=0.068) between the groups in SM images, both corneal endothelial cell count (P=0.003) and hexagonal cell ratio (P=0.002) were significantly lower in Type 2 and Type 3 pterygium patients compared to Type 1 and control groups.
Discussion: Corneal endothelial morphology was severely affected in type 2 and 3 pterygium. We think that type 2 and type 3 pterygium patients should be operated on as soon as they are diagnosed to prevent deterioration in corneal endothelial parameters.

Keywords: Pterygium, Specular microscope, Endothelial cell density, Hexagonality, Coefficient of variation

How to cite: Songur MS, Erkan E, Bayhan SA, Bayhan HA. Evaluation of changes in corneal endothelial morphology during the progression of pterygium by specular microscopy. J Surg Med. 2021;5(7):679-682.

Introduction

Pterygium is a common eye disease characterized by uncontrolled triangular-shaped growth of the conjunctival tissue over the cornea [1]. It can seriously affect vision by inducing astigmatism and in advanced cases, by obstructing the visual axis. Although the etiology of pterygium is not fully known, many factors are suspected in its pathogenesis. While some patients do not have any complaints, many patients may experience symptoms such as burning, stinging, irritation, watering, and foreign body sensation. In addition, it may cause deterioration of the refractive surface of the tear film, astigmatism due to shrinkage on the cornea, and decreased vision due to the closure of the visual axis [2]. Blurred vision or decreased visual acuity, cosmetic problems, chronic inflammation, and irritative symptoms are indications for pterygium surgery. Although degenerated tissue is surgically removed, recurrence may occur [3].

The corneal endothelium predominantly consists of non-regenerative single-layer hexagonal cells. Corneal endothelial cells keep the stroma dry by actively removing water, which is a vital function in maintaining normal corneal transparency. Corneal endothelial cells have very limited mitotic capacity. Therefore, when cell loss occurs, adjacent cells expand and shift to maintain endothelial continuity, which may increase polymegathism and pleomorphism [4]. Cell loss and endothelial status can be determined more precisely based on the evaluation of polymegathism and pleomorphism.

Specular microscopy (SM) is a non-invasive approach for qualitative, quantitative, and morphometric evaluation of corneal endothelial functions [5, 6]. It can assess the corneal thickness, cell density (CD) (the number of cells per mm^2 of the corneal endothelium), pleomorphism (cell shape variation in the endothelium), and the amount of polymegathism, which shows the variation in the individual cell area. While hexagonal cell ratio is used to evaluate pleomorphism, coefficient of variation, determined by the ratio of standard deviation to the mean cell area, is used to define polymegathism.

Pterygium is divided into 3 subgroups according to its clinical features. Type 1 pterygium involves less than 2 mm of the cornea; Type 2 pterygium advances 2-4 mm on the cornea; and type 3 pterygium, a.k.a., advanced stage pterygium, advances more than 4 mm on the cornea and involves the optic axis [7].

In this study, we aimed to evaluate the changes in corneal endothelial morphology during the progression of the pterygium with SM imaging.

Materials and methods

This case-control prospective study was conducted at our hospital's ophthalmology outpatient clinic between January 2021 and May 2021. Informed consent was obtained from all participants and ethics committee approval was granted by the Ethics Committee of our hospital (2017-KAEK-189_2021.03.10_02). The Helsinki Declaration Principles were adhered to throughout the study.

A power analysis was conducted using G*Power 3.1.9.2 (Faul, Erdfelder, Lang, & Buchner, 2014). The differences between the four groups were assessed using a one-way ANOVA test, with a low-medium effect size (d=0.5), and an alpha of 0.05. Based on these, a total of 124 participants were required to achieve a power of 0.99. Thirty-three eyes of 33 patients with Type 1 pterygium, 31 eyes of 31 patients with Type 2 pterygium, and 30 eyes of 30 patients with Type 3 pterygium were evaluated. Thirty right eyes of 30 age-and gender-matched healthy individuals were included as controls. Demographic characteristics of all participants, including age, gender, duration of illness, and used medications were recorded.

Patients with glaucoma, uveitis, retinal disease, diabetic or hypertensive retinopathy, epiretinal membrane, and retinal detachment, corneal disease, pseudoexfoliation syndrome, high myopia and hypermetropia (>6D), corneal opacity, ocular trauma and surgical history, individuals who could not cooperate during SM imaging, those using eye drops and contact lenses, and those with dementia, Parkinson's disease, epilepsy, vascular disease, and psychiatric diseases were excluded from the study.

A complete and detailed ophthalmologic evaluation including best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement (IOP) with Goldmann applanation tonometry, pachymetry, three-mirror contact lens gonioscopy, and fundoscopy were performed in all participants. The sizes of the pterygiums were noted. SM (Specular Microscope CEM-530, NIDEK) images were obtained in all participants and cell density (CD), hexagonal cell ratio (HEX), corneal thickness (CT), and coefficient of variation (CV) of the corneal endothelium were measured.

Statistical analysis

Statistical analysis was performed using the SPSS® 22.0 (Statistical Package for Social Sciences, IBM Inc., Chicago, IL, USA) package program. Descriptive statistics were presented. The Shapiro-Wilk test was used to evaluate the normality of distribution. The Chi-Square test was used to compare categorical variables. ANOVA and Post-hoc Tukey tests were used to compare normally distributed data, while The Kruskal-Wallis test was utilized to compare non-normally distributed data among the three groups. Mann Whitney-U Test was used for paired comparisons of non-normally distributed data. A *P*-value of less than 0.05 was considered statistically significant.

Results

Ninety-four eyes of 94 patients diagnosed with pterygium and 30 eyes of 30 healthy controls were included in the study. The patients were divided into three groups according to the size of their pterygium. The mean ages of the patients with Type 1, Type 2, Type 3 pterygium, and that of the control group were 42.93 (13.02) years, 43.80 (11.67) years, 45.20 (11.87) years, and 45.40 (14.77) years, respectively. The groups were similar in terms of age (P=0.855), gender (P=0.979), and intraocular pressure (P=0.732). The sociodemographic data of the patients are summarized in Table 1.

No significant difference was found between the groups in terms of corneal thickness (P=0.480) and coefficient of variation (P=0.068) in SM images. The corneal endothelial cell densities and hexagonal cells ratios of Type 1 pterygium patients and the control group were similar, while those of Type 2 and

Type 3 patients significantly differed from those of the control group and patients with Type 1 pterygium. SM findings are summarized in Table 2.

Table 1: Sociodemographic data of the groups

Parameter	Control Group (n=30)	Type 1 pterygium (n=33)	Type 2 pterygium (n=31)	Type 3 pterygium (n=30)	*P*-value
Sex (F/M)	10/20	12/21	12/19	11/19	0.979
Age	45.40(14.77)	42.93(13.02)	43.80(11.67)	45.20(11.87)	0.855
IOP (mmHg)	13.56(2.86)	14.15(3.07)	14.16(3.12)	13.50(3.17)	0.732
Pterygium length		1.53(0.24)	2.95(0.51)	4.63(0.46)	<0.001

IOP: Intraocular pressure. Continuous data are presented as mean (standard deviation).

Table 2: Distribution of specular microscopy findings by groups

	Control group (n=30)	Type 1 pterygium (n=33)	Type 2 pterygium (n=31)	Type 3 pterygium (n=30)	*P*-value
CT	539.70(30.42)	536.00(33.27)	530.93(30.83)	527.46(35.82)	0.480
CD	2460.06(275.71)	2447.03(235.60)[c]	2251.74(259.13)[a,b]	2245.90(384.57)[a,b]	0.003
CV	28.70(3.14)	29.18(2.73)	30.41(3.33)	30.63(4.01)	0.068
Hex	64.63(3.56)	64.36(3.65)[c]	61.96(2.08)[a,b]	61.76(3.98)[a,b]	0.002

CT: corneal thickness (μ), CD: the cell density in the corneal endothelium (cell/mm^2), CV: coefficient of variation (standard deviation of cell area/mean cell area μm^2), Hex: percentage of hexagonal cells (%). Continuous data are presented as mean (standard deviation).
Results of post hoc analysis: a: different from the control group, b: different from type 1 pterygium patients, c: different from type 2 pterygium patients

Discussion

In their SM study, Sousa et al. compared eyes with pterygium with the contralateral healthy eyes and found a negative correlation between pterygium size and endothelial cell density, with no difference in the other parameters [8]. Similarly, in the study by Hsu et al. [9] in which 90 patients with unilateral pterygium were evaluated and eyes with pterygium were compared with other normal eyes, there was a significant decrease in the number of corneal endothelial cells in eyes with pterygium. In our study, we divided patients into three groups based on the size of their pterygium and found no significant difference in any of the parameters between patients with Type 1 pterygium and the healthy controls. However, both the corneal cell density and the hexagonal cell ratio of pterygium patients with Types 2 and 3 differed from those of Type 1 patients and healthy controls. There was no significant difference between the groups in terms of corneal thickness, which was similar to findings reported by Hansen et al. [10], Gros-Otero et al. [11], and Kılıç et al [12]. In addition, no significant difference was found between any of the groups in terms of the coefficient of variation.

Although the pathophysiology of pterygium is still unknown, the involvement of genetic factors, proinflammatory cytokines, and ultraviolet (UV) light is suspected [13]. The incidence of pterygium is increased in individuals and populations exposed to excessive solar radiation. The ultraviolet light (UV) that causes this radiation affects the DNA, RNA, and extracellular matrix by initiating a chain reaction both inside and outside the cell. Kennedy et al. [14] reported that UV light induces mutations in the TP53 tumor suppressor gene in limbal basal cells in the cornea and causes the secretion of various cytokines, angiogenic and fibrogenic growth factors such as IL-1, IL-6, IL-8, and tumor necrosis factor-α. Girolamo et al. [15] reported that UVB stimulates the induction of matrix metalloproteinase-1 (MMP-1) in human ocular surface epithelial cells. Moreover, it has been reported that the expression of matrix metalloproteinases disrupts the basal membrane, causing an increase in the anterior margins of the pterygium [16].

Nolan et al. [17] found that UVB causes overexpression of heparin-binding epidermal growth factor (HB-EGF), which is a powerful mitogen and is considered a major driving force in the development of pterygium. Tsai et al. [18] investigated oxidative DNA damage and noted that UV radiation can damage conjunctival tissue directly through phototoxicity or indirectly through the generation of radical oxygen species (ROS). In particular, they found hydroxydeoxyguanosine (8-OHdG), which shows DNA damage, in pterygium tissue. Kau et al. [19] reported that there is a connection between oxidative stress caused by UV, conjunctival damage, and pterygium development.

Marcovici et al. found that vascular endothelial growth factor (VEGF) and von-Willebrand factor (vWF) were overexpressed in pterygium tissue and suggested that this is evidence of the vascular proliferative process that plays a role in the development of pterygium [20]. In another study on angiogenesis, Özdemir et al. reported lower nitric oxide (NO) levels in pterygium tissue compared to conjunctival tissue. They noted that this occurs due to the rich vascular structure in the pterygium tissue, which is the opposite of the NO increase that occurs under ischemic conditions [21].

Mootha et al. [22] reported that in long-term nasal pterygium, the underlying Bowman layer of the pterygium can dissolve due to fibroblast infiltration of the anterior stroma, and subsequently, Descemet's membrane and endothelial damage may occur in the cornea.

Based on these, we observe three main factors in the formation of pterygium: Mitogenicity, formation of a new vascular network, and remodeling of the extracellular matrix. Together, they stimulate aggressive growth on top of the cornea, creating new vascular and fibrotic tissue. Currently, surgery is the only option in pterygium treatment.

There were several limitations in our study, such as the low number of patients and difficulties in performing specular microscopy, especially in patients with type 3 pterygium. However, the fact that there is no previous study in the literature with a similar design increases the importance of this study. Further, extensive studies are warranted.

Conclusion

There was a significant decrease in corneal endothelial cell density and hexagonal cell ratio in Type 2 and 3 pterygium patients. This poses a serious risk for postoperative edema and decreased vision, especially among patients that require cataract surgery. We believe that while patients with Type 1 pterygium only require close follow-up, patients with Types 2 and 3 pterygium should be operated on as soon as they are diagnosed to prevent further damage to the corneal endothelium.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):683-686.
DOI: 10.28982/josam.955574

Journal of Surgery and Medicine
e-ISSN=2602-2079

Myocardial repolarization is affected in patients with diabetic retinopathy

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Ethics Committee Approval
Bolu Abant Izzet Baysal University Clinical Research Ethics Committee Approval, 2020/172, 07.07.2020
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Published
2021 July 26

Abstract

Background/Aim: Diabetes Mellitus (DM), considered the equivalent of coronary artery disease, is one cause of ventricular repolarization (VR) dispersion. Retinopathy is one of the vascular consequences of diabetes. The association between myocardial repolarization dispersion and diabetic retinopathy is not fully elucidated. We aimed to evaluate ventricular repolarization using Tp-e interval and corrected (c) Tp-e/QT ratio in DM patients with and without retinopathy.
Methods: A total of 124 diabetic subjects were included in this retrospective cohort study**.** All medical data were obtained from the electronic database of our university hospital. The subjects were divided into the no diabetic retinopathy (NDR) group (n=45), and the diabetic retinopathy (DR) group (n=79), which were compared in terms of demographic features, clinic and laboratory findings, and electrocardiographic findings such as QT, QTc, Tp-e, Tp-e/QT, Tp-e/QTc.
Results: The groups were similar in terms of demographic features (P>0.05). Both Tp-e interval and Tp-e/QTc were significantly prolonged in the DR group compared to the NDR group. There were significant correlations between Tp-e, Tp-e/QTc, DM duration, and age. In multivariate logistic regression analysis, Tp-e (OR=6.01, %95 CI=4.17-7.52, P=0.012), Tp-e/QTc (OR=1.215, 95% CI=0.874-1.612, P=0.029), and DM duration (OR=1.422, 95% CI= 1.146–1.712, P<0.001) were independent predictors of DR.
Conclusion: We showed that DM patients with retinopathy may also have an increased risk for sudden cardiac death due to ventricular arrhythmogenesis.

Keywords: Ventricular repolarization, Diabetic retinopathy, Sudden cardiac death, Tp-e interval, Tp-e/QTc interval

How to cite: Cosgun M, Sincer I, Erdogdu T, Disikirik T, Gunes Y, Mansiroglu AK, Erdal E, Topuz M. Myocardial repolarization is affected in patients with diabetic retinopathy. J Surg Med. 2021;5(7):683-686.

Introduction

Type 2 diabetes mellitus (DM) is a risk factor for both coronary artery disease (CAD) and atherosclerosis [1]. DM leads to the development of both micro- and macrovascular diseases [2]. On the other hand, it is well known that both micro- and macrovascular complications are independent risk factors for sudden cardiac death (SCD) among DM patients [3].

Retinopathy, one of the vascular complications of DM, is among the earliest findings of microvascular involvement and can lead to blindness [4]. The perivascular structural changes or new aberrant vessels are classified as non-proliferative or proliferative [5].

Ventricular repolarization (VR) anomalies in electrocardiography (ECG) are well-known markers for increased mortality risk [6-8]. Various ECG markers were proposed to predict people at elevated risk for ventricular arrhythmias [9, 10]. Even in patients with normal QTc values, the Tp-e interval, a new ECG marker, shows VR [11]. The transmural dispersion of repolarization in the left ventricle is indicated by the interval from the T wave peak to the end of the T wave (Tp-e) in the ECG. The ratio of Tp-e/QT has recently been used for VR distribution as a relatively new ECG marker [12]. Malignant ventricular arrhythmias are correlated with both the Tp-e value and the ratio of Tp-e/QT [13].

This study aimed to investigate whether type 2 DM patients with retinopathy have increased ventricular repolarization abnormalities, as calculated with Tp-e value and the ratio of Tp-e/QT.

Materials and methods

The study began after Bolu Abant Izzet Baysal University Clinical Research Ethics Committee (decision number: 2020/172) granted approval and was conducted according to the principles of the Helsinki Declaration. Participation was voluntary. All patients were informed about the study and their verbal and written consents were obtained.

This retrospective cohort study was performed at the Department of Cardiology in a university hospital in Turkey between January 2019 and May 2020. One hundred and twenty-four diabetic patients who visited the cardiology department between these dates and did not meet the exclusion criteria were included and divided into two groups: The diabetic group without retinopathy (NDR) (n=45) and patients with diabetic retinopathy (DR) (n=79).

All medical data of the subjects were obtained from the electronic database of the hospital. Patient's demographics and clinical characteristics including gender, age, smoking history, hypertension (HT), ischemic heart disease, and familial history, and laboratory parameters including serum fasting glucose, hemoglobin A1c, creatinine, hemoglobin, and total cholesterol and high- and low-density lipoprotein cholesterol were recorded. Additionally, diastolic, and systolic blood pressure (DBP and SBP), electrocardiographic and echocardiographic findings, the current smoking status of the patients were noted. Hypertension was diagnosed in at least two different measurements when SBP ≥140mmHg or DBP ≥90mmHg, or the patient was using any antihypertensive drugs. The body mass index (BMI) was calculated by weight in kilograms divided by the square of the height in meters.

Patients with a history of ischemic and valvular heart disease, cardiomyopathy, atrial fibrillation, implantation of the previous pacemaker, those using an antiarrhythmic drug affecting the ventricular repolarization duration (i.e., antiarrhythmic drugs, beta- and alpha-blocker, non-dihydropyridine calcium antagonist, digoxin, antifungal agents and antibacterial agents, antipsychotic agents, or antihistamines), patients with cancer, or other major illnesses, abnormal electrolyte values, abnormal thyroid function tests, low-amplitude T waves, U waves, and bundle branch block on their ECGs were excluded.

DM and retinopathy definition

Patients with a history of DM diagnosis and/or a prescription (insulin or anti-diabetic drugs) and/or fasting blood glucose ≥126 mg/dl and/or glycated hemoglobin (HbA1c) ≥6.5% were considered to have DM. International Clinical Diabetic Retinopathy Disease Severity Scale was used to diagnose the DR [14].

Electrocardiographic evaluation

After a 10-minute rest, twelve-lead ECGs were obtained in supine position with 10 mm/mV amplitude and 25 mm/s rate using a commercially available system (Nihon Kohen Cardiofax ECG-1950 VET). The ECG duration was 10 seconds, thus, there were 4 to 6 beats per lead, depending on the heart rate. Two cardiologists, blinded to the information of the patients, manually assessed ECGs using a magnifying glass (TorQ 150 mm Digital Caliper LCD). QT intervals were measured from the onset of the QRS complex until the end of the T wave, defined as its return to the baseline TP. The QT interval was calculated at the curve's nadir between the T and U waves if U waves were present.

The R-R and QT intervals were noted. QT dispersion (QTd) was calculated as the difference in precordial leads between the maximum and minimum QT intervals. The Bazett formula was used to measure the corrected QT (QTc) [15]. The Tp-e interval was measured from the T wave peak to the end of the T wave. JT intervals were calculated from the end of the QRS complex (J point) to the end of the T wave (JTend interval). Corrected JT (JTc) interval was calculated using the Bazett formula. Also calculated were the Tp-e/QT, Tp-e/QTc, Tp-e/JT, and Tp-e/JTc ratios. No patient had a measurable lead of less than nine. The intra- and interobserver differences for the measurements were less than 5%.

Statistical analysis

SPSS 18.0 Windows Statistical Package Program (SPSS Inc, Chicago, Illinois, USA) was used to analyze the data. Quantitative variables were expressed as mean (standard deviation (SD)) and qualitative variables, as numbers and percentages. Normally distributed parameters were analyzed with a one-way ANOVA test, and post-hoc tests with Tukey's HSD were conducted. The Kruskal-Wallis test was used to compare variables in various research subgroups for parameters with a heterogeneous distribution or in the case of variance inequality. In-group variations were analyzed with the Bonferroni-corrected Mann-Whitney U-test. Numeric and nominal data were assessed with Pearson's correlation and Spearman's correlation tests, respectively. Logistic regression

tests were used to evaluate the independent predictors of DR. A *P*-value <0.05 was considered significant.

Results

The demographic, clinical features, and laboratory results of the groups were similar (Table 1).

The mean Tp-e and median Tp-e/QT_{mean} values were significantly higher in the DR group compared to the NDR group (*P*=0.04 and *P*=0.002, respectively). In other electrocardiographic parameters, there were no major variations between the groups (Table 2).

Table 1: Baseline characteristics, clinic, and laboratory findings of the study groups

	Non-DR (n=45)	DR (n=79)	*P*-value
Age, years	64 (10)	62 (0.9)	0.39
Body mass index, kg/m^2	30 (5)	31 (5)	0.85
Male/female, n	23/22	41/38	0.16
Hypertension, %	28(62%)	57(62%)	0.09
Smoking, %	1(2%)	10(12%)	0.14
Family history, %	12(27%)	35(45%)	0.15
CAD history, %	19(42%)	31(30%)	0.22
DM duration, months	46 (12)	44 (13)	0.75
Fasting glucose, mg/dl	121.1 (32.4)	126.4 (33.5)	0.29
Hemoglobin A1c, %	7.1 (1.1)	7.3 (1.2)	0.52
LDL-cholesterol, mg/dl	107 (35)	115 (28)	0.21
HDL-cholesterol, mg/dl	49 (12)	41(10)	0.06
Triglyceride, mg/dl	135 (54)	155 (58)	0.019
Hemoglobin, mg/dl	13.1 (1.4)	13.5 (1.3)	0.39
Systolic BP, mmHg	136 (23)	132 (25)	0.56
Diastolic BP, mmHg	80 (13)	78 (11)	0.25
Creatinine, mg/dl	0.82(0.61-3.35)	0.87(0.65-5.49)	0.18
LA diameter, mm	36(22-48)	40(26-49)	0.03
LVEF, %	60(40-65)	57(45-65)	0.09

DR: Diabetic retinopathy, CAD: Coronary artery disease, DM: Diabetes Mellitus, SD: Standard deviation, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, BP: Blood Pressure, LA: Left atrium, LVEF: Left ventricular ejection fraction

Table 2: Electrocardiographic findings of the study groups

	Non-DR (n=45)	DR (n=79)	*P*-value
Tp-e, msn	71.62 (7.01)	82.15 (8.93)	<0.001
QT, msn	346.2 (33.0)	348.4 (27.6)	0.53
QTc, msn	393.7 (21.3)	388.7 (22.5)	0.29
JT, msn	253.9 (35.6)	255.9 (24.5)	0.49
JTc, msn	287.8 (25.9)	289.7 (27.7)	0.65
Tp-e/QT ratio	0.208 (0.024)	0.236 (0.025)	<0.001
TPe/QTc ratio	0.18(0.15-0.23)	0.22(0.15-0.26)	<0.001
TPe/JT ratio	0.29(0.20-43)	0.31(0.21-0.44)	0.19
Tp-e/JTc ratio	0.253 (0.034)	0.268 (0.042)	0.012
QRS, msn	90(64-126)	92(72-140)	0.70
QT dispersion	12(4-31)	13(5-36)	0.31

Correlation analysis showed that both Tp-e and Tp-e/QTc were significantly associated with DM duration and age (r=0.325/*P*<0.01, r=0.285/*P*<0.01 for DM duration and r=0.251/*P*=0.02, r=0.274/*P*=0.012 for age) (Table 3).

Variables, found to relate to DR in multivariate logistic regression analysis, were also assessed in univariate analysis. Tp-e (OR=6.01, 95% CI=4.17-7.52, *P*=0.012) and Tp-e/QTc (OR=1.215, 95% CI=0.874-1.612, *P*=0.029), together with DM duration (OR=1.422, 95% CI=1.146–1.712, *P*<0.001), were independent predictors of DR (Table 4).

Table 3: The correlation analysis results of Tp-e value and Tp-e/QTc ratio with the other study parameters in all patients

Parameters	Tp-e	Tp-e/QTc ratio
Age	(r=0.251/ *P*=0.02)	(r=0.274/ *P*=0.012)
Body mass index	(r=0.144/ *P*=0.31)	(r=0.187/ *P*=0.34)
DM duration	(r=0.325/ *P*<0.01)	(r=0.285/ *P*<0.01)
Glucose	(r=0.05/ *P*=0.74)	(r=0.08/ *P*=0.54)
LDL-C	(r=0.101/ *P*=0.42)	(r=0.133/ *P*=0.21)
LVEF	(r=-0.133/ *P*=0.11)	(r=-0.151/ *P*=0.20)
LA diameter	(r=0.114/ *P*=0.21)	(r=0.07/ *P*=0.82)

DM: Diabetes mellitus, LDL-C: Low-density lipoprotein cholesterol, LVEF: Left ventricular ejection fraction, LA: Left atrium

Table 4: Univariate and Multivariate logistic regression analysis showing parameters associated with DR

	Unadjusted OR/ 95%CI	*P*-value	Adjusted OR/ 95%CI	*P*-value
Age	0.92(0.26-1.84)	0.36		
Glucose	4.21(2.14-5.45)	0.23	2.021 /1.486–2.043	0.72
DM duration	3.12(2.97-3.29)	<0.001	1.422/1.146–1.712	<0.001
Tp-e/QTc	0.95(0.901-1.08)	0.012	1.215/0.874-1.612	0.029
Tp-e	8.31(6.77-10.32)	<0.001	6.01(4.17-7.52)	0.012
LA	2.32(0.97-3.57)	0.09	0.422/0.346–1.132	0.10
LVEF	1.44(0.38-2.81)	0.53		
Body mass index	0.78(0.62-1.35)	0.81		

DM: Diabetes mellitus, LA: Left atrium, LVEF: Left ventricular ejection fraction

Discussion

To the best of our knowledge, this is the first study to assess the relationship between DR and myocardial repolarization dispersion indexes. We observed that left ventricular repolarization indices, including Tp-e interval and Tp-e/QTc ratio, were substantially increased in the DR population compared to DM patients without retinopathy. Additionally, we found that DR can be predicted by Tp-e/QTc in DM patients.

As DR reflects microangiopathy, increases in Tp-e/QTc and Tp-e, observed in patients with DR led us to think that microangiopathy may influence ventricular myocardium electrical activity. Thus, microvascular circulation in diabetic patients' hearts was disturbed due to the prothrombotic and proinflammatory status, and autonomic neuropathy. This causes an increased risk of quiet myocardial infarction (MI), life-threatening ventricular arrhythmia, and even SCD [16]. In addition, there is an elevated risk of ventricular and atrial arrhythmias, perhaps due to structural defects in DM patients due to chronic hyperglycemia and increased fibrosis in the cardiac tissue [17, 18].

In the previous studies, traditional VR parameters such as QT, QTc, and QTc dispersion were significantly increased in the DR group compared to the group without DR [19-22]. In both DM patients and healthy individuals, QT interval prolongation predicts increased risk of all-cause and cardiovascular mortality [8, 23]. In this study, we wanted to investigate Tp-e and Tp-e/QT_{mean} intervals, and the ratio of Tp-e/QTc, which are relatively novel parameters in the electrocardiographic assessment of repolarization. In predicting arrhythmia, they were shown to be superior to the QT interval and QTd, and their prolongations are related to increased risk of arrhythmogenesis. Thus, even in patients with a normal QTc, the Tp-e value was proven to show VR dispersion [13, 24, 25].

Microvascular complications of DM are independent risk factors for SCD [3,26]. The most common microvascular complication of DM is DR [27]. Epidemiologic studies have shown the effects of hyperglycemia, hypertension, and dyslipidemia on the incidence and progression of DR. These risk factors are also predisposing factors for SCD [28-31]. Clemente et al. studied the effects of DM on VR parameters in 110 diabetic patients comparatively with 110 control subjects. The authors detected the significantly higher QTc_{max} and QTc_{mean} values, and QT, QTc, Tpeak-Tend, and jTpeak-jTend dispersions in diabetic patients compared to the control subjects. They concluded that diabetes led to VR prolongation and spatial dispersion, which may lead to electrical ventricular instability and potential malignant ventricular arrhythmias afterward [32]. However, Takebayashi et al. showed that QTc intervals were not related to

retinopathy in diabetic patients [33]. Besides, Veglio et al. revealed that no significant relationship existed between QT interval duration and DR [34]. Similarly, in our sample population, we did not find any significant differences in QT dispersion between the groups.

Patients with known CAD were excluded. There was also no statistically significant difference in terms of HT and hyperlipidemia between the groups. On the other hand, occult CAD may exist in diabetic patients, and silent coronary ischemia in this patient population might be responsible for prolonging the Tp-e interval. We found significant associations between DR and VR parameters. According to our results, we consider that it is crucial to assess these electrocardiographic parameters to determine the arrhythmia risk in DM patients with DR. We also showed that Tp-e value and ratio of Tp-e/QTc were predictors for DR development in regression analysis. In patients with DM, we suggest that increased VR might be correlated with the degree of DR. Our regression analysis revealed that the duration of DM was also significantly associated with DR. Since diabetic microvascular complications such as DR are associated with decreased life expectancy, prolonged VR parameters in patients with DM can be considered mortality markers in these patients. Nevertheless, more prospective, well-designed large-scale studies are needed to confirm the current findings, support our observations, obtain more substantial scientific evidence, and establish the prognostic value of increased VR parameters in DR patients.

Limitations

There were some limitations to our research. First, the ECG parameters of our sample were manually measured. Manual measurements have been acknowledged scientifically and several experiments have been conducted according to this approach, but the measurements carried out by a high-resolution monitor with digital ECG recordings are substantially more precise and standardized. Second, we had a relatively small sample size. Third, because it was not possible to conduct coronary angiography in clinical practice in all patients, subclinical ischemic heart disease may have been missed in the study group. Finally, we did not prospectively follow the patients for adverse cardiovascular outcomes.

This survey showed a strong correlation between diabetes and changes in the electrophysiological parameters that suggested prolonged and more heterogeneous repolarization of diabetic patients, in contrast to healthy subjects despite some methodological limitations. The greater susceptibility of these diabetic patients to cardiac arrhythmias could be associated with this fact. Therefore, for improved risk stratification of diabetic patients, it may be important to test these new markers for arrhythmogenic risk. Since these parameters are easy to assess, it may help to identify high-risk patients in daily clinical practice.

Conclusions

According to our study results, we think that myocardial VR parameters such as Tp-e value and ratio of Tp-e/QTc may be useful to assess and stratify DM patients who have retinopathy according to high-risk ventricular arrhythmia. Patients with DR may be at an increased risk of SCD, not only because of DM complications but also because of ventricular arrhythmias. Further studies are needed in patients with DR to assess the function of these parameters for predicting ventricular arrhythmias.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):687-690.
DOI: 10.28982/josam.928949

Journal of Surgery and Medicine
e-ISSN=2602-2079

The relationship between maxillary sinus retention cysts and nasal septum

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Ethics Committee Approval
This study was approved by Yozgat Bozok University Clinical Research Ethics Committee, on 24.02.2021 with the decision number 2017-KAEK-189_2021.02.24_04.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 July 26

Abstract

Background/Aim: The etiology of retention cysts of the maxillary sinuses (RCMs) and their relationship with the nasal septum is not fully elucidated. This study aimed to investigate the relationship between RCMs and the nasal septum.
Methods: In this retrospective cohort study, computed tomography (CT) images of 208 patients who underwent paranasal sinus CT (PNsCT) imaging in our otolaryngology clinic in 2020 were scanned retrospectively. The demographic characteristics of the patients were accessed through the hospital's electronic data recording system. The ages, genders, RCMs, and nasal septum statuses of all cases were noted.
Results: RCM was significantly related to nasal septum deviation (NSD) to the right (P=0.001), while it was not related to NSD to the left (P=0.5). When the nasal septum was in the midline, the risk of developing RCMs was significantly reduced (P=0.007). The direction of septum deviation and the presence of RCMs were significantly related. Right NSD was an independent risk factor for the development of RCMs and increased the risk by 2.2-fold (P=0.002).
Conclusion: RCMs, while thought to be asymptomatic and regress spontaneously, should be followed due to the possibility of transformation to antrochoanal polyp (ACP), and surgery should be considered, especially in symptomatic cases.

Keywords: Maxillary sinus, Retention cysts, Septum deviation, Etiology

How to cite: Dağıstan H, Cengiz C, Can İH. The relationship between maxillary sinus retention cysts and nasal septum. J Surg Med. 2021;5(7):687-690.

Introduction

Retention cysts of the maxillary sinuses (RCMs) occur because of seromucinous glands' ductal obstruction in the sinus mucosa. Accumulating mucus causes cystic dilatation of the gland [1]. The prevalence of RCMs ranges from 3.2 to 35.6 % [2]. They are radiographically smooth-surfaced, round-shaped masses with radiopaque appearances, which develop from the sinus wall, and mostly, from the sinus floor [3].

In the literature, spontaneous regression and disappearance rates of RCMs are reported between 17.6 and 38%, and RCMs are generally believed to be self-limiting [3]. They are mostly asymptomatic and detected incidentally. However, recent studies report that RCMs are associated with various symptoms such as nasal and postnasal discharge, nasal congestion, facial pain, and headache. The etiology of RCMs has not been fully elucidated. [4].

Nasal septal deviation (NSD) is one of the main causes of upper airway obstruction [5]. NSD can cause sinus pathologies by narrowing the middle meatus [6]. In addition, NSD can affect the mucociliary activity and cause sinusoidal infections [7]. The prevalence of NSD ranges between 13.1-89.7 % in recent studies [8, 9]. In our opinion, narrowing of the nasal passage by NSD may prevent proper airflow, disrupt sinus drainage, and cause retention cyst formation.

This study aimed to investigate the relationship between RCMs and the nasal septum by evaluating the computed tomography (CT) images of patients who underwent paranasal sinus computed tomography (PNS/CT).

Materials and methods

The CT images of 208 patients who visited the otolaryngology clinic of a tertiary hospital in 2020 and underwent PNS/CT for any reason were retrospectively scanned. This study was approved by Yozgat Bozok University Clinical Research Ethics Committee on 24.02.2021 with the decision number 2017-KAEK-189_2021.02.24_04 and conducted per the Helsinki Declaration. Informed consent was obtained from all individuals included in the study.

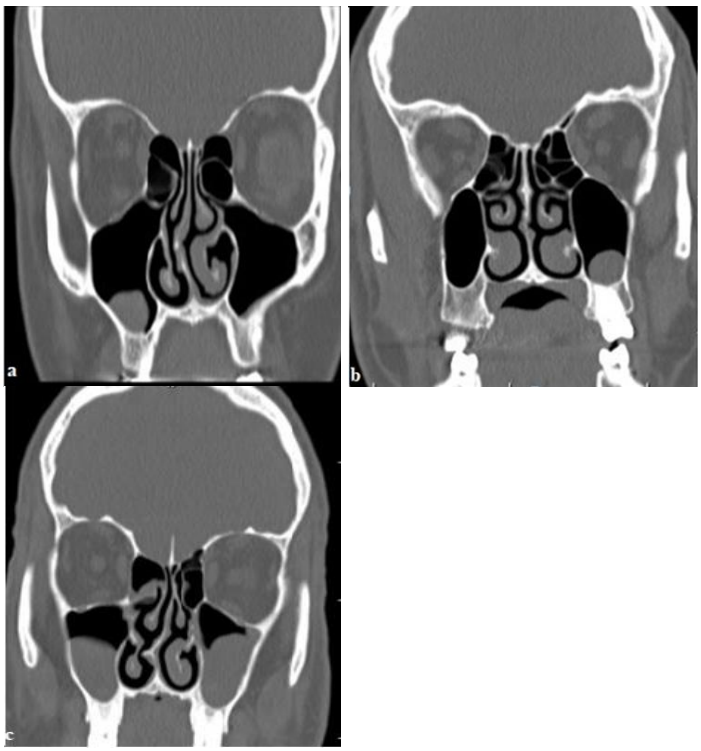
Patients with previous septal or sinus surgery, immunodeficiency, cystic fibrosis, nasal polyposis, a nasal mass, and acute or chronic sinusitis were excluded from the study. All CT images of the remaining patients obtained between 01.01.2020-31.12.2020 were included. The demographic characteristics of the patients were accessed through the hospital's electronic data recording system. Ages, genders, RCMs, and nasal septum statuses of all cases were noted.

The presence of retention cysts in the left and right maxillary sinuses and the direction of NSD were evaluated separately. The relationship between the direction of NSD and RCMs was investigated. Figure 1 shows RCMs with different nasal septa.

Statistical analysis

Statistical Package for the Social Sciences (version 22.0, IBM Inc., Chicago, IL, USA) software was used for statistical analysis. Continuous data were shown as mean (standard deviation) and categorical data as n (%). The Chi-square test was used to evaluate categorical data between groups. Logistic regression was used to determine the risk ratio. A *P*-value of <0.05 was considered statistically significant.

Figure 1: Paranasal sinus computed tomography views of maxillary sinus and nasal septum. (a) The nasal septum is deviated to right and retention cyst is found on the floor of the right maxillary sinus. (b) The nasal septum is in the midline and retention cyst is on the floor of the left maxillary sinus. (c) The nasal septum is deviated to right and retention cysts are found on the floors of bilateral maxillary sinuses.



Results

There were 119 (57.2%) males and 89 (42.8%) females in our patient group. There was no significant difference between the genders in terms of the presence of RCMs (*P*=0.087) (Table 1). The mean age of the patients was 38.07 (14.15) years. RCMs were detected in 72 (34.6%) of the CT images. The nasal septum was in the midline in 19, deviated to the right in 35, and deviated to the left in 18 patients. RCMs were on the right side in 28 (38.9%), on the left side in 19 (26.4%), and bilateral in 25 (34.7%) cases (Table 2). RCM was significantly related to NSD to the right (*P*=0.001), while it was not related to NSD to the left (*P*=0.5). When the nasal septum was in the midline, the risk of developing RCMs was significantly reduced (*P*=0.007) (Table 3). Right NSD was an independent risk factor for the development of RCMs and increased the risk by 2.29-fold (*P*=0.002) (Table 4).

Table 1: Distribution of RCMs by gender

		Gender		
		M	F	*P*-value
RCMs	Negative	72	64	0.087
		60.5%	71.9%	
	Positive	47	25	
		39.5%	28.1%	
Total		119	89	
		100.0%	100.0%	

RCMs: Retention Cysts of the Maxillary sinuses

Table 2: Patients' RCMs and NSD distribution frequency

	NSD right side		NSD left side		Septum into the midline	
RCMs	n	%	n	%	n	%
Right	11	15.3	10	13.9	7	9.7
Left	12	16.7	2	2.8	5	6.9
Bilateral	12	16.7	6	8.3	7	9.7

RCMs: Retention Cysts of the Maxillary sinuses, NSD: Nasal Septal Deviation

Table 3: Relationship between RCMs and NSD

		RCMs -	RCMs +	*P*-value
NSD Left Side	Negative	96	54	
		70.6%	75.0%	0.500
	Positive	40	18	
		29.4%	25.0%	
NSD Right Side	Negative	102	37	
		75.0%	51.4%	0.001
	Positive	34	35	
		25.0%	48.6%	
Nasal Septum into midline	Negative	74	53	
		54.4%	73.6%	0.007
	Positive	62	19	
		45.6%	26.4%	

RCMs: Retention Cysts of the Maxillary sinuses, NSD: Nasal Septal Deviation

Table 4: Regression analysis of independent risk factors in RCMs

Nasal septum	*P*-value	Relative risk	95% Confidence Interval	
			Lower	Upper
NSD right side	0.026	2.288	1.103	4.745
Into midline	0.320	0.681	0.319	1.452
NSD left side	0.500	0.800	0.418	1.530

RCMs: Retention Cysts of the Maxillary sinuses, NSD: Nasal Septal Deviation

Discussion

RCM is generally thought to be a self-limiting disease and the spontaneous regression and disappearance rates of RCMs range between 17.6 and 38% in the literature [3]. Wang et al. [3] followed 40 patients with RCMs for an average of 60 months to report that the retention cyst decreased in size or disappeared in 50% and increased in size in 27.8%. Therefore, they suggested that if the cysts did not show a significant change in size over 48 months, they would remain the same size over the long term. They suggested that in the absence of associated complications, a "wait and see" approach may be an appropriate management strategy for retention cysts.

The etiology of RCMs has not been fully elucidated. It has been stated that sinusitis, allergic rhinitis, barotrauma, and dental disease can cause the development of MSRKs [4]. Previous studies report that 18%-83.5% of patients with retention cysts have a history of allergies and 10 to 66.7% have sinusitis [10, 11]. Wang et al. [3] reported that 22.5% of these patients had a history of allergic rhinitis and 20 % were diagnosed with sinusitis.

Climate, humidity, and altitude are also stated among the etiological factors for RCMs. In their study conducted in two centers with different climatic, humidity, and altitude conditions, Omezli et al. examined 17,659 panoramic graphs and found that the prevalence of RCMs was 1.6% at high humidity and low altitudes, while it was 0.4% at low humidity and high altitudes. Based on these results, they suggested that the probability of developing RCMs significantly increased in high humidity and low altitude [12]. Contrarily, Gürsoy et al. [13] investigated the etiology of antrochoanal polyp (ACP) and found a significantly higher prevalence of retention cysts in the ACP group. The lack of a histological difference between maxillary sinus retention cysts and the cystic part of the ACP within the maxillary sinus supports the hypothesis that retention cysts may be precursor lesions of ACPs [14]. Berg et al. [14] stated that chronic inflammation may cause occlusion of small seromucinous glands on the mucosal surface and that retention cysts formed as a result of this occlusion may be responsible for the formation of ACP. This hypothesis is based on the shared histological features of cystic ACP and retention cysts. Frosini et al. [15] explained the conversion of retention cyst to ACP using Bernoulli's theorem. These studies, which show the possibility of RCM transformation into ACP despite the possibility of spontaneous regression, indicate that more attention should be paid to RCMs clinically.

Recent studies report that RCMs may cause symptoms such as nasal and postnasal discharge, nasal congestion, facial pain, and headache [11, 16]. In the study of Busaba and Kieff [16], all patients with RCMs reported facial pain or pressure in the sinus area. Similarly, a headache was reported by 63% of patients in the study of Hadar et al. [11] on symptomatic RCMs. Albu et al. reported that 60% had a feeling of pressure or pain on the face, 27.5% had nasal congestion, and 12.5% had a nasal discharge. In the same study, they found no relationship between the size of the cyst and the severity of the symptoms; surgical removal of the cyst did not provide a significant improvement in symptoms and suggested that surgery should aim to restore ventilation and drainage of the maxillary sinus [4].

The relationship of NSD with paranasal sinus disease continues to be debated among otolaryngologists [17]. A marked deviation of part or all of the nasal septum may not only obstruct nasal breathing but also lead to a disease in the lateral nasal wall and sequentially, in the paranasal sinuses [18]. The NSD can narrow the middle meatus by pushing the concha sideways. In addition to nasal congestion, it also exerts pressure on neighboring structures. This disrupts the drainage pathways, affects mucosal ciliary function with contact, and disrupts normal mucus drainage, resulting in obstruction of all sinuses and secondary nasal infections [18, 19].

Poorey [19] found a highly significant statistical correlation between the deviation angle and sinus mucosal hypertrophy in his study, in which he evaluated the effects of NSD on sinus diseases. More maxillary sinus mucosal changes were observed in patients with increased angles. Yousem et al. [20] evaluated the morphological features predisposing to sinusitis and reported that patients with evidence of sinusitis on CT scan had a higher degree of septal deviation than those without. They also found that sinusitis rates were not significantly different ipsilateral and contralateral to the septal deviation side. Calhoun et al. [21] examined paranasal sinus CT images of both asymptomatic and symptomatic patients and demonstrated a strong correlation between NSD and sinus disease. Elahi et al. [7] evaluated paraseptal structural changes and pathologies caused by nasal septum deviation in an adult population with a clinical diagnosis of chronic rhinosinusitis and reported that deviation and paraseptal pathologies were correlated [22]. We found that NSD to the right significantly increased the risk of the RCMs by 2.29-fold.

Kepekçi et al. [23] examined the relationship between sinonasal anatomical variations and RCMs and showed that right-sided RCMs were significantly higher in male patients. Similar results were also shown in the study of Omezli et al. [12]. Contrary to these studies, the RCMs in our study did not differ with gender.

Limitations

The limitations of our study include the lack of a classification of the severity and localization of NSD and measuring the size of the RCMs. The fact that we did not evaluate patient symptoms can be considered another limitation.

Conclusion

Although thought to be asymptomatic and regress spontaneously, the possibility of transformation to ACP increases the clinical importance of RCMs. We think that early surgical treatment of these patients may be preventive since NSD was a risk factor for the development of RCMs. Further research is needed to determine the correlation between the presence of RCMs and NSD and other paranasal anatomical pathologies, their degree, and clinical findings.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):691-694.
DOI: 10.28982/josam.806578

Journal of Surgery and Medicine
e-ISSN=2602-2079

The effect of vulvar lichen sclerosus on quality of life and sexual functioning

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Ethics Committee Approval
Ethics approval was obtained from the Ethics and Research Committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital (REF: 2017/119). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 July 26

Abstract

Background/Aim: Vulvar lichen sclerosus (VLS) is a chronic inflammatory condition that has the potential to cause sexual dysfunction and reduction in patients' life quality. We aimed to evaluate the quality of life and sexual function in female patients with VLS.
Methods: This prospective case-control study was conducted with women who presented to the gynecology clinic with a biopsy-proven diagnosis of VLS or for routine gynecological check-ups between June 2017-January 2018. The patients were grouped according to the presence or absence of VLS. Effects of VLS on quality of life and sexual functions were analyzed with the Dermatology Life Quality Index (DLQI) and Female Sexual Function Index (FSFI) questionnaires.
Results: A total of 86 women were included in this study. Thirty-seven VLS patients were compared with 49 patients without VLS. The total DLQI scores of the VLS and control groups were 6.14 (6.87) and 1.92 (2.41), respectively (P=0.001), and the total FSFI scores, 15.42 and 24.22, respectively (P<0.001). Subgroup analyses revealed that the two groups significantly differed in terms of sexual desire, arousal, orgasm, satisfaction, and pain (P<0.001), but not in terms of lubrication (P=0.741).
Conclusion: Vulvar lichen sclerosus negatively affects the quality of life and sexual function. Questionnaires such as DLQI and FSFI are useful tools for the assessment of sexual function and quality of life in these patients. Since these patients may be hesitant to report their sexual problems, healthcare professionals should interrogate them in this regard during the early stages of management.

Keywords: Lichen sclerosus, Vulva, Quality of life, Sexual function

How to cite: Helvacıoğlu Ö, Topkarci Z, Helvacioglu Ç, Kavak A. The effect of vulvar lichen sclerosus on quality of life and sexual functioning. J Surg Med. 2021;5(7):691-694.

Introduction

Vulvar lichen sclerosus (VLS) is a progressive, inflammatory dermatosis characterized by porcelain-white sclerotic plates in the anogenital region [1]. It is usually diagnosed in postmenopausal women. Although its etiology is unknown, autoimmune, genetic, hormonal, and infectious factors are thought to play roles in its etiopathogenesis [2]. VLS can also be triggered by trauma in a patient with a genetic predisposition. While pruritus is the main symptom of VLS, dyspareunia, burning sensation and dysesthesia can also be present [1]. It has the potential to cause permanent anatomical deformities in the anogenital region if left untreated. Effacement of the labia minora and clitoris are the most frequent deformities encountered in these patients. Long-term lesions bear the risk of transformation to squamous cell carcinoma [3]. Pruritus, dyspareunia, and deformities have the potential to influence patients' psychosexual health and quality of life.

In this study, we aimed to investigate the impact of VLS on the quality of life and sexual function of women.

Materials and methods

This prospective observational study was conducted with patients who presented to the gynecology clinic of Bakirkoy Dr. Sadi Konuk Training and Research Hospital between June 2017 and January 2018. Ethics committee approval was obtained from the Ethics and Research Committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital (REF: 2017/05/06). Patients with recently diagnosed, biopsy-proven VLS (VLS group) and those who presented for a routine gynecological check-up and did not use any estrogen-containing medications (control group) were included in this study. Exclusion criteria comprised being younger than 18 years of age, having mental disorders, and not agreeing to participate. One of the researchers interviewed the participants face-to-face after obtaining their informed consent. Validated Turkish versions of DLQI (Appendix 1) and FSFI (Appendix 2) questionnaires were completed by the patients during these interviews for assessment of the quality of life and sexual function, respectively [4, 5]. Demographic parameters of the participants including age, body mass index (BMI), menopausal status, and comorbidities were noted.

Statistical analysis

Statistical analysis of the numerical variables was performed using SPSS (Statistical Package for the Social Sciences) 23 software (IBM Corporation, Armonk, New York, US). Frequencies and percentages were calculated for demographic parameters. Cronbach's alpha score was used in the reliability analysis of the dataset. Mann Whitney U test was used for the comparison of two independent groups. A *P*-value <0.05 was considered statistically significant.

Results

The demographic parameters of the study patients are presented in Table 1.

The mean age of the patients in the VLS and control groups were 54.08 (10.0) years and 52.14 (9.02) years, respectively. The two groups were similar in terms of patient age, BMI, and menopausal status ($P>0.05$ for each).

The quality-of-life scores were higher in the VLS group than in the control group (Table 2). The difference was significant for total scores ($P<0.001$) and scores on symptomatology, embarrassment, and self-consciousness ($P<0.001$), social or leisure activities ($P<0.001$), interpersonal relationships ($P=0.024$), and working or studying performance ($P<0.001$).

Table 1: Demographic data of the study participants

	VLS n=37	Control n=49	*P*-value
	$\bar{X}$ SD	$\bar{X}$ SD	
Age	54.08 10.50	52.14 9.02	>0.05
BMI	25.3 6.5	24.1 4.4	>0.05
Postmenopausal	n=14 37.84%	n=19 38.7%	>0.05

Table 2: Comparison of the VLS and Control groups in terms of DLQI

	VLS (n=37) Mean (SD)	Control (n=49) Mean (SD)	* *P*-value
Total DLQI Score	6.14 (6.87)	1.92 (2.41)	0.001
Symptoms and Feelings	2.05 (1.68)	0.47(0.92	<0.001
Daily Activities	1.11(1.52	0.43 (0.74)	0.024
Leisure	0.89 (1.59)	0.35 (0.56)	0.327
Personal Relationships	1.3 (1.65)	0.29 (0.54)	0.001
Work or School	0.57 (0.87)	0.14 (0.41)	0.004
Treatment	0.22 (0.53)	0.24 (0.52)	0.661

*Mann Whitney-U Test

The two groups significantly differed in terms of sexual desire ($P<0.001$), sexual arousal ($P<0.001$), orgasm ($P<0.001$), satisfaction ($P<0.001$), and pain ($P<0.001$) (Table 3) but were similar in terms of lubrication ($P=0.194$). Mean FSFI scores were higher than the control group in all subgroups except for lubrication.

Table 3: Comparison of the VLS and Control groups in terms of FSFI

	VLS (n=37) Mean (SD)	Control (n=49) Mean (SD)	* *P*-value
Total FSFI Score	15.42 (8.85)	24.22 (7,67)	<0.001
Desire	2.69 (1.23)	4.07(0.89)	<0.001
Arousal	2.16 (1.5)	4.07 (1.61)	<0.001
Lubrication	2.84 (1.89)	4.1 (1.59)	0.194
Orgasm	2.54 (1.84)	4.13 (1.63)	<0.001
Satisfaction	2.79 (2.11)	4.24 (1.72)	<0.001
Pain	2.4 (1.75)	3.62 (1.33)	<0.001

*Mann Whitney-U Test

Discussion

The self-inspection of the vulva is difficult due to its anatomical location. Since the overlying skin is folded, most vulvar skin lesions can be overlooked. In addition to the specific vulvar dermatoses, various systemic dermatoses can also involve the vulva [6]. Therefore, the diagnosis of vulvar diseases might be challenging and may necessitate a multidisciplinary approach.

Lichen sclerosus (LS) is a rare, chronic inflammatory disease that mainly affects the anogenital region [7]. It has a bimodal age distribution; its incidence peaks at prepubertal and postmenopausal ages. Even though several environmental and genetic factors were accused, it is believed that autoimmunity and chronic inflammation play essential roles in its pathogenesis [8-10]. Karadag et al. [11] investigated 350 LS patients, 98% of which had vulvar involvement, and reported that autoimmune antibodies (anti-thyroid, anti-nuclear, anti-mitochondrial antibodies) were detected in 22%.

The main symptoms of the patients with VLS are pruritus, burning sensation, pain, and dyspareunia. However, dysuria, constipation, and other gastrointestinal symptoms can

also be present provided that urinary and gastrointestinal tracts are also involved [12].

Dyspareunia and other sexual problems encountered in VLS patients can be due to three main reasons [13]: The skin gets thinner and more sensitive in VLS; these changes may lead to tears and dyspareunia. Besides, fear of pain and anxiety triggers dyspareunia by reducing the arousal and contraction of the pelvic muscles during sexual intercourse. Anatomical deformities including clitoral effacement, labial fusion, and introital stenosis can also contribute to dyspareunia, orgasmic dysfunction, and other sexual problems.

Based on our results, VLS has a significant impact on the quality of life and sexual function of the patients. The mean DLQI score was significantly higher in the VLS group when compared with the control group.

The quality of life was reduced in 40% (n=15) of the VLS patients (DQLI ≥6). Since DLQI scores also reflect the disease-related anxiety level, the reduction in the life quality of these patients may be –at least partly- due to their anxiety [14].

Several dermatoses have the potential to lower life quality [15-17]. Kiebert et al. [18] found that the mean DLQI was 6.6 among female patients diagnosed with atopic dermatitis. In a Spanish study, the mean DLQI score of patients with psoriasis was 5.3. The mean DLQI of our VLS patients was similar to the mean scores of the patients with atopic dermatitis, hyperhidrosis, psoriasis, and dermatomyositis [15].

Basak et al. [19] analyzed the quality of life of the patients who were diagnosed with frequent dermatologic diseases and found that the scores of the first and second questions of DLQI were the highest in papulosquamous skin disorders (psoriasis and lichen planus). These questions assess the symptomatology, embarrassment, and self-consciousness of the patients. In line with this finding, our analysis revealed that the highest scores were obtained in questions 1 and 2. The presence of subjective complaints such as pruritus, pain, and burning sensation shows that DLQI is not only affected by disease-related anxiety but also by organic reasons. In the study reported by Cheng et al., the authors found that mean DLQI was lower in vulvar dermatitis and vulvar erosive lichen planus patients, and they ascribed this finding to better treatment response and less pain in these patients [17].

Hedwig et al. analyzed the impact of VLS on sexual function, which revealed that FSFI scores of VLS and control patients were 15.42 and 24.22, respectively [20], similar to our findings. Dalziel et al. denoted that dyspareunia was significantly more frequent, and the frequency of sexual intercourse was significantly lower in VLS patients when compared with the control group [21]. These findings are also in line with ours: We found a significant difference between the VLS and control groups in terms of arousal and pain scores. Haefner et al. stated that both the frequency of sexual intercourse and sexual satisfaction decreased due to dyspareunia in patients with VLS [22].

Several studies showed that topical treatments were useful for pain relief in women with VLS [7-8, 21-22]; however, these treatments did not necessarily lead to an improvement in sexual function. Two studies showed that topical immunomodulators could provide symptomatic relief and histopathological improvement in VLS patients [22, 23], nevertheless, sexual dysfunction could be permanent despite these positive changes. It is also unclear whether increased awareness regarding the risk of sexual dysfunction leads to more prompt patient management and increased quality of life [13].

Although it is known that reduced arousal and pain impedes lubrication, our analysis revealed that VLS and control group patients were similar in terms of lubrication scores [21]. We attribute this finding to the possibility of patients' hesitancy to communicate about this issue. Besides, the VLS stage may be associated with the severity of sexual dysfunction [24]. In patients who have VLS at an earlier stage without any scar formation and related complications such as introital stenosis, there may not be any significant reduction in lubrication function.

Treatment of VLS is essential, not only because of its impact on the quality of life and sexual function of the patients but also due to the risk of squamous cell cancer in the long term [3]. Topical and intradermal (intralesional) corticosteroids constitute the first-line treatment of VLS [8]. Care should be taken regarding the risk of regional atrophy and systemic adverse effects [23].

Topical calcineurin inhibitors such as tacrolimus and pimecrolimus are used for second line treatment [12]. Long-term treatment with these agents does not lead to regional atrophy, which is their main advantage over corticosteroids [2]. Other treatment options are oral acitretin, cyclosporin, methotrexate, topical progesterone, testosterone, ultraviolet A1 phototherapy, and photodynamic therapy [1, 8-9]. However, in complicated VLS which presents with structural deformities, severe adhesions, and scar formation, surgical treatment is indicated [25, 26]. Fourchette, introital stenosis, posterior fissure, and scars can be treated by vulvoperineoplasty [2].

Limitations

One of the limitations of our study is the absence of data regarding VLS stages. Some studies showed that advanced age, postmenopausal state, low educational status, singleness, physical and psychological health problems, negative sexual experiences were predictors of sexual dysfunction [27-29]. There is a strong relationship between sexual satisfaction and menopausal state [27]. Vaginal atrophy, dryness, urinary incontinence, and infections can be encountered in postmenopausal patients, and can lead to a reduction in sexual activity. The presence of a 'physical' disease in their genitalia might have affected our VLS patients psychologically and led to a decrease in sexual desire. However, we did not analyze the psychological impact of VLS in our study. Besides, there were no data on the use of lubricating agents, the role of sex therapy, and other treatments.

Conclusion

Despite its weaknesses, we conclude that VLS is associated with female sexual dysfunction. Since patients may be hesitant to verbalize their sexual problems, physicians taking care of these patients should have a low threshold to apply the relevant questionnaires during their clinical encounters with these patients.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):695-699.
DOI: 10.28982/josam.825313

Journal of Surgery and Medicine
e-ISSN=2602-2079

Comparable anatomical and functional success to younger patients in endoscopic dacryocystorhinostomy patients of older age

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Abstract

Background/Aim: Endoscopic dacryocystorhinostomy (EDCR) has many advantages over the external method, with comparable anatomical and functional success rates. Delayed wound healing is reported to be associated with older age in previous studies. In this study, we aimed to assess the effect of age on the functional and anatomic success of our EDCR results.

Methods: A total of 55 patients with nasolacrimal duct obstruction (NLDO) were included in this retrospective cohort study. Patients were managed with either EDCR alone or EDCR combined with nasal septoplasty in our hospital. The patients were divided into two groups as Group 1 (20-54 years old) and Group 2 (55-77 years old) according to age.

Results: The mean ages of the patients in Groups 1 and 2 were 38.53 (9.55) years and 66.24 (6.36) years, respectively (P<0.001). EDCR was performed on 30 nasolacrimal ducts in Group 1 and 38 nasolacrimal ducts in Group 2. Forty-one cases (60.3%) were managed only with EDCR, and 27 (39.7%) patients underwent septoplasty surgery in addition to EDCR due to septum deviation. There was no significant difference between the groups in terms of anatomical and functional success (P=0.239 and P=0.233).

Conclusion: Our results showed that comparable anatomical and surgical success rates are possible in NLDO in older patients compared with younger patients. This result may encourage surgeons with question marks about the success of the EDCR in older age NLDO patients.

Keywords: Endoscopic dacryocystorhinostomy, Age, Epiphora, Nasolacrimal duct obstruction

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Ethics Committee Approval
Bozok University Clinical Research Ethics Committee, 28/05/2020, 2017-KAEK-189_2020.05.28_08
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 July 28

How to cite: Erkan E, Çıkrıkçı S, Ağdaş F. Comparable anatomical and functional success to younger patients in endoscopic dacryocystorhinostomy patients of older age. J Surg Med. 2021;5(7):695-699.

Introduction

Recent advancements in the endoscopy systems, endoscopic intranasal imaging, and intervention capabilities make it possible to perform various open procedures with the endoscopic methods. Endoscopic dacryocystorhinostomy (EDCR) was first introduced in 1989 by McDonogh and Meiring [1] and became popular in nasolacrimal duct obstruction (NLDO) today. Indications for EDCR include primary and secondary (acquired) NLDO (trauma, nasal or sinus inflammation, surgery, neoplasm), functional outflow obstruction, and history of dacryocystitis.

In patients with nasolacrimal duct obstruction, when compared with external surgery, EDCR appears to be favorable in many ways, such as the absence of an external incision scar, shorter operative time, lower intraoperative bleeding, and rapid postoperative recovery of the orbicularis oculi muscle [2, 3].

Working with multiple instruments in a narrow surgical field requires experience. Synechia formation between the ostium and middle turbinate, orbital perforation risk, narrow surgical field due to possible nasal septum deviation, granuloma formation in the ostium, expensive equipment, and small rhinostomy are disadvantages of the endonasal method [4-7].

In this retrospective study, we evaluated our EDCR results in patients with epiphora and nasolacrimal duct obstruction. Our primary objective was to assess the effect of age on the functional and anatomic success of our EDCR operations.

Materials and methods

Patients with a complaint of epiphora who presented to the Yozgat City Hospital otorhinolaryngology outpatient clinic between June 2017 and June 2019 were included in this study. These patients were evaluated by endoscopic nasal examination, dacryoscintigraphy, and paranasal sinus computed tomography (PNCT), and nasolacrimal lavage was performed by an ophthalmologist. Patients with ocular surface disease, appositional lid abnormalities, poor pump function, and neurogenic lacrimal hypersecretory disorders were excluded from the study. Surgical treatment was planned for patients with an obstruction in nasolacrimal lavage and lacrimal sac or a distal obstruction in dacryoscintigraphy.

Nasal endoscopy and anterior rhinoscopy were performed to evaluate the nasal cavity and identify additional nasal pathologies (nasal septum deviation, location of deviation, sinusitis, polyp, anatomical variations, anomalies, etc.). Patients were planned for a combined operation of EDCR + septoplasty if the anterior and middle parts of the nasal septum obscured the view of the surgical field on the side of the planned EDCR.

The anatomical and functional success of the performed surgery was evaluated according to the examination findings after 6 months. We used the criteria described by Olver in this evaluation [8].

Olver [8] suggested that lacrimal surgeons should consider 3 criteria for evaluating success in DCR surgery, either external or endonasal. These criteria include:

1. Evaluate the results at least 6 months after surgery and at least 3 months after tube removal.
2. Evaluate subjective success based on the patient's symptoms.
3. Anatomic success should be based on (i) patency in syringing and (ii) the presence of a functioning rhinostomy.

The latter is evaluated using the functional endoscopic dye test, which is positive when 2% fluorescein instilled in the conjunctival fornix is seen emerging from the rhinostomy a few seconds later [8].

The minimum follow-up period after surgery was 6 months. Silicone tubes were removed at the 3rd postoperative month.

All patients were informed about the procedures and possible complications were explained. Informed consent forms were obtained from the patients.

The study protocol was approved by Yozgat Bozok University Clinical Research Ethics Committee on 28 May 2020 with the decision number 2017-KAEK-189_2020.05.28_06 and adhered to the principles of the Helsinki Declaration.

Surgical technique

All patients were operated under general anesthesia with the endotracheal tube out of the way of the endoscope and instruments. During the procedure, a 0-degree rigid endoscope, metal probe, punctum dilatators, small forceps, 3.0 mm straight diamond burr, sickle knife, and silicone stent were used. In case of significant ipsilateral septal deviation, septoplasty was performed before EDCR with an incision contralateral to the septum deviation. A mixture of 0.0125mg/ml epinephrine and 20mg/ml lidocaine hydrochloride was diluted with saline and injected into the middle turbinate, middle turbinate adhesion, and lateral nasal wall towards the maxillary line using a dental syringe. A square incision with an edge length of 1 cm was made on the mucosa in front of the middle turbinate attachment with a sickle knife. Using the elevator, the mucosa was elevated and removed with the periosteum. Bone tissue was exposed and made visible using a diamond burr. The lacrimal canaliculus was enlarged with a punctum dilatator from the lower punctum, which was first advanced vertically, then rotated horizontally and advanced until the dilatator met lacrimal bone, the hard stop. The punctum dilatator was again rotated vertically into the lacrimal sac. The back-and-forth movement of the dilatator was visualized as tenting of the sac with an endoscope. An incision was made on the medial wall of the lacrimal sac, which was removed with forceps. After the punctum dilator was withdrawn, the silicone stent was advanced through the lower punctum into the lacrimal sac until the metal tip of the silicon stent was visualized out of the window opened in the lacrimal sac wall. Then, the silicone stent was advanced from the upper punctum and the same procedures were repeated as per the lower punctum. The metal tips of the silicone stents were cut and the two ends of the silicone tube were tied with 10 knots and secured. The operation was ended after hemostasis was achieved.

All patients were given oral amoxicillin and clavulanate combination for 5 days postoperatively. In case of penicillin allergy, clarithromycin was administered. Patients were given nasal irrigation solution or nasal spray and called for control on the 10th postoperative day. Silicone stents were removed after 3 months and followed for at least 6 months. The success rates of

the surgical procedure were evaluated at the 6th postoperative month.

Statistical analysis

Demographic features, postoperative complications, and surgical success rates at the sixth month were analyzed. SPSS (Statistical Package for Social Science, Worldwide Headquarters SPSS Inc.) package program (version 22.0) was used for statistical analysis. Continuous data were expressed as mean (standard deviation), and categorical data, as numbers and percentages. Chi-square test, Fisher's exact test, and Student's t-test were used for intergroup analysis. A *P*-value <0.05 with a 95% confidence interval was considered statistically significant.

Results

A total of 68 EDCR surgeries, 42 unilateral and 13 bilateral, were performed on 55 patients. All patients had epiphora. Five patients had a history of dacryocystitis. Fifty-one (75%) patients were female and 17 (25%) were male. A total of 68 EDCR surgeries were performed in 13 patients bilaterally (19.1%) and 42 patients (80.9%) unilaterally. The demographic characteristics of all patients are shown in Table 1.

Table 1: Demographic Data of Patients

	Value
Age, years, mean (SD)	54.01 (15.9) (20-77)
Gender, n (%)	
Female	51 (75%)
Male	17 (25%)
Surgical Side, n (%)	
Right	35 (51.5%)
Left	33 (48.5%)
Bilateral	13 (%19.1)
Medical History, n (%)	
Hypertension	21 (30.9%)
Diabetes Mellitus	6 (8.8%)
Anticoagulant/Antiplatelet Use	8 (11.8%)
Lacrimal History (n)	
Epiphora	68
Dacryocystitis	5
Punctum Injury	1

SD: Standard deviation

The mean age of the patients was 54.01 (range: 20-77) years. Since studies investigating the effect of age on EDCR results are limited, patients were divided into two groups according to age, as Group 1 (20-54 years old) and Group 2 (55-77 years old). There were 30 patients in Group 1 and 38 patients in Group 2. The mean age of Groups 1 and 2 were 38.5 (range 20-54) years and 66.2 (range 55-77) years, respectively. The two groups were similar in terms of gender and surgical side (*P*=0.163 and *P*=0.489 respectively). Forty-one cases (60.3%) were managed with EDCR alone, and septoplasty was performed in 27 (39.7%) cases additionally due to septum deviation. The postoperative complications were noted. The minimum follow-up period was 6 months. Tubes were removed at the 3rd postoperative month. Anatomical and functional success were evaluated according to the criteria described by Olver et al. (8). The overall anatomical and functional success rates were 92.7% (63 cases) and 89.7% (61 cases), respectively; while anatomical and functional failure rates were 7.3% (5 cases) and 10.3% (7 cases), respectively. In Group 1, anatomical success was achieved in 20 patients (96.7%), and functional success, in 28 cases (93.3%). There were anatomical and functional failures in 1 (3.3%) and 2 (6.7%) cases, respectively. In Group 2, anatomical and functional success were achieved in 34 cases (89.5%) and 33 cases (86.8%), respectively. In this group, there were anatomical and functional failures in 4 (10.5%) and 2 (6.7%) cases, respectively. There was no significant difference between the groups in terms of anatomical (*P*=0.239) and functional success (*P*=0.233) (Table 2 and 3).

Table 2: Surgical Data of Patients

	Patient number (n)	Percent (%)
Type of Surgery		
EDCR	41	60.3
EDCR+Septoplasty	27	39.7
Functional Outcome		
Successful	61	89.7
Unsuccessful	7	10.3
Anatomic Outcome		
Successful	63	92.7
Unsuccessful	5	7.3
Complication		
Periorbital Swelling	3	4.4
Synechia	4	5.9
Fistula	1	1.5

EDCR: Endoscopic dacryocystorhinostomy

Table 3: Demographic and Surgical Data of Age Groups

	Group 1 (20-54 years)	Group 2 (55-77 years)	*P*-value
EDCR Procedures (n)	30	38	
Age (years, mean (SD)	38.53 (9.55)	66.24 (6.36)	<0.000
Gender (n,)			0.163
Female	25	26	
Man	5	12	
Surgical Side (n)			0.489
Right	14	11	
Left	16	17	
Medical History (n)			
Hypertension	5	16	0.040
Diabetes Mellitus	0	6	0.031
Anticoagulant/Antiplatelet Use	0	8	0.007
Functional Outcome			0.233
Successful	28	33	
Unsuccessful	2	5	
Anatomic Outcome			0.239
Successful	29	34	
Unsuccessful	1	4	

P<0.05 statistically significant

There were no major complications during and after the surgery. During follow-up, 3 patients had periorbital swelling, 4 patients had nasal synechia and 1 patient had fistula to the skin (Table 2).

There was a statistically significant increase in hypertension, diabetes mellitus, and anticoagulant/antiplatelet drug use with age (*P*=0.040, *P*=0.031, and *P*=0.007, respectively) (Table 3).

Discussion

EDCR is the treatment of choice in NLDO. Due to rapid advancements in endoscopic surgical instruments, comparable success rates with the external method, and other favorable features, EDCR gained popularity over the years. Anatomical success rates in EDCR range from 84 to 95% [9-13]. In our study, our anatomical success rate was 92,7% similar to the literature. Various factors that might influence the success of EDCR are largely investigated [9, 13, 14]. However, the effect of age on EDCR outcomes remains to be clarified and not much data is available.

After an anatomically successful EDCR, some patients still complain about tearing. This is called “functional failure” by experienced lacrimal surgeons [15]. The functional failure rates are reported to vary between 1.7% and 4.7% in primary EDCR and between 5% and 12% in revision EDCR [10, 11, 14]. In the retrospective analysis of 61 failed EDCR procedures performed by Baek et al., functional failure was seen in 15% of patients [12]. In this study, age and history of diabetes mellitus were significantly related to functional failure. This functional failure in elderly patients may also be associated with age-related

changes in the eyelid [9]. In our study, the functional failure rate was 10.3%, similar to the literature.

Shams et al. evaluated 65 patients (69% transnasal) with anatomical success but functional failure in a multicenter study. All cases had recurrent or permanent and symptomatic epiphora with a Munk score of 2 to 4. These patients were not resistant to lacrimal irrigation and/or had no positive endoscopic dye test results [15]. In these patients, successful treatment can be achieved with surgical methods such as eyelid tightening procedures, tightening of eyelid laxity, repeat silicone stent intubation, Lester-Jones tube, endoscopic corticosteroid application, and punctoplasty [12, 15].

Manometric measurements of lacrimal sac pressure can offer quantitative and objective information about the failure but include insertion of a catheter into the lacrimal sac which may alter the physiologic course of tear outflow [16]. According to Kamel et al. [16], positive pressure was detected in cases with epiphora and in patients with failed DCR. They also reported that the endoscopic approach is superior to external DCR in terms of manometric measurements. They concluded that the suction power of the pump mechanism is more effective after endoscopic DCR than external DCR. Detorakis et al. [17] stated that lacrimal manometry might not be an ideal indicator of physiologic outflow due to the interventional nature of the method and evaluated successful DCR patients using MRI. They found that lacrimal pump function was better preserved in endonasal DCR than external DCR.

Studies showing the effect of age on EDCR results in patients with primary nasolacrimal duct obstruction are limited. Age may affect the functional outcome by increasing comorbid problems and compromising wound healing. It should be emphasized to the lacrimal surgeon that careful preoperative examination of the eyelid, punctum, and conjunctiva before EDCR, especially in elderly patients, is imperative [9]. In a study by Cohen et al. [18], 10-year results of patients who underwent primary EDCR were examined. They concluded that advanced age, smoking, postoperative epiphora, and male gender were associated with long-term failure. Patients should be informed that the rate of failure is higher in this group of patients [18].

Zenke et al. [19] and Dolmetsch et al. [20] stated that there was no significant relationship between age and EDCR success, but included all primary, congenital, and revision EDCR patients in their studies. Jae et al. [21] analyzed the effect of age on 441 EDCR patients. They did not find any significant difference between the groups in terms of anatomical success but reported that functional success was significantly lower in the older group. Mak et al. [22] evaluated the prognostic factors of 83 patients who underwent primary EDCR. In this study, he suggested that young patients had a higher failure rate, and this may be related to a higher degree of fibrosis. The unsuccessful group in this study included a total of 5 patients, which may be interpreted as an insufficient number of subjects.

Kim et al. [23] compared the success rates of only silicone tube intubation with the combination of conjunctival resection and silicone tube intubation in patients with nasolacrimal duct obstruction. It was concluded that performing resection for the relaxed plica semilunares increases the success of silicone tube intubation. They interpreted the reduction of tear meniscus height and area as the success of the resection procedure. According to this study, it may be beneficial to correct the eyelid and conjunctival problems in combination with EDCR to increase anatomical and functional success in the treatment of epiphora in elderly patients.

The reported rate of concomitant EDCR and septoplasty ranges from 11.9 to 57% [11, 24-31]. Per the literature, 39.7% of our cases were managed with a combined procedure. Koval et al. [25] postulated that as an adjunctive procedure performed to facilitate the main procedure, septoplasty does not affect EDCR results. However, some articles are reporting that sinonasal anomalies might influence the surgical results of EDCR [26, 30].

Miyake et al. [32] investigated the quality of life using Sino-Nasal Outcomes Test (SNOT)-22. They reported well tolerance of EDCR and after 30-90 days of surgery, nasal symptoms associated with quality of life did not show any decline. The concomitant performance of septoplasty in the setting of asymptomatic septal deviation did not confer any benefit in terms of symptoms of nasal obstruction.

The strength of this study is that all patients had the same surgery for NLDO treatment, and two experienced surgeons took part in the operation at the same time. Also, we excluded patients with lid abnormalities, which increase the homogeneity of our patient group in terms of epiphora etiology. None of our patients underwent surgery for the eyelid and conjunctiva.

Our results show that EDCR is an effective and reliable procedure without major complications or an incision scar that will cause cosmetic problems on the face. EDCR increases patient's quality of life in the treatment of NLDO. A careful nasal examination is imperative in NLDO. Septoplasty should be performed before EDCR in patients with septal deviation and NLDO. Our results indicate that age does not affect EDCR results in terms of anatomical and functional success.

Limitations

The relatively small size of our patient group can be a limitation to our study.

Conclusion

Our results indicate that age does not affect EDCR results in terms of anatomical and functional success. We can propose that surgeons with doubts of success in older NLDO patients can perform EDCR either alone or combined with septoplasty with similar success rates to those of younger NLDO patients. Future studies with a larger group of patients might better establish the exact relationship between age and EDCR results.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):700-704.
DOI: 10.28982/josam.817897

Research article

Journal of Surgery and Medicine
e-ISSN-2602-2079

The role of sonoelastography in the evaluation of hepatic fibrosis in pediatric patients

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Ethics Committee Approval
The study protocol was approved by the Institutional Ethics Committee (Gazi University Ethics Committee, approval study number 27/06/2012-280.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 July 28

Abstract

Background/Aim: Hepatic fibrosis is caused by excessive accumulation of collagen-containing extracellular matrix proteins in chronic liver diseases. The gold standard for determining the degree of liver fibrosis is liver biopsy, which is an invasive method with complication risks. This study aimed to evaluate the potential role of ultrasound elastography, a non-invasive method, in the assessment of hepatic fibrosis among pediatric patients.
Methods: Twenty-four pediatric (0-18 years) patients with chronic liver disease and suspected hepatic fibrosis were included in this study. All patients were evaluated with B-mode and sonoelastography using Hitachi EUB 7500 digital ultrasound equipment. The biopsy procedure was performed on all patients a week after sonoelastography. Elastographic scores of liver parenchyma were categorized into four main groups, nonfibrotic, mild, moderate, and severe fibrosis. Strain index values were calculated. The elastographic scores and mean strain index values of the liver parenchyma were correlated with their pathological diagnosis.
Results: Elastographic scores and strain index values were significant for the presence of hepatic fibrosis (P=0.001 and P=0.006 respectively). Elastography has 100% sensitivity and 83.3% specificity to distinguish hepatic fibrosis when the cut-off value of strain index is 1.03.
Conclusion: Our findings support that real-time elastography is a non-invasive method for the diagnosis and staging of hepatic fibrosis with the potential to prevent recurrent biopsy and complications.

Keywords: Liver cirrhosis, Sonoelastography, Hepatic fibrosis

How to cite: Bilgin E, Bilgin EY, Oktar SO. The role of sonoelastography in the evaluation of hepatic fibrosis in pediatric patients. J Surg Med. 2021;5(7):700-704.

Introduction

Hepatic fibrosis is caused by excessive accumulation of collagen-containing extracellular matrix proteins in chronic liver diseases. Advanced liver fibrosis may result in cirrhosis, liver failure, and portal hypertension, all of which may require liver transplantation [1]. The gold standard for determining the degree of liver fibrosis in patients with chronic hepatitis is liver biopsy [2].

The histopathological examination of the tissue sample obtained from the liver by percutaneous, transjugular, laparoscopic methods, or perioperatively determines the etiological factor that causes the pathology and the degree of liver damage. An evaluation of response to treatment is also possible with repeated biopsies. Although the percutaneous method is used most often, biopsies can be performed using transjugular, laparoscopic, and perioperative methods.

The mortality rate of percutaneous liver biopsy is 0.009%, and some minor (13.6%) and major complications (1.0%) may develop afterward. These complications include pain (30%), bleeding, temporary hypotension, perforation of the gallbladder, haemobilia, pneumothorax, pneumoperitoneum, septic shock, subphrenic abscess, intrahepatic arteriovenous fistula, and carcinoid crisis. Also, sampling errors, at least 6 to 12 hours of hospitalization, and high costs are the disadvantages of biopsy [3-5].

Many studies report that ultrasonography can predict liver cirrhosis or advanced fibrosis. In the evaluation of cirrhosis in chronic liver diseases, grayscale ultrasonography reveals findings such as changes in liver surface nodularity, blunted liver edge, and roughened parenchymal structure. It is shown in the studies that the most sensitive sonographic finding of advanced fibrosis is liver surface nodularity. In addition, in ultrasonography, liver capsule thickness, the maximum oblique diameter of the right lobe, the diameters of the main portal vein and the right and left portal veins, the thickness of the gallbladder wall, the size of the spleen, the diameter of the splenic vein and the portal vein blood flow rate are related to the degree of fibrosis [6].

Elastography is a relative tissue stiffness mapping technique. Ultrasonographic elastography (sonoelastography) is a noninvasive imaging technique that is based on the determination of the stiffness and flexibility properties of the tissues by applying repetitive pressure effect on the tissue to figure out their spatial displacement (strain). Hard tissues or tissues that differ from their surroundings in terms of elasticity (tissues formed by cancer cells in breast and prostate cancer) respond with less displacement to the change of the pressure applied than the surrounding tissues [7,8]. Displacements at each point of the texture are encoded in different colors by real-time scanners superimposed on the B-mode review. The image that appears after coding is the elastogram of the tissue. Color coding can be done in grayscale or color. For example, in color coding, colors traced from yellow to red represent soft tissues, while green and blue indicate hard tissues. The colors may differ with devices.

Materials and methods

Twenty-four patients in the pediatric age group with a pre-diagnosis of chronic liver disease who were referred to the radiology department with a biopsy request between October 2011 and October 2012 were included in this prospective cohort study. The study protocol was approved by Gazi University, Institutional Ethics Committee with the number 27/06/2012-280. The procedure was explained to all the patients and their relatives, and informed consent forms were obtained. The biopsies were performed one week after the sonoelastographic examination.

The d-value method, developed by Cohen, was used in the calculation of the effect size. According to similar academic studies that reported the d value and based on the ANOVA test, the total sample size was calculated as 24 patients with d=0.91, α=0.05 (type-1 error), 1-β =0.90 (power) using G-power version 3.1) package program.

Sonographic examinations were conducted by two radiologists in the semi-bright ultrasonography room. The imaging was performed with a digital ultrasonography device that had real-time elastography software (Hitachi EUB 7500) using a 13–8 MHz linear transducer. In all cases, after B-mode examination, elastography mode was switched and real-time elastography images were obtained through the 13–8 MHz linear transducer.

After the elastograms were obtained, the liver parenchyma and the strain of the intercostal muscles were measured and proportioned with the help of ROI. The first measurement that was adjusted to include the liver parenchyma observed on the elastogram was determined as A, and the strain value of intercostal muscles on the same elastogram was determined as B. The ratio of these two values (B/A) was considered the strain index (SI). In 16 of the 24 patients participating in the study, this value was measured and recorded at least 3 times. In the other 8 cases, the measurements could not be performed due to patient-related causes. For the evaluation of elastograms, elastography scoring was made using the information from the literature (Table 1) [9].

Table 1: Elastography scores

Score	Comment	Elastographic view of liver parenchyma
1	Soft	Uniform light green area; in favor of no fibrotic activity
2	Substantially soft	Partially blue regions in the light green area
3	Substantially hard	Light green and blue colors are mixed.
4	Hard	Mostly blue areas

Nowadays, the most widely used histopathological evaluation methods are Knodell, Modified Ishak, and Metavir staging methods [10]. Modified Ishak classification was used in our study [11]. In the evaluation made by an experienced pathologist from our hospital, cases without fibrosis were evaluated as F0. Patients with fibrous enlargement and/or short fibrous septae in the portal area were evaluated as slightly fibrotic (F1), cases with fibrous enlargement in most portal areas and cases with rare or prominent porto-portal, porto-central bridging necrosis were evaluated as moderately fibrotic (F2), and patients with the presence of rare nodules or with a diagnosis of cirrhosis in addition to prominent bridging were considered highly fibrotic (F3).

Statistical analysis

SPSS (Statistical Package for the Social Sciences) version 25.0 (IBM Corp., Armonk, NY, USA) program was used for statistical analysis of the data. Descriptive statistical methods (number, percentage, mean, median, standard deviation, etc.), the Kruskal-Wallis-H test, and the Mann-Whitney U test were used to assess the quantitative difference between the groups.

Multiple comparisons were made using Bonferroni correction subgroup analysis in groups where the difference was significant in the Kruskal-Wallis analysis. ROC analysis was used to determine the most appropriate strain index positive cut margin for hepatic fibrosis. The results were evaluated at a 95% confidence interval and *P*-value <0.05 significance level.

Results

The ages of 24 patients in this study ranged between 0 and 18 years. There were 8 females and 16 males. In histopathological analyses, 8 had no fibrotic activity (F0), 5 had mild fibrosis (F1), 9 had moderate fibrosis (F2), and 2 had advanced fibrosis (F3).

In the sonoelastography examination performed blinded to the histopathological diagnoses, the elastography scores of patients with (n=16) and without fibrosis (16) ranged between 1-3 (Figure 1) and 2-4 (Figure 2), respectively. The mean elastography scores of the non-fibrotic and fibrotic patients were 1.75 (0.707) and 2.94 (0.772), respectively. Elastography scores were significant (*P*=0.001) in showing the presence of hepatic fibrosis.

Figure 1: Liver parenchyma elastography score 1 in a nonfibrotic patient (F0)

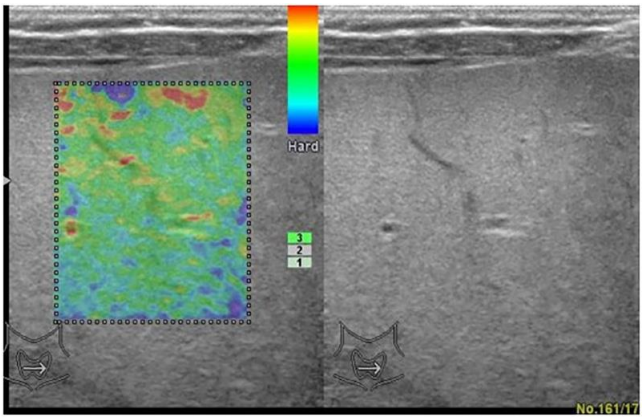
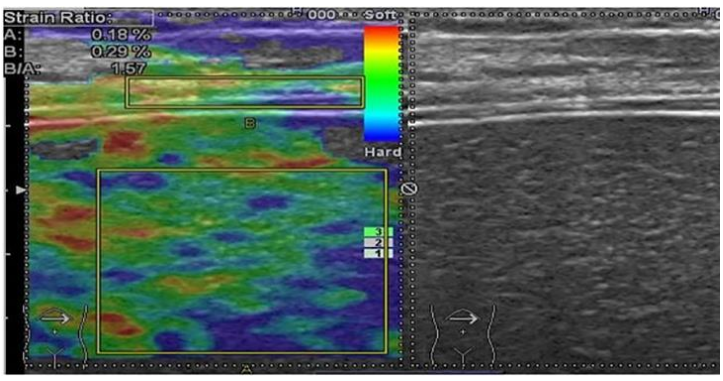


Figure 2: Liver parenchyma elastography score 3 with moderate fibrotic activity (F2)



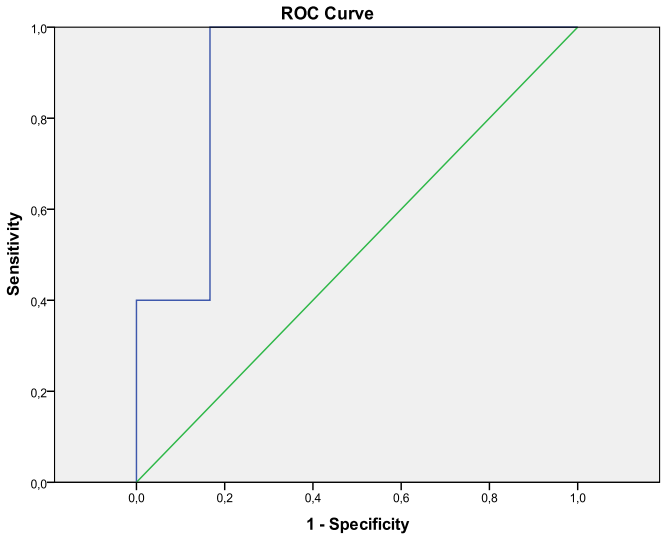
The elastography scores of patients with mild (F1), and moderate fibrosis (F2) ranged between 2-3, and 2-4, respectively, while those of all patients with advanced fibrosis (F4) were 4. When patients with moderate to advanced fibrosis were grouped, a significant difference was found between the cases with mild and moderate-advanced fibrosis (*P*=0.037). Mean strain index values of the non-fibrotic and fibrotic patients were 0.69 (0.56) and 1.76 (0.56), respectively. The mean strain index was 1.45 (0.21) in patients with mild fibrosis, and 1.88 (0.58) in patients with moderate to advanced fibrosis (Table 2). The ROC curve is presented in Figure 3. The area under the curve (AUC) was 0.92 and accordingly, the strain index had a significant diagnostic value (*P*=0.006). ROC analysis was performed with the available data, and the optimal strain index score cut-off point for hepatic fibrosis was 1.03, with 100% sensitivity, 83.3% specificity, a positive predictive value of 93.8%, and a negative predictive value of 100%.

Table 2: Distribution of mean strain ratios according to stages of hepatic fibrosis

	Elastographic score					
	n	Mean	(SD)	Range	K-W	*P*-value
Modified ISHAK Classification					14.443	0.001*
F(0) No hepatic fibrosis[a]	8	1.75	(0.71)	1-3	a vs b	0.289
F(1) Mild hepatic fibrosis[b]	5	2.20	(0.45)	2-3	a vs c	<0.001*
F(2&3) Moderate&severe fibrosis[c]	11(9+2)	3.27	(0.65)	2-4	b vs c	0.037*
	Strain index					
	n	Mean	(SD)	Range	Z	*P*-value
Hepatic fibrosis					-2.770	0.006*
No	6	0.69	(0.56)	0.2-1.7		
Yes	10	1.76	(0.56)	1.1-3.1		

* *P*<0.05, K-W: Kruskal Wallis-H Test, Z: Mann Whitney-U Test, SD: Standard Deviation

Figure 3: ROC curve for strain index values



Discussion

Hepatic fibrosis is caused by excessive accumulation of collagen-containing extracellular matrix proteins in chronic liver diseases. Advanced liver fibrosis may result in cirrhosis, liver failure, and portal hypertension, and require liver transplantation. Staging of hepatic fibrosis is important in terms of prognosis, follow-up, and treatment [12, 13].

Liver biopsy has been used for over a hundred years. Although it is the gold standard for staging hepatic fibrosis, some difficulties may arise due to the invasiveness of the procedure. The mortality rate of percutaneous liver biopsy is 0.009%, and studies are showing that some minor (13.6%) and major complications (1.0%) may develop after the liver biopsy, including pain, bleeding, temporary hypotension, perforation of the gallbladder, haemobilia, pneumothorax, pneumoperitoneum, septic shock, subphrenic abscess and intrahepatic arteriovenous fistulae. The heterogeneity of the amount of fibrosis in the right and left lobes leads to an evaluation error in approximately 10-30% of the cases. In addition, the difference in assessment among pathologists is reported as approximately 20% in studies.

Also, sampling error, at least 6 to 12 hours of hospitalization, and high costs are among its disadvantages; therefore, evaluation of fibrosis by noninvasive methods has gained importance [3, 5, 14, 15].

In the evaluation of chronic liver diseases, findings such as nodularity, blunted liver edge and roughened parenchymal structure are detected on B-mode ultrasonography. In their study with 103 chronic liver disease patients, Nishiura et al. [16] showed that these findings can be used to differentiate nonfibrotic and mildly fibrotic livers from those with moderate to advanced fibrosis. In their study with 156 chronic viral hepatitis patients, Chih-Ching Choong et al. [6] showed that the sonographically most sensitive finding of advanced fibrosis is liver surface nodularity, but these parameters are not sufficient in the diagnosis of early-stage fibrosis. Caudate lobe hypertrophy was compatible with advanced fibrosis in ultrasonography. Liver surface irregularity is an objective sign indicating cirrhosis [17, 18].

Many imaging methods are used to evaluate hepatic fibrosis and new methods continue to be developed. Sonoelastography is one of them. Elastography is a non-invasive relative tissue stiffness mapping technique that began to be used experimentally by Ophir et al. [19] in the late 1980s. It is based on the repetitive compression effect applied on the tissue to determine the spatial displacement (strain) of the tissues according to their stiffness and flexibility. Under the same force, hard tissues are less deformed and respond with less strain than soft tissues [7,8]. If there is a different hardness in the tissue during compression (stress), it can be separated from the surrounding tissue according to the strain index.

Sonoelastography methods are classified as semi-static (compression elastography) and dynamic (shear wave elastography). In compression elastography, tissue elasticity measurements can be obtained qualitatively (with color-coding) or semi-quantitatively (with strain index measurement). Shear wave elastography uses the acoustic radiation force of the ultrasound wave to push the tissue, and no manual compression is required.

The first study on the diagnosis and staging of hepatic fibrosis was published in 2007 by Friedrich-Rust et al. [20]. This study included 79 patients with chronic hepatitis and 20 healthy participants. Elastography scores were obtained by a computer program with the images obtained in this study. When these scores were combined with laboratory results, the area under the curve for the diagnosis of prominent fibrosis was 0.93 according to the ROC analysis.

In the study of Morikawa et al. [21] including 101 patients diagnosed with hepatitis C and 10 healthy participants, the sensitivity and specificity of sonoelastography in the diagnosis of hepatic fibrosis were 84.1% and 82.7%, respectively. Fujimoto et al. [7] performed a sonoelastography study with 43 chronic hepatitis C patients and showed that the degree of fibrosis increased with the elastography score.

In a study conducted on 111 patients who underwent biopsy for rejection after liver transplantation, the patients were evaluated by shear wave elastography and in patients with significant fibrosis (F2, F3, or F4 according to METAVIR classification), the average elastography value was above 1.76. The specificity and sensitivity of elastography in fibrosis classification were 79% and 77%, respectively. The authors concluded that in the elastography examination performed after liver transplantation, patients with an elastography value<1.76 do not have significant fibrosis and the biopsy procedure can be postponed [22].

A meta-analysis assessed 528 studies about shear wave elastography (SWE) and showed that SWE has high sensitivity and specificity for detecting and staging hepatic fibrosis in patients with ≥F2 Metavir-score. As a non-invasive procedure, elastography is highly suitable for detecting significant fibrosis, and therapeutic outcomes after surgery, e.g., transplantation [23].

In addition, MR elastography, which can be used to demonstrate diffuse liver diseases, investigate fibrosis, differentiate malignant and benign liver masses, and evaluate the response to treatment, has begun to be included in routine workup as a non-invasive diagnostic method [24].

We referred to the literature in elastography scoring. Elastography scores of 1, 2, 3, and 4 define normal liver parenchyma, mild, moderate, and advanced fibrosis, respectively. The elastography score was not 1 in any of the cases with fibrosis and ranged between 1-3 in 8 cases without fibrosis. In only one non-fibrotic case, the elastography score was 3. Elastography score was significant in detecting hepatic fibrosis.

Due to the small number of cases in our study, cases with moderate and advanced fibrosis were evaluated in the same group. In the statistical study, although significant results were obtained in the separation of mild and moderate-advanced fibrosis in sonoelastography, no significant results were found in the distinction of nonfibrotic cases and mild fibrosis.

In our study, strain index values, which we consider to be more objective than the elastography score, were also used. When minimum strain index cut-off was 1.03, its sensitivity and specificity in distinguishing hepatic fibrosis were 100% and 83.3%, respectively, with positive and negative predictive values of 90.9%, and 100%, respectively, and an area under the curve of 0.9.

Limitations

Our study has some limitations, the most prominent ones including its single-center nature, and the low number of cases. We had to group patients with moderate and severe fibrosis. Long-term follow-up, which could not be performed in this study, should provide more information about the effectiveness of sonoelastography in hepatic fibrosis staging.

Conclusion

Although biopsy is the gold standard in the diagnosis and staging of hepatic fibrosis, we have the impression that sonoelastography is a noninvasive method that can contribute to the diagnosis and staging of hepatic fibrosis in the pediatric age group. Therefore, real-time sonoelastography can reduce biopsy repetitions and related possible complications. We think that this will help clinicians in the diagnosis and follow-up of hepatic fibrosis.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):705-709.
DOI: 10.28982/josam.935324

Journal of Surgery and Medicine
e-ISSN-2602-2079

Color Doppler ultrasonography findings of vertebral arteries: A correlation with 64-slice CTA

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Ethics Committee Approval
The study was approved by the Ethical Committee of Ankara Research and Training Hospital (2010/385-3162).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 July 28

Abstract

Background/Aim: Although normal Color Doppler US (CDU) findings of the carotid system were described by many studies, normal findings of the vertebral system have not been studied extensively. This study aimed to evaluate vertebral artery CDU hemodynamic and morphologic findings in patients with normal vertebral arteries (VAs) on 64-slice Computed Tomography Angiography (CTA) and investigate the correlation between RDUS and CTA in evaluating the VA anatomy.
Methods: In this retrospective cohort analysis, the patients referred to our radiology department for CTA who had normal VA anatomy underwent a CDU for visualization of the orifice and segments (V1-V2) of the VA. Peak systolic velocity (PSV), and end-diastolic velocity (EDV) were measured in V1 while PSV, EDV were measured and resistive index and FV were calculated in V2. The presence of hypoplasia and dominance were noted.
Results: A total of 77 patients who had normal vertebral arteries on CTA were included in this study. CDU findings were highly consistent with multislice CTA findings regarding the measurement of VA diameter (ICC=0.856, ICC=0.830), hypoplasia (kappa=0.488), and dominance (kappa=0.752). No consistency was found between the two modalities in the visualization of the orifice and V1 segment of the VAs on both sides. CTA was able to show the orifice and the V1 segment in all cases, while the success rate was lower in CDU, especially in terms of visualizing the orifice of VA. VA FV was not significantly different between the patients with and without vertebrobasilar insufficiency (P=0.300).
Conclusion: CDU findings were consistent with 64-slice CTA findings in VA diameter measurement and the diagnosis of hypoplasia and dominance. However, CTA is more successful than RDUS in evaluating the vertebral artery orifice and V1 segment, the most common sites of atherosclerotic involvement. There was no significant difference between the patients with and without VBI symptoms in evaluating FV.

Keywords: Vertebral artery, Doppler ultrasound, Computed tomography angiography, Vertebrobasilar insufficiency

How to cite: Yılmaz BK, Ergun E, Koşar PN, Karataş BŞ, Turgut AT. Color Doppler ultrasonography findings of vertebral arteries: A correlation with 64-slice CTA. J Surg Med. 2021;5(7):705-709.

Introduction

Vertebral arteries (VA) were not paid as much attention as the carotid arteries, possibly due to their anatomic location, which limits their surgical accessibility. However, in the last decade, the treatment of the VA has improved, partly resulting from advances in balloon angioplasty or stenting techniques as well as improvements in new generation ultrasound imaging [1, 2].

Intra-arterial digital subtraction angiography (DSA) is still the standard of choice in radiological diagnosis and assessment of vascular lesions located above the aortic arch and proximal to the cranium. Nevertheless, DSA has its complications, such as neurological, non-neurological (4%), and persistent neurological deficits (0.07-0.5%) [3-5]. Thus, DSA does not seem to be suitable as a screening tool [6]. Color Doppler ultrasonography (CDU) and computed tomography angiography (CTA) are used as alternative imaging modalities to DSA [7]. Since CDU is repeatable, easy to perform, and cost-effective, it has been widely used in the diagnosis of obstructive diseases of the cerebral vessels [2, 8]. CTA has increasingly been used in the diagnosis of VA pathologies and anatomical variations as it provides important information regarding the structure and pathology of V3 and V4 segments, which are poorly viewed by CDU [9].

The diagnosis of vertebrobasilar insufficiency (VBI) is a clinical challenge because its manifestations are subjective and difficult to quantify [2]. While some authors suggest that symptoms are caused by thromboembolism, others advocate that it results from a hemodynamic phenomenon due to the reduction of net blood flow velocity in VAs [10]. Clinically, it frequently presents with symptoms such as vertigo, dysarthria, and sometimes ataxia, and hemiparesis [11]. Flow volume (FV) is an important parameter for the evaluation of brain perfusion and a noninvasive assessment of FV, which is possible with the CDU.

The purpose of this study was to evaluate diameter, flow volume (FV), and mean velocities of the normal VA verified by computed tomography angiography (CTA) and determine a threshold value for the FV.

Materials and methods

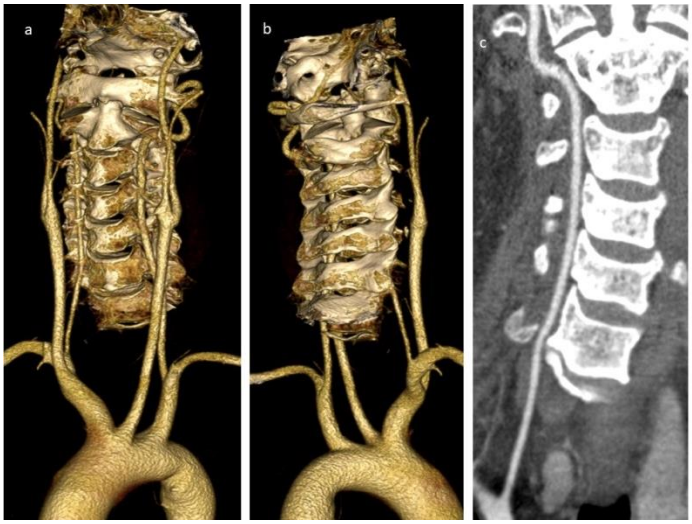
Between August 2009 and October 2010, 135 consecutive patients with a suspected transient ischemic attack, cerebrovascular disease, or VBI were referred to our Radiology Department for CTA to evaluate the vertebral arteries. Patients with bilateral normal vertebral arteries were included in the study. Normal VA was defined as one with homogenous contrast filling and no vessel wall abnormalities, stenosis/occlusion in the CTA.

Twenty-nine patients were excluded from the study because of the presence of vertebral artery stenosis or occlusion. Twenty-five patients with higher than 50% stenosis in the anterior circulation and four patients with bilateral severe ICA hypoplasia were excluded since these conditions might affect VA flow parameters. Four patients in whom CDU was not completed due to non-cooperation were also excluded. The final study group of this retrospective cohort study included a total of 77 patients. Power analysis revealed a minimum number of patients of $n = 70$ to obtain a power of 95 % for an alpha significance level of 0.05.

The study was conducted per the Strobe Cohort guideline. Of the forty cases, all had clinical signs of VBI (such as vertigo, drop attacks, tinnitus, and ataxia).

CTA was performed using a 64-slice CT scanner (Aqullion 64, Toshiba, Tokyo, Japan) with the following parameters: mAs:440, kV:120, slice thickness:3 mm, 512x512, FOV:320 mm, pitch 0.641 for all patients. Before the procedure, a 20 Gauge venous line was introduced into the antecubital vein and 75 ml of 350 mg/ml non-ionic contrast media was injected through the cannula followed by 20 ml of physiologic saline flushing. The area between the aortic arch and the Willis polygon was screened caudo-cranially. Optimal timing for scanning was decided manually by starting the image acquisition as soon as the contrast medium arrived in the internal carotid artery (ICA) at the level of 1-2 cervical vertebrae. Subsequently, CTA raw data were transformed to a remote workstation (Vitrea 2; Vital Images Inc., Minnetonka, Minn. USA) to achieve further processing of the images (Figures 1 a, b, c).

Figure 1: a, b, c: Normal CTA, 3D VR (volume rendering) AP, PA oblique and coronal CPR (curved planer reformate) images of vertebral artery

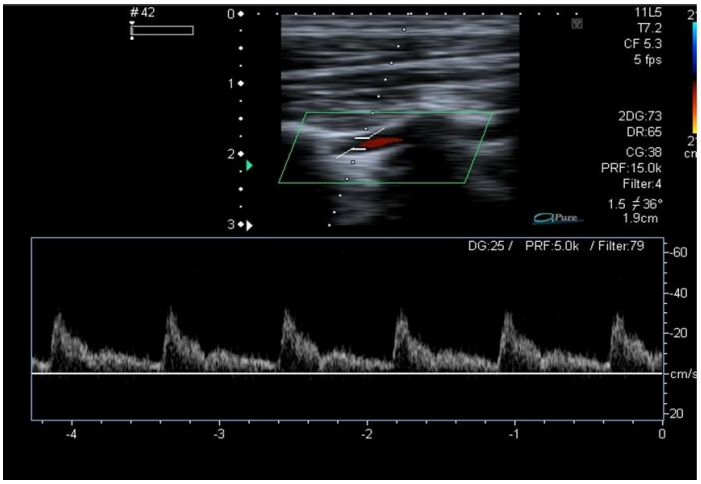


CDU was performed by an experienced sonographer with more than 4 years of experience using a device with adequate standards (SA-660A; Toshiba, Tokyo, Japan) equipped with a 6-7.5 Mhz linear transducer. Patients were in the supine position; their necks were slightly extended, and their faces were positioned opposite the examined side. First, the orifice of the VA and V1 and V2 segments were evaluated. Next, the orifice of the VA and V1 were visualized in B-mode. Then, flow dynamics were measured in color and spectral modes. Peak systolic velocity (PSV) and end-diastolic velocity (EDV) were measured through the V1 segment where its course is most parallel to the cervical axis.

V2 lumen measurements were performed at the C5-C6 level between the two intimal layers vertically to the longitudinal axis of VA. The presence of hypoplasia and dominance were noted. PSV, EDV, resistive index (RI), and FV were calculated. The viewability of the orifice of the VA and V1 was noted. Spectral sampling interval was placed centrally to the vessel and Doppler angle to lie between 30-60 degrees. All measurements were performed three times and mean values were calculated (Figure 2). CDU examination and CTA interpretation were

performed by two different radiologists who were blinded to each other's results.

Figure 2: Normal Doppler spectral pattern of vertebral artery



VA hypoplasia was defined as the presence of an artery lumen diameter of less than 2 mm. RI was calculated using the following formula: PSV- EDV/PSV. All analyses were performed for both vertebral arteries in each patient. The diameter was expressed as mm, flow rates as cm/sec, and blood flow volume as ml/min.

Ethics approval

The study was approved by the Ethics Committee of Ankara Research and Training Hospital (2010/ 385-3162) and conducted following the principles of the Helsinki Declaration.

Statistical analysis

All statistical analyses were performed using SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA)

Continuous variables were expressed as mean (standard deviation) and categorical variables, as percentages. Independent samples t-test and Mann Whitney test were used for comparison of CDU parameters between genders. Independent samples t-test was used for comparison of CDU parameters between subjects with and without VBI. For assessment of the consistency between CTA and CDU findings, the kappa test was used for dominance and hypoplasia, the ICC test (intra-class correlation coefficient test) was used for diameter, and the McNemar test was used for viewability of the orifice of the VA and V1. Differences were considered significant when $P<0.05$.

Results

A total of 34 males (44.2%) and 43 (55.8%) females with a mean age of 53.6 (13.5) years (range: 19-87 years) were included in this study.

In CDU, the mean diameter of the VA was 3.4 (0.6) (range 1.8-5.0) mm on the right and 3.7 (0.7) (range 2.1-6) mm on the left, whereas in CTA, the mean diameter of the VA was 3.6 (0.6) mm on the right and 3.7(0.7) mm on the left. Diameter measurements in CDU were significantly consistent with those in CTA (ICC=0.856, ICC=0.830). Evaluation of dominance by CDU and CTA are presented in Table 1. CDU findings were significantly consistent with those of CTA (kappa=0.752).

Table 1: Number and percentage of right, left dominance, or co-dominance number according to CDU and CTA

	Right (n, %)	Left (n, %)	Codominant (n, %)
CDUS	30 (38.9%)	43 (55.8%)	3 (5.1%)
CTA	34 (42.8%)	42 (54.5%)	1 (2.5%)

CDU: Color Doppler ultrasonography, CTA: computed tomography angiography

Hypoplasia of the vertebral artery was present in one case (1.2%) according to CDU and in three cases (3.8%) according to CTA. CDU and CTA findings were significantly consistent (kappa=0.488). In CDU, the mean diameter of the right VA and FV of the left VA were significantly higher in males compared to females ($P=0.007$, $P=0.028$).

For the right and left VAs, the CDU findings were not consistent with those of CTA concerning the viewability of the orifice of the VA ($P=0$ for both right and left) and V1 segment ($P=0.01$, $P=0.06$ for right and left respectively).

The orifice of the VA and the V1 segment could be visualized by CTA in all cases, whereas the success of CDU was lower (Tables 2, 3). Table 4 shows the level and percentage of the entrance of the VAs to the transverse foramina. Table 5 shows the diameter, FV, and CDU velocity parameters in right and left vertebral arteries. One patient (1.3%) had left VA originating from the arcus aorta and two patients had duplicated left V1 VA. Neither variation was detected by CDU.

Table 2: Visualization rates of the VA orifice by CDU and CTA

Side	Number of patients visualized on CDU	CDU percent	Number of patients visualized on CTA	CTA percent
Right	53	68.8%	77	100%
Left	41	53.2%	77	100%

CDU: Color Doppler ultrasonography, CTA: computed tomography angiography, VA: vertebral artery

Table 3: Visualization rates of the V1 for right and left VA by CDU and CTA

Side	Number of cases visualized on CDU	Percent	Number of patients visualized on CTA	CTA percent
Right	66	85.7%	77	100%
Left	65	84.7%	77	100%

CDU: Color Doppler ultrasonography, CTA: computed tomography angiography, VA: vertebral artery

Table 4: Entrance level of VA to transverse foramina

	Number of cases	%
C6	144	93.5%
C5	9	5.8%
C4	1	0.6%
Total	154	100%

VA: vertebral artery

Table 5: Diameter, flow volume, and Doppler velocity parameters of normal VA on CTA on the right and left sides

	Right	Left
Diameter	3.4 (0.6) (1.8-5.0)	3.7 (0.7) (2.1-6.0)
Flow volume	78.6 (49.4) (10-310)	97.6 (53.6) (20-260)
V2 PSV	24.3 (10.9) (8.0-83.0)	24.2 (9.4) (6.0-63.0)
V2 EDV	8.9 (3.8) (3.0-24.0)	8.9 (3.6) (4-25)
RI	0.63 (0.070) (0.46-0.83)	0.63 (0.080) (0.43-0.81)
V1 PSV	29.2 (11.1) (13.0-65.0)	30.5 (9.2) (10.0-53.0)
V1 EDV	10.5 (6.7) (4.0-46.0)	11.0 (3.9) (4.0-21.0)
V2/V1 PSV	0.88 (0.38) (0.36-2.86)	0.85 (0.44) (0.24-3.50)
V2/V1 EDV	0.99 (0.54) (0.22-3.29)	0.90 (0.45) (0.28-3.57)

VA: vertebral artery, CTA: computed tomography angiography, PSV: peak systolic velocity; EDV: end-diastolic velocity, RI: resistive index

There were 40 cases (51.9%) with VBI symptoms (such as vertigo, drop attacks, tinnitus, and ataxia) while symptoms were associated with the anterior system (the patients which were evaluated for carotid artery stenosis) in 37 of cases (48.1%).

No significant difference was found between the patients with and without VBI symptoms regarding the FV ($P=0.300$).

Discussion

DSA is still the gold standard for the assessment of vertebrobasilar system pathologies. However, its elevated cost and possible complications have led to the development of novel non-invasive imaging techniques as screening tools. Being the first-line assessment tool of the VA, CDU has several advantages: It is a non-invasive, bedside tool that is cost-effective, and easy to perform. Its disadvantages in the

assessment of VA cannot be standardized since the method is highly user-dependent and VA itself causes potential challenges due to its anatomic properties [12-15]. CDU provides a rough assessment regarding the hemodynamics of VA and posterior cerebral circulation. However, ipsilateral posterior circulation is evaluated indirectly. Therefore, a substantial number of pathologies may be overlooked [2, 12].

Multidimensional CTA technology has marked an era in CTA and allowed the visualization of the whole carotid and VA vascularity, including intracranial segments. CTA is preferred in the diagnosis of VA diseases for two reasons. First, atherosclerotic changes in the origin of the vessel may be easily visualized. Second, it allows the evaluation of the vessel wall adjacent to the lumen [10]. On the other hand, ionizing radiation and nephrotoxic contrast medium use are among the major disadvantages of CTA.

Although there have been several studies providing knowledge and normal values regarding the VA, few studies have sought to determine whether there is a correlation between CTA and CDU findings in the diagnosis of VA disease. Pucher et al. [16] reported that CDU was moderately correlated with CTA and had significant clinical limitations.

In our study, CDU findings were consistent with those of CTA regarding the right and left VA diameter measurements, determination of hypoplasia, and dominance (ICC=0.842, ICC=0,799 kappa=0.788, kappa=0.7693). To the best of our knowledge, such a relationship has not yet been investigated in the literature.

In our study, the left VA was the dominant side in 54-55% of the cases. Zwiebel et al. [17] reported that left VA dominance was more common than right VA dominance (73%). However, there have been other studies reporting co-dominance of VAs or right VA dominance [18, 19].

The reported thresholds for VA hypoplasia range between 2 mm-3 mm [18-21]. The frequency of VA hypoplasia in a healthy population ranges between 2-9%. In our study, 2 mm was accepted as the threshold for VA hypoplasia. We found that hypoplasia was present in 1.2% and 3.8% of patients according to CDU and CTA evaluation, respectively. The frequency of hypoplasia in CTA was consistent with that reported in the literature.

In our study, in CDU, the diameter of the right VA was significantly larger and FV was significantly higher in males compared to females. While some studies report that total VA FV is lower in females compared to males, other studies suggest otherwise [22].

Atherosclerosis is the most common VA pathology throughout its pre-cranial course and most seen in the first segment, particularly in the orifice. Thus, accurate visualization of the origin is crucial. Left VA lies deeper than the subclavian artery in contrast to the right VA and its origin is located more medially. In addition, although the VA rarely originates directly from the aortic arch on the right side, its origin is on the arch in up to 8% of cases on the left side [23, 24]. Therefore, visualization of the left VA origin may be harder compared to the right side [25]. In our study, the CDU visualization rate of the right VA orifice was higher than left (68.8% and 53.2% for the right and left, respectively). In previous studies, the visualization rate of the orifice was highly variable and ranged between 60-94% on the right side and 59-76% on the left side [1, 9, 18, 19, 26-28]. However, CTA visualization of the orifice of both VA and V1 segments was achieved in all cases, suggesting the superiority of CTA.

Normal hemodynamic features of VA were defined in several studies and different results were reported [18-20, 29-31]. Sheel et al. [32] reported that the VA flow rate was above 40 in healthy individuals. However, Benedict and Jackson [10] suggested that a flow rate of 20 cm/sec was normal and <20 cm/sec was insufficient. In our study, the mean PSV of V2 was 23.7 (8.8) and the mean EDV was 8.7(3.5) in the right VA, while they were 23.0 (7.3) and 8.5 (2.9) on the left VA, respectively. In our study, PSV values were lower than the literature, while EDV values were similar.

The threshold value for insufficiency is 200 ml/min in some studies. Benedict et al. reported that flow volumes were below 200 ml/min in patients with VBI. Kafadar et al. [6] reported that they found a flow volume of <200 ml/min in 55% of their patients. In the study of Kızılkılıç et al. [2], the FV of the VAs were below 200 mL/min in 81.7% of the patients who did not have clinical manifestations of VBI and in 71% of the patients who did. We found that FV did not significantly differ between patients with or without clinical signs of VBI, similar to these authors. This result supports the claim that FV should not be regarded as the sole criterion for diagnosis of VBI since clinical symptoms of VBI might emerge even when the VA FV is within the normal range [2, 8]. Therefore, additional parameters should also be added to the routine CDU examination of patients with a clinical suspicion for VBI. However, in contrast to the carotid system, a CDU examination of the vertebral arteries has not been standardized because threshold values for velocity have not been well defined in large prospective studies, although studies that report thresholds for significant stenosis exist [16, 33].

Limitations

The main limitation of our study was that although our patients had normal vertebral arteries on CTA, they were not completely healthy and had neurological complaints. Second, we did not assess interobserver variability for the study. We performed 3 measurements to decrease measurement mistakes and the mean was calculated.

To the best of our knowledge, there has been no study investigating whether CDU findings were consistent with those of CTA for visualization of the VA orifice and V1 segment, diameter measurements, determination of hypoplasia, and dominance, which constitutes the strength of our study.

Conclusion

Our study provides important data regarding the morphologic and hemodynamic characteristics of 154 vertebral arteries of 77 patients with normal VA anatomies on CTA. We think that our results would contribute to the identification of normal ranges of VA in the Turkish population and help to make a more reliable diagnosis of VA pathologies.

CDU findings are consistent with those of CTA for the determination of VA diameter and identification of hypoplasia or dominance. However, CDU has significant limitations in visualizing the orifice of the VA, which is the most common site

of atherosclerosis. CTA enables visualization of the vertebral artery through its entire course including its orifice and V4 segment (which is impossible to visualize with CDU); hence, it is superior to the CDU in revealing anatomical details, variations, and anomalies as well as pathological processes.

Acknowledgments

I would like to thank Dr. Cennet Şahin who supported me during the preparation of this article.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):710-714.
DOI: 10.28982/josam.938792

Journal of Surgery and Medicine
e-ISSN=2602-2079

Approach to difficult urethral catheterizations in male patients during the Covid-19 pandemic

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Ethics Committee Approval
The ethics committee approval was obtained from Erzurum Regional Training and Research Hospital (Approval number: 2021/03-42). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 July 28

Abstract

Background/Aim: Difficult urethral catheterization (DUC) is a frequent urological emergency in daily practice. Anticoagulant and antiaggregant drugs, included in the treatment protocols for COVID-19, tend to increase the risk of possible complications of alternative interventions, such as cystoscopy and suprapubic percutaneous cystostomy. Therefore, a less invasive method is needed in patients with DUC. This study aims to evaluate the results of Foley catheter insertion and urethral dilatation over a hydrophilic guidewire in patients with DUC.

Methods: A total of 23 male patients who visited the urology outpatient clinic or were referred due to urinary retention or inability to place a Foley catheter in the last 8 months were included in this case series. The patient charts were evaluated retrospectively. After the hydrophilic guidewire, blindly advanced from the urethral meatus under sterile conditions, reached the bladder, a Foley catheter was placed over the guidewire. In cases of urethral stricture, dilatation was performed over the guidewire with the help of hydrophilic S-Curve dilators, and a Foley catheter of suitable diameter was placed.

Results: A Foley catheter was successfully placed in 22 out of 23 patients. Urethral dilatation was performed in 13 patients due to urethral stricture, and a transurethral Foley catheter was placed in the other 10 patients without the need for dilatation. Although most of our patients (17 of 23 patients) were receiving anticoagulant or antiaggregant treatment during the procedure, no significant hemorrhagic complications occurred. A Foley catheter could not be placed in one patient with this technique; a percutaneous cystostomy catheter was placed instead.

Conclusion: The results of this study, conducted during the COVID-19 pandemic, show that our technique is safe and successful. We believe that our technique will be useful in preventing additional surgical interventions due to complications, especially during this pandemic.

Keywords: Difficult urethral catheterization, Hydrophilic guidewire, Urethral dilatation, COVID-19

How to cite: Koçakgöl H. Approach to difficult urethral catheterizations in male patients during the Covid-19 pandemic. J Surg Med. 2021;5(7):710-714.

Introduction

Difficult urethral catheterization in male patients is one of the most common urological emergencies. The main barrier pathologies are urethral stricture, benign prostatic hyperplasia, prostate cancer, bladder neck contracture, a false passage, and phimosis. In some cases, the urethral passage is normal; however, due to the anxiety of the patients and tight external sphincters, a catheter may not be placed [1]. During the COVID-19 pandemic, health care providers were advised to postpone surgical interventions and reduce anesthetic procedures, except for life-threatening conditions [2, 3]. In our case, we chose a less invasive method to reduce the need for additional surgery in difficult urethral catheterizations and studied its outcomes. The technique involved advancing a Foley catheter or performing urethral dilation over a transurethral, blindly advanced hydrophilic guidewire, which is less invasive compared to suprapubic cystostomy and endoscopic transurethral catheterization.

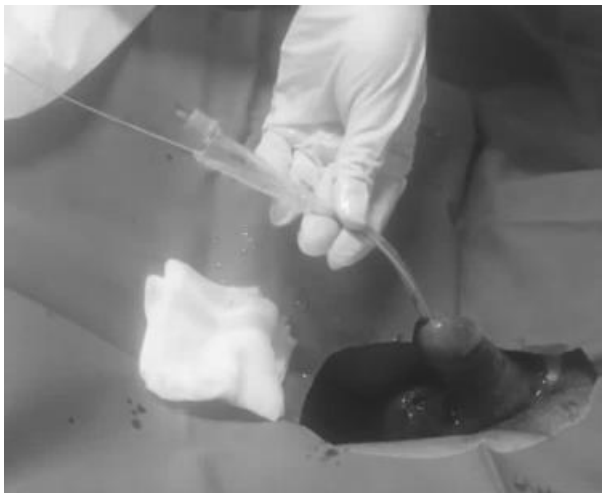
Materials and methods

The ethics committee approval was obtained from Erzurum Regional Training and Research Hospital (Approval number: 2021/03-42). The data of patients who were referred to the urology department of the University of Health Sciences, Erzurum Regional Training and Research Hospital because of an inability to place a transurethral catheter within 8 months were retrospectively reviewed. All male patients with or without COVID-19 disease who were catheterized with the help of a hydrophilic guidewire were included in the study. Patients who could not be catheterized over the guidewire at the penile urethra level and needed dilatation were considered to have a urethral stricture. Patients in whom a Foley catheter balloon was inflated in the urethra before being referred to us, who had undergone repeated transurethral catheterization attempts and underwent catheterization with the help of a hydrophilic guidewire without dilatation were considered to have a false passage. Retrograde urography or urethro-cystoscopy was not performed for diagnosis due to pandemic conditions.

Technique

First, anamnesis was obtained from the patient to analyze the etiology. Antisepsis was achieved with betadine in the genital and suprapubic areas. A sterile cover with a hole was placed so that the penis was exposed. To provide local anesthesia, we applied a lubricating gel containing 2% lidocaine to the urethra and waited for 5 minutes. A 12-16 Fr (French) Foley catheter was advanced gently through the urethra. If catheterization failed, the soft end of a sterile hydrophilic guidewire wetted with saline was blindly advanced through the urethra. The open passage in the urethra was searched for by moving the guidewire back and forth at the point it was stuck. When necessary, a gel was applied from the urethral meatus, and the procedure was repeated. In cases where there was doubt about the guidewire's placement, ultrasonography was used to check whether it was in the bladder. Then, the 12 Fr or 14 Fr Foley catheter was cut slightly, protecting the balloon, and the probe canal was exposed from the tip. Because the Foley catheter was cut slightly from the tip, the rounded, non-traumatic structure of the probe tip was preserved. The Foley catheter was then advanced into the bladder over the guidewire (Figure 1). When the catheter could move easily, the guidewire was taken out. After urinary output was observed, the procedure was terminated by inflating the Foley catheter in the bladder.

Figure 1: Foley catheter is advanced into the bladder over the guidewire



In cases where the Foley catheter could not be passed over the guidewire, after making sure that the guidewire reached the bladder, it was advanced approximately 30-40 cm further to make a few turns within the bladder. This was done to prevent possible bladder traumas during the dilatation procedure. First, an 8 Fr feeding catheter or 8 Fr Cook® hydrophilic S-Curve dilator was advanced into the bladder over the guidewire. When the catheter reached the bladder, it was taken out to continue an upper dilatation. The guidewire was then examined for urine droplets, as was done in the nephrostomy procedure. In suspicious cases or the absence of urine droplets, suprapubic ultrasonography was used to check whether the guidewire was in the bladder. Hydrophilic S-Curve dilators were used at 2 Fr intervals for the dilatation process (Figure 2). Starting with an 8 Fr or a 10 Fr S-Curve dilator, a stricture in the urethra was dilated up to 14-18 Fr according to the patient's tolerance to pain. During the dilatation or while the catheter was being advanced over the guidewire, the assisting healthcare personnel was asked to hold the distal end of the guidewire while paying attention to sterile conditions. During the dilatation procedure, utmost care was taken not to migrate the guidewire out. Depending on the dilatation level, one of the Foley catheters, up to 12-16 Fr, was advanced into the bladder over the guidewire by cutting the ends. The catheter, which was advanced without significant resistance to the bladder, was kept in the bladder, the guidewire was taken out and urine output was checked. After making sure that the catheter was in the bladder, the catheter balloon was inflated.

Figure 2: S- Curve urethral dilators

Results

Twenty-three male patients who underwent transurethral catheterization with the aid of a hydrophilic guidewire were included in the study. The average age of the patients was 76.4 years. Five were from the urology outpatient clinic, 9 patients were referred from the intensive care unit, 4 were from the inpatient clinic, and the remaining 5 were from the emergency outpatient clinic. Eight patients received treatment for COVID-19, all of which received anticoagulant/antiaggregants, in addition to 9 of the 15 non-COVID-19 patients (Table 1). A transurethral Foley catheter was successfully placed in 22 of the 23 patients (95.6%). In 13 of the patients who had a Foley catheter successfully placed, the catheter could not be advanced on the initial attempt over the guidewire starting distally from the bulbo-membranous urethra (BMU). In these patients, urethral dilatation was performed before the placement of the Foley catheter. Although there was mild urethrorrhagia during dilatation in these patients, it resolved with the possible tampon effect of the catheter immediately after the Foley catheter was placed. In 3 of the other 10 patients, a catheter had been inflated in the urethra before they were referred. In patients presenting with false passage and urethrorrhagia, the correct path was found with the guidewire and the Foley catheter was successfully placed. In 7 patients in which the Foley catheter did not pass the bulbomembranous urethra, the catheter was placed successfully without dilatation. These patients were thought to have false urethral passage or prostatomegaly. However, an endoscopic procedure could not be performed on these patients for differential diagnosis due to the pandemic conditions.

Table 1: The demographic and clinical features of the patients

No	Age	Department	Clinical Scenario	Antiaggregant/ Anticoagulant	*Covid 19	*Success
1	74	Emergency Outpatient Clinic	Urethral Stricture	Acetylsalicylic acid + clopidogrel	-	+
2	78	Intensive Care Unit	Urethral Stricture	Enoxaparin sodium	+	+
3	80	Emergency Outpatient Clinic	Urethral Stricture	Rivaroxaban	-	+
4	78	Intensive Care Unit	Urethral Stricture	Acetylsalicylic acid + clopidogrel	-	+
5	82	Intensive Care Unit	False passage	Acetylsalicylic acid	-	+
6	82	Intensive Care Unit	Urethral Stricture	Acetylsalicylic acid	+	+
7	80	Inpatient Clinic	Prostatomegaly/ False passage	-	-	+
8	75	Intensive Care Unit	Prostatomegaly/ False passage	Acetylsalicylic acid	+	+
9	74	Emergency Outpatient Clinic	Urethral Stricture	Enoxaparin sodium	+	+
10	66	Inpatient Clinic	Urethral Stricture	-	-	+
11	79	Inpatient Clinic	Urethral Stricture	Acetylsalicylic acid + Enoxaparin sodium	-	+
12	83	Urology Outpatient Clinic	Urethral Stricture	-	-	+
13	64	Emergency Outpatient Clinic	Prostatomegaly/ False passage	-	-	-
14	75	Urology Outpatient Clinic	Prostatomegaly/ False passage	-	-	+
15	77	Urology Outpatient Clinic	Prostatomegaly/ False passage	Acetylsalicylic acid	-	+
16	82	Urology Outpatient Clinic	Urethral Stricture	-	-	+
17	80	Urology Outpatient Clinic	Urethral Stricture	Rivaroxaban	-	+
18	61	Intensive Care Unit	Urethral Stricture	Enoxaparin sodium	+	+
19	79	Intensive Care Unit	Prostatomegaly/ False passage	Acetylsalicylic acid + enoxaparin sodium	+	+
20	79	Inpatient Clinic	False passage	Enoxaparin sodium	+	+
21	88	Intensive Care Unit	Prostatomegaly/ False passage	Acetylsalicylic acid + enoxaparin sodium	+	+
22	78	Emergency Outpatient Clinic	Urethral Stricture	Acetylsalicylic acid	-	+
23	65	Intensive Care Unit	False Passage	Clopidogrel + enoxaparin sodium	-	+

* (+) used for yes, (-) used for no

No complications developed in our patients, except for the insignificant temporary urethrorrhagia that developed in those with urethral strictures. The technique was unsuccessful in 1 patient. In this patient, no catheter or guidewire could pass from the posterior urethra. An endoscopic procedure for diagnosis could not be performed due to the patient's comorbidities and pandemic conditions. A percutaneous cystostomy catheter was placed.

Discussion

Foley catheter insertion into the bladder is a common procedure that is used to monitor urine output, in severe micturition difficulty or complete urinary retention. It is sometimes not possible to place a transurethral Foley catheter on the initial attempt. The failure to place a Foley catheter is a challenging condition that disturbs the patient and the physician and often needs to be solved immediately. It is frequently encountered by urologists in their daily work [1]. Percutaneous cystostomy catheterization, which is frequently used in daily urology practice, is more invasive and can lead to serious complications, such as hematuria, hemorrhage due to perivesical tissue injuries, peritoneum, rectum, bowel injury, and ileus [4].

The COVID-19 virus, which was first detected in Wuhan, China, in December 2019, soon turned into a global pandemic, one that severely affected our country as well. Our hospital has taken a central responsibility in combating this disease from the moment it began to spread in our city. This pandemic, which has caused us to reconsider our habits in all areas, has made it necessary for us to renew our approaches in daily urological procedures. The 2020 European Urology guidelines include recommendations for the COVID-19 pandemic period. These guidelines classified patients into four categories, and it was recommended that surgical interventions be delayed for up to 6 months in non-life-threatening situations [3].

Due to the prothrombotic events observed at a high rate in COVID-19 patients, anticoagulant and antiaggregant agents were included in treatment protocols since the beginning of the pandemic [5]. However, using agents that can cause bleeding diathesis may increase the risk of hematuria or hemorrhage in adjacent tissues during an invasive procedure such as a percutaneous suprapubic cystostomy [4]. Depending on the types of complications that develop, an additional surgical procedure may be required under anesthesia, which may cause additional risks for both the patient and the team involved in the procedure [6]. In our study, all COVID-19 patients and 10 (66.6%) of the other 15 patients were receiving antiaggregant or anticoagulant treatment. Eight (61.5%) of the 13 patients who underwent urethral dilatation were receiving anticoagulant or antiaggregant treatment. Despite the high rate of anticoagulant and antiaggregant treatment in our study, no major hemorrhage complications developed; therefore, none of our patients required additional surgery.

Table 2: Literature studies related the difficult urethral catheterization

Author/year	Clinical Scenario	Abstract, method, and technique of the study	Success rate (%)
Krikler et al. 1989 [8]	Difficult urethral catheterization	After accessing the bladder with a flexible cystoscope, the guidewire is pushed into the bladder through the cystoscope. After the cystoscope is removed by leaving the guidewire in the transurethral pathway, the Foley catheter with a trimmed tip is pushed into the bladder over the guidewire. There is no recommendation about urethral strictures in this study. A suprapubic cystostomy was recommended for patients with contraindications, false passage, or urethral diverticula.	–
Lowe et al. 1992 [7]	False passage secondary to the traumatization of the urethra, transurethral resection of the prostate, early removal of the catheter after radical prostatectomy	A peel-away sheath is placed on the cystoscope or resectoscope, providing access to the bladder under direct vision. With the sheath left in the urethra, the cystoscope is removed, and the Foley catheter is placed into the bladder through the sheath. The sheath is taken out. The procedures of 3 of 20 patients failed due to 2 peel-away sheaths kinking and 1 patient having an erection.	85%
Beaghler et al. 1994 [15]	Patients who cannot undergo transurethral catheterization in the emergency room, intensive care unit, or operating room and require a urology consultation	A 0.038-inch guidewire inserted through a cystoscope is advanced under direct vision into the bladder beyond the obstruction in the urethra. After dilatation is provided with 6-12 Fr, then 12-18 Fr Nottingham dilatators over the guidewire, the Council-type urethral catheter is placed into the bladder over the guidewire. This study was conducted with 54 patients, and the procedure failed in only 2 patients due to extensive bladder contracture.	96%
Blitz et al. 1995 [16]	Difficult urethral catheterization	After accessing the bladder with a cystoscope, a rigid hydrophilic guidewire is inserted into the bladder. A transurethral catheterization is then achieved through the guidewire by opening a hole at the tip of the transurethral catheter with a 16 G (gauge) needle. In the study conducted with 8 patients, the procedure succeeded in all. Internal urethrotomy was performed in 2 of the patients at the same time.	100%
Freid and Smith 1996 [10]	In conditions where a Foley catheter cannot be placed, and an emergency cystoscopy cannot be performed	After the guidewire is blindly advanced from the urethra to the bladder, an open-ended 7 Fr ureteral catheter is sent to the bladder over the guidewire and the urine output is controlled by taking it out of the guidewire. A 0.038 PTFE-coated hydrophilic guidewire is then pushed through the 7 Fr catheter. On this guidewire/catheter unit, an 18 Fr Graham-type transurethral catheter, or a 16 Fr Council-type transurethral catheter is placed after dilatation. In the study conducted with 20 patients, the technique failed in 1 patient with a pinhole urethral stricture.	95%
Rozanski et al. 1998 [9]	Patients in whom a Foley catheter cannot be placed after transurethral prostate incision or resection	A 6 Fr ureterorenoscope is inserted into a 22 Fr Foley catheter. After the Foley catheter is trimmed from the tip and accessed to the bladder under direct vision, keeping the Foley catheter in the bladder the ureterorenoscope is taken out. The procedure was performed on 2 patients.	100%
Zammit and German 2004 [11]	Patients in whom a transurethral Foley catheter cannot be placed on the initial attempt	A 0.89 mm diameter hydrophilic guidewire, which is blindly advanced through the urethra, is advanced approximately 20 cm further after reaching the bladder. Then, the Foley catheter is sent to the bladder through the catheter guidewire through a hole opened with an 18 G needle. In failed cases, dilatation is performed with the help of a 6-12 Fr flexible ureterorenoscopy introducer. The number of patients and the success rate were not reported in the study.	–
Mistry et al. 2007 [12]	Patients who cannot use a 12Fr or 18Fr Foley catheter in acute urinary retention	A 12 Fr or 18 Fr hydrophilic transurethral catheter is pushed into the bladder. The guidewire is placed into the bladder through the catheter. After the hydrophilic catheter is taken out, a Council-type catheter is placed into the bladder over the guidewire. The procedure was successful on 30 of 44 patients. The next stage was performed with a flexible or rigid cystoscope in the patients whose procedure failed.	68.2%

Various techniques were presented for inserting a transurethral catheter through the difficult male urethra. These techniques, for which we give a detailed summary of the literature in Table 2, include urethral dilatation and Foley catheter insertion, if necessary, following the advancement of a guidewire into the bladder under direct vision with flexible or rigid urethroscopy [7-9], after accessing the bladder with a sheath placed on a cystoscope or resectoscope, leaving the sheath in the urethra and placing a Foley catheter through the sheath [7], inserting a guidewire with a flexible cystoscope followed by inserting a Foley catheter over the guidewire [8] and providing access to the bladder with a ureterorenoscope placed in a 22 Fr Foley catheter [1,9]. Another technique provides access to the bladder with a hydrophilic guidewire that is blindly advanced from the urethral meatus. A Foley catheter is placed over the guidewire, and if there is a urethral stricture, dilatation is performed [10, 11]. Mistry et al. [12] tested a method in which, after they advanced a 14 Fr or 18 Fr hydrophilic catheter from the urethra to the bladder, they took the catheter out by inserting a guidewire into the bladder through the catheter. In the next step, they placed Council-type catheters transurethrally over the guidewire. However, this method was successful in only 30 of 44 patients (68.2%). Villanueva et al. [13] evaluated the approach of 142 urology assistants in difficult urethral catheterizations in a 2010 survey conducted in the U.S. This survey asked about the approach to difficult urethral catheterizations (DUCs) in three different clinical scenarios, as follows: 1. The catheter passed the BMU and the patient had prostatic surgery 2. The catheter passed the BMU, and the patient has no history of any urologic surgery 3. The catheter could not pass the BMU, and the patient has no significant urologic history.

The survey found that flexible cystoscope (74%, 62%, 63%) and blind guide wire advancement from the urethra (15%, 23%, 20%) techniques were preferred the most. Although transurethral catheterization by the aid of flexible cystoscope technique seems more advantageous at first glance, it requires well-equipped facilities such as an operating room.

In the guidelines prepared for the COVID-19 pandemic, the Italian Research Urology Network (RUN) recommended avoiding advanced anesthetic procedures as much as possible and using local anesthesia [2]. Simonato et al. [14] recommended postponing actual curative treatment after transurethral or suprapubic catheterization in patients who developed urinary retention during the COVID-19 pandemic period. Hence, more practical approaches have become necessary. Zammit and German [11] performed urethral dilatation up to 12 Fr with ureteral catheters over a hydrophilic guidewire that was blindly advanced from the urethra to the bladder. Then, dilation was achieved by advancing an 18 Fr sheath over the 12 Fr catheter, and finally, a 16 Fr Foley catheter was placed over the guidewire. Although this technique overlaps with our technique, there are essential differences. Using an 18 Fr sheath directly over a 12 Fr dilator can be disadvantageous in terms of traumatizing the urethral tissue, and it can be more difficult for the patient to tolerate. Because it provides step-by-step dilatation at 2 Fr intervals, the hydrophilic S-Curve dilator set we used seems to be advantageous in terms of protecting the urethral tissue and enhancing the patient's tolerance.

Thanks to this technique, a catheter can be placed successfully, providing treatment opportunities to patients with urethral strictures using dilatation. It is especially noteworthy that our technique can be performed under all conditions with very few instruments since we encounter these patients under

different conditions, including emergency rooms or small health institutions where endourological facilities are limited.

Both Simonato et al. [14] and the EAU guidelines [3] recommend that the curative treatment of such patients be postponed to a relatively uncertain time such as 'after the pandemic' or for 6 months. Thanks to this technique, performing dilatation for a urethral stricture will allow these patients to experience this waiting period more comfortably.

Limitations

Due to the COVID-19 pandemic conditions, the patients could not be assessed with endoscopic procedures for definitive differential diagnosis and curative treatment.

Conclusion

The presented technique is an easy, useful, and safe approach in patients with DUC. Urethral catheterization was performed with a high success rate (95.6%) without additional interventions under different conditions. It is noteworthy that although most patients (73.9%) were using antiaggregants or anticoagulants, there were no serious complications.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):715-717.
DOI: 10.28982/josam.828571

Journal of Surgery and Medicine
e-ISSN=2602-2079

The effect of turmeric on primary dysmenorrhea: Prospective case-control study

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Ethics Committee Approval
This study was approved by Batman Maternity and Child Health Hospital review board (Number: 2020-7)
ClinicalTrials.gov Identifier: NCT04183556
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 July 29

Abstract

Background/Aim: Turmeric is an ancient spice and is still a part of dietary traditions, especially in Asian populations. It has been linked to anti-inflammatory effects; thus, it may be effective in dysmenorrhea which occurs due to inflammatory events. The use of turmeric in the treatment of dysmenorrhea is unclear. We aimed to compare the effectiveness of turmeric when included in dysmenorrhea treatment.

Methods: Nulliparous patients with primary dysmenorrhea (PD) who met the inclusion criteria were included in our prospective case-control study. After the diagnosis of PD was confirmed by the clinician, patients were asked to choose one of the covered papers that wrote group 1 (Control, n=75) and group 2 (Case, n=75), after which they received their related treatment from the doctor in another examination room. Naproxen (750 mg/day) was prescribed to all patients, and 1 g/day turmeric powder was added to the treatment protocol of Group 2 patients as a food supplement to be consumed *peroral* during menstrual bleeding. The turmeric supplements were given to the patients by the assisting nurse. The two groups were asked to score their pain with a visual analog scale (VAS) before and after the treatment, which were comparatively analyzed. All patients signed informed consent forms before the study began.

Results: The two groups were similar in terms of age (22.7 years vs. 23.5 years, p=0.408). The overall median pain score of the study population before the treatment was 9.17 (range: 5-10), which decreased to 2.81 (range: 1-5) after the treatment, with a Z-score of -10.64. The decrease in VAS scores was significant in both groups (P=0.001 for both). The percentage of VAS score decrease (61.7% vs 76.8%) and the absolute score decrease (5.6 vs 7.0) were significantly higher in Group 2 compared to Group 1 (P=0.001, for both).

Conclusion: Turmeric may have a role in PD treatment. Naproxen is an effective agent in PD treatment and concomitant use with turmeric improves pain scores. Further controlled randomized studies investigating turmeric use in PD treatment and its mechanism of action may contribute to the literature.

Keywords: Naproxen, Primary dysmenorrhea, Turmeric, Visual analog scale

How to cite: Okuyan E, Günakan E, Atac H, Çakmak H. The effect of turmeric on primary dysmenorrhea: Prospective case-control study. J Surg Med. 2021;5(7):715-717.

Introduction

Primary dysmenorrhea (PD) has a cyclic pattern and occurs in the hypogastric region during the menstrual period. It is frequent and the severity of complaints varies on a patient basis. The pain usually begins a few hours before menstruation and lasts for about 2 or 3 days [1]. The diagnosis is confirmed by excluding the other disorders in the differential diagnosis.

Most women underestimate dysmenorrhea or consider it a part of menstruation; thus, women who need or require treatment visit the gynecologists. The incidence of dysmenorrhea ranges between 45-95% [2].

The well-accepted theory in the pathophysiology of dysmenorrhea is the prostaglandin (PG) theory. At the beginning of menstruation, PGE2 and PGF2 are released from endometrial sloughing, resulting in an inflammatory process, dysrhythmic uterine contractions, decreased blood flow, and ischemia [3]. Higher levels of endometrial prostaglandins and good response to non-steroidal anti-inflammatory drugs (NSAID) which inhibit prostaglandin synthesis through inhibiting cyclooxygenase (COX) enzymes support this theory [4,5], on which the treatment of PD was predominantly formed.

Naproxen, an NSAID that inhibits both Cox 1 and 2 enzymes, is one of the first-line treatment options in primary dysmenorrhea treatment [6, 7].

Turmeric is derived from Curcuma longa and includes curcuminoids such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin. It is a member of some regional diets as a spice and has been used as a drug since ancient times in numerous Asian cultures. The estimated dietary intake of turmeric is approximately 2.5 g/day [8]. Various studies regarding the safe dosage of turmeric suggest that it can be consumed up to 12 g/day [9]. Its anti-inflammatory effects by inhibiting enzymes such as Cox, 5-lipoxygenase, cytosolic phospholipase A2 were demonstrated in many studies [10-12].

Considering this information, we thought that turmeric may have a positive effect on PD treatment and conducted this original research.

Materials and methods

This study was approved by Batman Maternity and Child Health Hospital review board (Number: 2020-7), ClinicalTrials.gov ID: NCT04183556) and conducted per the Declaration of Helsinki. A total of 149 patients were included and evaluated in two groups as Group 1, which received naproxen treatment only, and Group 2, which received naproxen + turmeric (1gr/day turmeric in powder form as a dietary supplement) treatment. Nulliparous patients with PD who met the following inclusion criteria were included in the study: Being between 15-45 years of age, and nulliparous, having regular menstrual cycles, BMI<25 kg/m^2, no systemic diseases, no history of suspected endometriosis, adenomyosis, gynecologic anatomical disorders or abnormalities, gynecologic discharge or pelvic inflammatory disease, no history of drug use, naproxen, or turmeric allergy, and not smoking or consuming alcohol.

After the diagnosis of PD was confirmed by the clinician, patients were asked to choose one of the covered papers that wrote group 1 and group 2, after which they received their related treatment from the doctor in another examination room. Naproxen (750 mg/day) was prescribed to all patients, and 1 g/day turmeric powder was added to the treatment protocol of Group 2 patients as a food supplement to be consumed peroral during menstrual bleeding. The turmeric supplements were given to the patients by the assisting nurse. The two groups were asked to score their pain with a visual analog scale (VAS) before and after the treatment, which were comparatively analyzed. All patients signed informed consent forms before the study began.

Both groups included 75 patients at the end of recruitment, then, one patient in Group 2 decided to leave the study. Finally, groups 1 and 2 included 75 and 74 patients, respectively. None of the patients experienced any side effects or hypersensitivity.

Statistical analysis

Statistical analysis of the data was performed using the SPSS v.15.0 (Statistical Package for Social Sciences, Chicago, IL, USA) package software. Descriptive analyses were conducted. The Wilcoxon and independent samples T-test were used to compare the groups. *P*-value <0.05 was considered statistically significant.

Results

This study included 149 patients with 75 in Group 1 and 74 in Group 2. The two groups were similar in terms of age (mean ages: 22.7 vs. 23.5, p=0.408). The median VAS pain score of the study population was 9.17 (range: 5-10). Before the treatment, the VAS scores were similar between the groups; however, the mean score of Group 2 was significantly lower than that of Group 1 after the treatment (3.47 vs 2.14, P=0.001) (Table 1).

Table 1: Evaluation of pain scores before and after treatment

	VAS Score	*P*-value
Before treatment		
Study population	9.17 (1.0)	
Group 1	9.12 (0.9)	0.568
Group 2	9.22 (1.0)	
After treatment		
Study population	2.8 (1.1)	
Group 1	3.47 (9.77)	<0.001
Group 2	2.14 (0.88)	

The mean VAS score of the entire study population significantly decreased from 9.17 to 2.81 (range: 1-5) with a Z-score of -10.64 following treatment (P=0.001). The decrease in VAS scores was significant in both groups (P=0.001 for both); however, the percentage of VAS score decrease (61.7% vs 76.8%), and the absolute score decrease (5.6 vs 7.0) were significantly higher in Group 2 (P=0.001 for both) (Table 2).

Table 2: Evaluation of the decrease in VAS scores

	Group 1	Group 2	*P*-value
VAS Z-score	-7.58	-7.53	
VAS score change rate	61.7%	76.8%	<0.001
VAS score change in numbers	5.6	7.0	<0.001

Discussion

We evaluated the effect of turmeric in a group of patients with PD and found significant results. The strengths of our study include its strict selection criteria and homogenous patient characteristics. Patients in both groups benefited from treatment, as indicated by the significantly lowered VAS scores after treatment. The VAS scores of Group 2 decreased

significantly more than those of Group 1, showing that turmeric may improve the success of PD treatment.

Dysmenorrhea is a frequent disorder that is usually considered a normal part of women's lives. When present, it decreases the quality of life significantly [13]. Most women do not seek treatment. While some do not want drug therapy, others turn to alternative therapies. Thus, one can estimate that it has a much higher frequency than expected.

The history of dysmenorrhea treatment dates to early ages when plants or plant-derived foods were used in traditional medicine. Numerous studies were conducted on paramedical dysmenorrhea treatment. Ginger, German chamomile, cinnamon, Damask rose, dill, fennel, fenugreek, or guava are some examples of plant-derived supplements researched for the treatment of dysmenorrhea [14, 15].

Turmeric is an ancient spice and is still a part of dietary traditions, especially in Asian populations [8]. It was linked to antioxidant, and anti-inflammatory effects [16, 17]. The inflammatory process underlying the PD pathophysiology, and the afore-mentioned effects of turmeric constituted the core of our study. We aimed to evaluate whether the addition of turmeric to standard treatment improved dysmenorrhea treatment outcomes.

NSAIDs are the well-accepted first-line treatment in PD [18]. Naproxen, an NSAID, reversibly inhibits both Cox-1 and Cox-2 enzymes, thus preventing PG synthesis. It is an effective agent in dysmenorrhea treatment [19]. Although the decrease in survey scores differed on a patient basis, patients in both groups benefited from the treatment as expected and stated lower pain scores after treatment. This result resembled those in the literature about the effectiveness of Naproxen and NSAIDs in dysmenorrhea. The patients in Group 2 had significantly lower VAS pain scores compared to Group 1, which indicates that turmeric use improved the PD treatment. This may be due to the anti-inflammatory and antioxidant effects of turmeric. An unknown pattern of analgesia may also be playing a role in this process. Another point is that turmeric is a familiar supplement that is frequently used in regional diets. This also may have caused a placebo effect on the self-evaluation of patients.

Overall, patients with PD benefited from turmeric treatment. This is important because turmeric is a common dietary supplement with a wide safety window, and limited negative effects [20]. It may play a role in PD treatment as an added or alternative option in selected patient groups such as those who do not prefer or have not benefited from drug therapy.

Conclusion

Turmeric is a widely used dietary supplement that may play a role in PD treatment. Naproxen is an effective agent against PD and its concomitant use with turmeric improves pain scores. Further controlled randomized studies investigating turmeric use in PD treatment and its mechanism of action may contribute to the literature.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):718-723.
DOI: 10.28982/josam.796290

Journal of Surgery and Medicine
e-ISSN=2602-2079

Burnout, compassion fatigue and suicidal ideation in oncology healthcare professionals

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Abstract

Central to the practice of oncology is the mental and physical resilience of the oncology clinician and the associated care providers. Healthcare professionals working with cancer patients have considerable risk for burnout; however, the mental health of oncology healthcare professionals has received little attention in the literature. The increasingly high rates of burnout and suicide in the field of medical and specifically oncological practice have rendered this area of research in psycho-oncology critical. Oncology presents the practitioner with unique and challenging issues that contribute to burnout, depression and, in some cases, suicide. Working with patients at or nearing the end of life and the administrative and insurance demands they often face in order to obtain needed oncotherapeutic medications, onerous workloads and long working hours, administrative record demands and staying abreast with expanding oncologic knowledge for practice may at times be overwhelming. This work reviews recent research in the field of burnout and compassion fatigue in oncology healthcare workers and posits recommendations for interventions to ameliorate the status quo.

Keywords: Burnout, Compassion fatigue, Oncology, Psychology, Suicidal ideation

Points of significance

- There is relatively little reported in the literature regarding the incidence of burnout among oncology healthcare professionals, both across the African continent and globally, the rates of which are increasing as numbers of diagnoses rise and workload increases.
- The importance of recognizing and addressing stress and burnout in healthcare workers, with its effect of suboptimal patient care, higher staff turnover and poorer quality of life measures of staff is emphasized.
- Burnout and suicidal ideation in oncology professionals is now regarded as a public health epidemic worldwide. In this review, some possible interventions to ameliorate the status quo are posited.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 July 11

How to cite: van Oers H. Burnout, compassion fatigue and suicidal ideation in oncology healthcare professionals. J Surg Med. 2021;5(7):718-723.

Introduction

The incidence of cancer is rising globally, including a rapid rise in Africa, with a corresponding need for more oncology professionals [1, 2]. This increasing need for palliative care leads to multiple challenges and stressful situations for healthcare professionals [3]. Oncologists are at high risk of impaired psychological wellbeing and burnout syndrome due to the emotionally exacting nature of their work, the many cumulative stressors they face and personality factors [4-8]. Within the African context, studies have shown that African oncologists falling under the scope of the African Organization for Research and Training in Cancer (AORTIC) network have a significantly higher clinical workload and lower job satisfaction than oncologists elsewhere in the world [1].

Studies show that few physicians are confronted with death and grieving as often as oncologists and that patient loss is an intrinsic part of clinical oncology [4]. In Africa, the mortality incidence is markedly higher than in higher-income countries (0.66 in Africa while in Europe it stands at 0.40, and in the USA, at 0.29). This disparity can be largely ascribed to the fact that approximately 80% of patients in Africa are diagnosed with cancer at a more advanced stage, the limited health system infrastructure, a paucity of specialized health personnel and patients' inability to afford oncology treatment [1]. Frustration caused by limited treatment success and continued exposure to fatal disease renders oncologists particularly vulnerable to stress, burnout and suicidal ideation (SI) [9, 10]. However, it is broadly acknowledged that physicians frequently do not recognize symptoms of their burnout, and seldom seek help [11].

Burnout affects physicians, patients, and the healthcare system. It disrupts perceptions of personal well-being and increases the risks of SI, absenteeism, and poorer medical productivity [11-13]. Physicians who report symptoms of burnout have higher turnover rates, represent higher prevalence of substance abuse and numerous malpractice claims [11]. Suboptimal physician mental wellbeing is related to poorer patient care and a risk of medical errors. Patients of burned-out physicians report decreased satisfaction with their care, and undergo more unnecessary tests and consultations [5,14]. Research demonstrates that burnout in the healthcare professions has increased in the past decade with statistics indicating that approximately 54 % of physicians and between 10%-70% of nurses are burnt out [10, 15-17]. In terms of gender, studies show that female oncologists report greater grief responses to patient loss and more emotional distress and burnout than male oncologists [4].

Oncology nursing has been found to be a source of significant stress for nurses, particularly for novice nurses who may be inadequately prepared to care for patients at the end-of-life stage [18].

Prior research has identified heavy workload as a key predictor of burnout. Compassion fatigue (CF) among oncology healthcare professionals has received less attention despite this specialty's particular risk of CF [5]. Burnout, CF, and SI are multifactorial issues that include the healthcare professional's socioeconomic stresses, lifestyle factors, loss of autonomy in the workplace and the demands of changing regulations which all pose a burden on healthcare professionals at different stages of their careers [10].

Identification of burnout is critical not only for healthcare professionals' quality of life, but also for the well-being of patients. Additional risk factors for burnout, such as young age, lack of family supportive network and the effects of burnout and CF demonstrate the need for better screening tools for burnout [19]).

Stress

Stress and burnout differ. Burnout refers to work-related issues, unlike stress, which may be experienced in all aspects, and is defined as any unpleasant emotional experience accompanied by predictable biochemical, physiological, and behavioral changes [20]. Stress is characterized by over-engagement, hyperactivity and loss of energy which may lead to anxiety. Conversely, burnout is characterized by disengagement, feelings of helplessness/hopelessness and loss of motivation which may lead to detachment and depression [21].

Recent research into stress has explored the link between work effort, or the effort necessary to meet job demands, and the reward for job performance. Imbalance in the relationship between effort and reward has been linked to the dysregulation of the hypothalamic-pituitary axis which may be the mechanism through which job stress leads to physical illness [11].

The result may be the development of the well documented symptoms of stress including accelerated respiration, tachycardia, and headache. Other symptoms, including psychiatric disorders, are more subtle and often not recognized as such. These may include difficulty in interpersonal relationships, apathy towards people or activities, irritability, and anxiety. In terms of professional performance, lower productivity, relationship problems, procrastination and decreased performance may result. Studies suggest that psychosomatic symptoms, such as chest pains, headache and fatigue seem to occur more frequently than psychological symptoms, such as depression and anxiety [22].

According to Selye's General Adaptation Syndrome [23], stress can be subdivided into three phases: Alert, resistance and exhaustion. The alert stage occurs when a stressor disturbs homeostasis and the rate of bodily functions increases to mobilize the system against attack resulting in symptoms such as perspiration, tachycardia, and hypertension. The function of this phase is to consolidate the physiological response to the stressor. The resistance phase is an attempt to recover the imbalance of the initial phase by attempting to resist the negatively perceived consequences of the stressor and may manifest as fatigue and memory problems as a result of the depletion of energy. At this stage the system will try to adapt to the stressor and the symptoms of the first phase will be reduced or eliminated. However, if the body is not able to reestablish homeostasis because the stressor is chronic and excessive, the system will begin to show signs of adaptation failure, reaching the third phase of exhaustion. If the stressor continues to weaken the system, energy reserves are depleted. Systems begin to break down and become more susceptible to a range of biopsychosocial symptoms. At this stage, symptoms of the alarm phase revert, but are now irreversible. The consequence is that

the individual will present with a high degree of physical impairment [22, 24].

Burnout

Burnout, first described in the 1970s, refers to a prolonged reaction to chronic emotional and interpersonal work-related stressors where a perceived dissonance exists between job demands and available resources [20, 25]. Burnout is a multidimensional work-related syndrome. It is defined as a stress-related condition characterized by *emotional exhaustion*, or feelings of emptiness and physical and emotional fatigue, *depersonalization*, or negative or impersonal attitudes towards others, or treating them as objects rather than human beings and the *diminution of personal accomplishment*, or feelings of failure and a decrease in self-esteem [26-28]. Studies suggest that burnout is highly prevalent within the healthcare professions due to the intensity and continuous nature of contact with patients receiving care [29].

The literature suggests that the patient-physician relationship is one of the most gratifying areas of practice. However, it can also be a significant source of stress [4]. Workload, in particular, is a consistent predictor of burnout in oncology. Studies regarding physicians have linked a range of objective and subjective workload factors to burnout, including work hours, number of nights on call, perceptions of work as overwhelming and overall perceived job stress [5, 30]. Further factors are communication difficulties and emotional aspects of relating with patients and colleagues [31].

The symptoms of burnout typically develop slowly, are triggered by multi-causal factors, and are seldom identified in the early stages [29]. The primary symptoms of burnout may be emotional exhaustion, a sense of ineffectiveness or dissatisfaction with work, which can result in a growing cynicism and detachment from work. Poor sleep, concentration problems, social withdrawal, interpersonal conflicts, and poor judgment may be present. Physicians with burnout are more likely to incur errors, and their patients tend to be less satisfied with the quality of their care [32]. Studies show that burnout is associated with mental illness, substance abuse, emotional exhaustion, depersonalization, and suicide [5].

Recent research regarding gender differences in burnout rates in oncology physicians observed that although female oncologists reported more distress and burnout, higher levels of grief following patient death correlated with greater emotional distress in both genders. For male oncologists, the correlation between grief reactions and emotional distress was observed at moderate levels of burnout, suggesting that male oncologists already suffering from burnout are more vulnerable to grief and distress than female oncologists. The possibility exists that burnout leads to more pronounced sensitization in oncologists, causing greater vulnerability to patient loss and distress than either one of these factors alone [4].

Further, age is significantly correlated to health professional burnout. A recent study found that as age increased, burnout potential decreased [33]. Recent research in Europe suggests that over 70% of young oncologists at early career stage are at risk for burnout [2, 32]. While making complex decisions about disease management, supervising the application of toxic therapies, long working hours, and continually facing patients suffering and dying, younger oncologists also face increased administration, medico-legal issues, rising expectations and reduced resources [34]. A recent survey of oncologists in the USA suggested that burnout seems to peak in the first year of practice and subsequently decreases in the second and third years, with improvements in fatigue, quality of life, and work/life balance [35].While younger age and female gender constitute risk factors for burnout, single relationship status, not having children, higher student loan debt and longer hours spent seeing patients also represent high risk [36]. The lack of work-life balance, living alone and inadequate vacation time are further risk factors.

In the African context, studies suggest that African oncologists tend to be substantially older than oncologists in other parts of the world which indicates that without new models of healthcare and an increase in capacity, clinical workload volumes, already higher than elsewhere, might worsen in the coming years, rendering burnout an increasing risk [1].

Compassion fatigue (CF)

CF and burnout may coexist but are two distinct entities. Where burnout is caused by stressors related to the work environment and may include loss of empathy, CF results from the stress of the bond between caregiver and patient, and although empathy is preserved, the caregiver becomes overwhelmed by the trauma to which they are exposed. While burnout refers to the clinician's interaction with the environment, CF (also termed vicarious traumatization) arises more from the relationship between the physician and the patient and the stress of caring for patients, through the protracted and traumatic continuum of diagnosis, difficult treatment regimens and the management of intractable pain which patients often suffer [36, 37]. Research suggests that the more empathic the carer, the more they are at risk of absorbing the stress of their patients and developing CF [38].

The symptoms of CF differ in nature to those of burnout. While the signs of burnout comprise emotional exhaustion (EE) or dissatisfaction with work, CF may compromise the physician's ability to care for patients as a consequence of the impairment in ability to empathize with the patient due to exposure to trauma and suffering [39]. The symptomatology resembles that of posttraumatic stress disorder (PTSD), ranging from avoidance of situations where the patient is suffering to intrusive thoughts with feelings of distress or physiological reactions to reminders of a patient's traumatic experience as well as numbness, hyperarousal, and exhaustion in terms of confronting distressing clinical situations [32, 40].

Among the multiple stressors that may lead to CF in healthcare professionals are the unpredictable course of terminal illness, family distress and the need to assist patients who are facing death without social support [41].

CF is seldom examined among clinicians, even in specialties such as oncology which involve continuing exposure to the stress of death and dying. CF is a phenomenon typically understood to encompass both being too exhausted to care and a need to forsake a sense of compassion in an effort to protect the individual from despair [5].

Relationship between burnout and CF

While burnout and CF may appear to be similar in that caregivers may lose the ability to care for patients, the underlying mechanism differs. Burnout is linked to occupational factors such as the exhaustion that comes about as a result of chronic overwork and caring for others. Burnout may affect a worker in any field of work and describes the incapacity of an individual with low work satisfaction primarily due to demands that are beyond their ability [40]. In contrast, CF is typical to the caring professions and is linked to exposure to extremely stressful events associated with patients' pain and suffering [26]. Burnout can be experienced without exposure to others' trauma whereas CF is directly linked to secondary traumatic stress. Burnout may arise from minor chronic stressors that accumulate from day to day and over a period of time become overwhelming, whereas CF may result from exposure to a single extremely stressful event such as a traumatized patient. CF may emerge suddenly, and recovery tends to be faster [5, 40, 41].

Some studies have found a significant correlation between burnout and CF, suggesting that these are similar phenomena and there may be an overlay of one or more of the components of these phenomena [40]. Other studies suggest that burnout is a pre-condition for CF, while further research proposes that the concept of burnout is outdated and should be replaced by CF in describing the phenomenon in oncology healthcare professionals [26].

Suicidal ideation (SI)

SI may be defined as an alteration of one's thought process where ending his or her life is the preferred avenue to seeking options to cope with stressors at the time. Burnout plays a key role in SI [5, 42]. Research shows that there are significant relationships between EE and SI and between depersonalization and SI [43, 44]. Physician, nurse and student burnout and suicide is currently regarded as a public health epidemic worldwide, with nurses and physicians having higher rates of suicide than the general population. Some studies suggest that physician burnout is associated with a doubled risk of SI, and the suicide rate amongst male physicians being 40% higher than males in the general population and amongst female physicians, 130% higher than females in the general population [28, 45]. Some studies suggest that female physicians have higher suicide rates, which may possibly be due to their social family role or to unequal professional status integration [46].

A recent study found that stressors associated with SI in physicians included personal, financial, health and occupational difficulties and that ideation was more likely in the face of multiple stressors. Work disengagement, or an uncaring, distanced and cynical attitude towards the work or colleagues, and sickness presenteeism, or working despite illness, were strongly associated with thoughts of suicide [47]. SI is also associated with complaints procedures against practitioners [48]. Those physicians espousing SI were found to lack personal support structures from faculty, peers, staff, and family [49, 50].

Suicidal physicians encounter additional barriers to care, compared with the general population. Whereas both groups face concerns about stigma, lack of time and lack of access to care, physicians have the added burden of concerns regarding confidentiality, and fear of discrimination in licensing [51].

Personality as a specific risk factor

Not all individuals experiencing similar working conditions develop burnout, suggesting that individual factors determine its development. Personality factors pay a key role in burnout development since they are relevant in defining the way and the efficacy with which the individual approaches work [52]. Personality is also related to the individual's perception of work tasks as more or less stressful. Studies suggest that anxious individuals are more vulnerable to job stress and that personality factors are important in the occurrence of burnout syndrome in health professionals [8].

Studies examining personality factors in healthcare professionals have identified neuroticism as a factor strongly associated with burnout. Elevated levels of neuroticism appear to render the individual more prone to anger, anxiety, depression and stress, less adept at controlling their emotions in stressful situations and with immature defense mechanisms which elevate their levels of exhaustion [8].

Recent studies suggest that EE and depersonalization correlate positively with neuroticism [53, 54] but negatively with agreeableness, conscientiousness, extraversion, and personal accomplishment. Further, EE and depersonalization correlate positively with anxiety and depression, which are negatively correlated with personal accomplishment [52].

Conscientiousness, perfectionism and narcissism have been identified as common personality traits in healthcare professionals. Perfectionism or the attempt to constantly improve and the setting of overly high standards of performance may lead to hyper-critical self-evaluation. Exhaustion in this context is not due only to the task, but how the individual relates to it. Narcissism, or the need to make achievements visible and be recognized for them, is a further personality factor identified as a risk factor for burnout particularly in terms of EE and depersonalization [8].

Studies report that individuals with low esteem exhibit limited coping resources, leading to increased psychological distress and problems in controlling stressful events. The initial result is the experience of EE which is often the earliest manifestation of burnout [27].

In relation to personality types, a Type A profile, or individuals who display impulsivity, competitiveness, and impatience and who have difficulties managing job stress, has been found to correlate with burnout. Healthcare professionals who exhibit these behaviors appear to have higher levels of job anxiety and EE leading to greater vulnerability to burnout [8].

A Type D, or individuals who experience a wide range of negative emotions but suppress these emotions due to social inhibition, have been found to be at 5 times higher risk of burnout [55]. These individuals tend to employ more passive and maladaptive avoidance coping strategies, such as resignation and withdrawal which are associated with increased levels of perceived stress and linked to higher levels of burnout symptoms [56].

Studies suggest that certain personality factors are associated with the choice of training in healthcare professions and with levels of stress, satisfaction and burnout, with most

healthcare professionals tending towards an anxious, emotional temperament, characterized by the need to care for others. This temperament may render them particularly vulnerable to anxiety, stress and burnout [8].

Risk factors for CF include the traumatic stress of families, failure to recognize one's own experiences of secondary traumatization, and an unhealthy work culture [57].

In sum, there appears to be a significant correlation between health professional burnout and personality traits. More extraverted, open, and agreeable individuals are less likely to experience burnout while more narcissistic and perfectionistic individuals are more at risk [33].

Protective factors

Personality traits that buffer the negative effect of job demands and act as protective factors against job stress have been identified. Research posits suggests that elements of emotional intelligence (EI), defined as skills for understanding, perceiving, and adapting one's emotions and their relationship with engagement and job performance, and individuals' perceived self-efficacy with regard to their ability to control their surroundings, as burnout protection factors [58]. Thus, cognitive empathy, self-esteem and high affective empathy with patients are associated with less burnout and CF [8].

Other factors include adequate social support, self and occupational development and self-awareness [40]. Research suggests that a good work/life balance, adequate vacation time and access to support services are requirements to address burnout. A recent study highlighted the importance of a supportive supervisor with whom communication could be open [57].

Positive challenges at work, a sense of mastery of the work and commitment to the organization have been associated with decreased levels of burnout and CF [59].

Resilience or the ability to recover from adverse events, may protect professionals from the stresses of the work environment and the tendency to burnout. Studies suggest that several characteristics facilitate resilience: EI, empathy, self-compassion, and mindfulness are all associated with higher resilience and less EE. This expands on other studies of factors associated with less burnout such as more social support, less fatigue and stress. However, more interventional research is warranted [34, 60].

Strategies to manage burnout

Evidence suggests that self-care, both mental and physical, can improve wellbeing. Interventions found to reduce burnout can be classified into the two categories of *physician-directed* interventions focused on individuals, and *organizational* interventions focused on the work environment. Physician-directed interventions include mindfulness techniques, stress management and cognitive behavioral therapy (CBT) to improve job competence, communication skills and personal coping mechanisms. Organization-directed interventions imply simple changes in the work schedule and environment, the implementation of tasks designed to lower stress levels, such as reductions in workload through improved teamwork, alterations in evaluation, increasing participation in decision-making, supervision to improve job control and more fundamental improvements in the operation of healthcare systems. These interventions have been associated with significant reductions in EE and depersonalization and have been shown to have greater effects when compared to individual interventions [13].

A technique gaining popularity involves the cultivation of self-awareness and mindfulness-based practices. Research suggests that participation in a mindful communication program may be associated with both short-and long-term improvement in burnout among physicians [61]. A recent study shows that a strategy of appreciative inquiry and meditation was associated with decreases in burnout and mood disturbances and showed increases in levels of empathy. Further, physician discussion groups incorporating mindfulness and shared experiences led to a 15% reduction in rates of depersonalization over a three-month period which was sustained over twelve months. There was, however, no impact on stress reduction, symptoms of depression, and overall quality of life or job satisfaction [36].

Meditation has been demonstrated to combat symptoms of burnout and mindfulness training is suggested to be beneficial in decreasing anxiety and perceived work stress. Individual professional life coaching for stress management has been shown to be successful but there is little data to suggest the long-term benefit of particular stress management interventions in preventing burnout [11].

Conclusion

As cancer diagnoses increase annually, especially in Africa, rising levels of stress will be experienced by oncology healthcare workers. Given the known consequences of high stress, leading to burnout and CF, it is essential to raise awareness regarding the prevalence of mental health issues within this population and identify and address those individuals in distress. Failure to do so would have profound implications for the quality of life of both physicians, nursing staff and patients. Wider acknowledgment of the inherent stressors associated with current oncology practice may have the effect of destigmatizing burnout and render support for these healthcare professionals more conventional and accessible.

There is consensus in the literature that prevention of burnout appears to be more beneficial than treatment. Broader study of the issues associated with increased stress and burnout may lead to improved methods of addressing these problems to lessen the load of physicians and nursing staff working in an already difficult and psychologically challenging discipline of medicine. It is a matter of urgency that governments and health systems improve oncologist-to-patient ratios and develop innovative models of capacity building, staff retention and skills advancement to bolster cancer care systems, both globally and across continental Africa.

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This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2021;5(7):724-726.
DOI: 10.28982/josam.844756

Journal of Surgery and Medicine
e-ISSN: 2602-2079

A rare cause of abdominal cyst in the neonatal period: Hydrometrocolpos

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Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 July 29

Abstract

Hydrometrocolpos is a clinical condition that arises from vaginal outflow obstruction during fetal life and rarely manifests with an abdominal cystic mass in the neonatal period. In cases with delayed diagnosis, urinary complications, respiratory distress, and gastrointestinal obstructions may occur and thus a prompt diagnosis is of prime importance for the prevention of such complications via surgical drainage and repair. In the present study, we report on a neonatal hydrometrocolpos case manifesting as an abdominal cyst associated with intrauterine vaginal atresia and causing bilateral hydronephrosis, urosepsis, and respiratory distress.

Keywords: Hydrometrocolpos, Neonate, Cystic mass

Introduction

Hydrometrocolpos (HMC) is a clinical condition characterized by the expansion of the vagina and uterus due to the accumulation of cervicovaginal secretions produced by the uterine and cervical glands in the presence of vaginal outflow obstruction during fetal life [1]. This condition may occur in 1 in 5,000-10,000 live female births [2]. HMC may be caused by an imperforate hymen, vaginal or cervical atresia, and vaginal septum. Hydrocolpos associated with vaginal atresia is caused by the failure of canalization of the proximal vaginal plate and may manifest as an abdominal mass in the neonatal period or with other symptoms in later ages such as abdominal pain, pelvic mass, primary amenorrhea, and urinary dysfunction [3]. The mass effect of hydrocolpos on the adjacent organs may result in various complications including lower extremity edema, urinary retention, hydroureteronephrosis, urosepsis, endometriosis [4]. Prompt diagnosis and drainage of hydrocolpos are highly important for preventing these complications.

In the present study, we report on a neonate with an antenatal diagnosis of an abdominal cyst, who was admitted with bilateral hydronephrosis, urosepsis, respiratory distress, and an abdominal cyst. She was diagnosed with HMC associated with vaginal atresia, which is an extremely rare entity.

How to cite: Basaranoğlu M, Karaman S, Avcı V, Ayengin K, Karaman E. A rare cause of abdominal cyst in the neonatal period: Hydrometrocolpos. J Surg Med. 2021;5(7):724-726.

Case presentation

A 27-day-old girl was referred to our clinic after being diagnosed with an abdominal cystic mass during the antenatal period. Physical examination revealed tachypnea and subcostal and intercostal retractions. An abdominal examination revealed marked distension and a well-circumscribed, stiff, mobile, palpable mass measuring 9x7 cm in diameter, extending from the pelvis to the umbilicus. Ultrasonography (USG) revealed a thick-walled, midline abdominopelvic mass measuring 10x7.5 cm with dense content and internal echoes. Additionally, the renal pelvicalyceal system was dilated bilaterally, and grade 2-3 hydronephrosis was detected on the left, and grade 3 hydronephrosis was detected on the right. The patient received continuous oxygen support due to respiratory distress caused by the mass effect. A nasogastric catheter was inserted due to abdominal distension. Antibiotic therapy was initiated according to culture-antibiogram results due to the detection of pyuria in urinalysis and bacterial growth in urine culture. An abdominal magnetic resonance imaging (MRI) scan confirmed the mass as a mesenteric cyst.

Intraoperative exploration showed an expanded cervix and uterus. The cervix had a diameter of 10x8 cm, was edematous, and anchored to the neighboring tissues (Figure 1). An incision made on the posterior cervix led to the discharge of a large amount of seromucinous fluid (Figure 2). After fluid aspiration, it was noticed that the catheter passed through the cervix could not be advanced to the vagina. Subsequently, due to the presence of vaginal atresia, a lumen was formed on the outer vaginal wall by making a cross-shaped incision with the aid of the vaginal bump established under the guidance of the catheter. The surgery was finalized by placing a 10 Fr catheter for drainage (Figure 3). An echocardiogram (ECHO) performed for the assessment of additional abnormalities indicated the presence of a partial pulmonary venous return anomaly (PAPVC). Following the surgery, the complaints of abdominal distension and respiratory distress regressed, and spontaneous urination occurred. The patient was discharged uneventfully.

The patient's family consented to participate in this study.

Figure 1: An expanded cervix and uterus

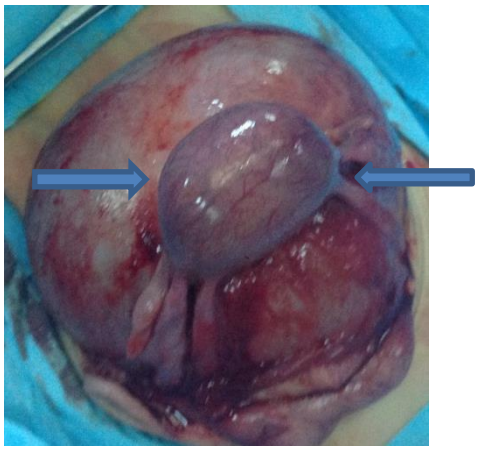


Figure 2: An incision made on the posterior cervix

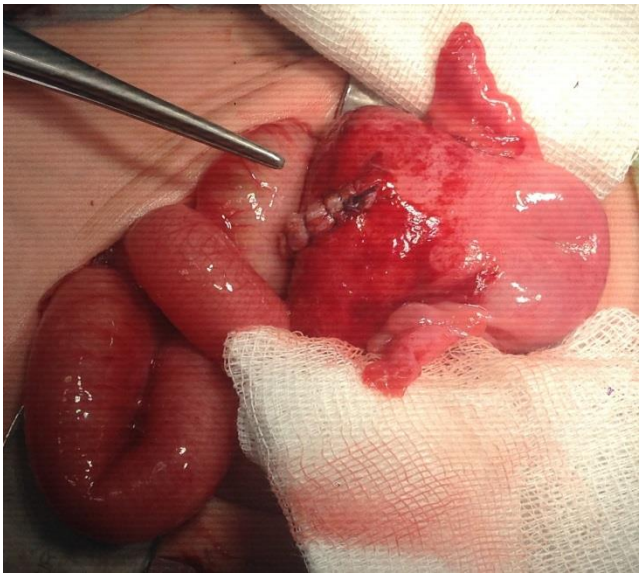
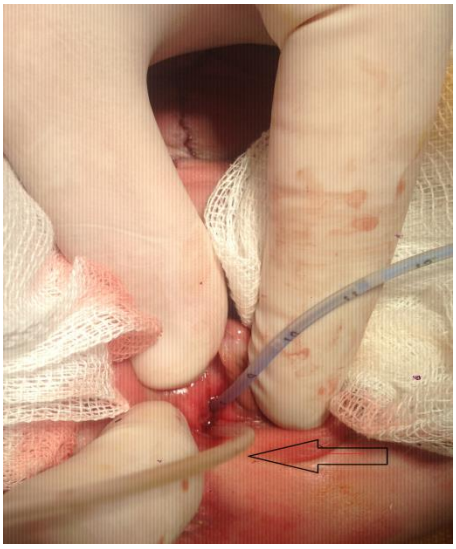


Figure 3: The catheter used for drainage



Discussion

Hydrocolpos is defined as the accumulation of secretions in the vagina while HMC refers to the accumulation of secretions both in the vagina and uterus [5]. HMC is mostly caused by imperforate hymen and rarely caused by other conditions including labial adhesions, transverse vaginal septum, vaginal atresia, vaginal agenesis, and cloacal malformations [6]. The HMC arising from vaginal atresia is an extremely rare neonatal condition commonly presenting with an abdominopelvic mass [3]. The mass often occurs as a result of increased mucus secretion by the uterine and cervical glands stimulated by maternal estradiol in the presence of vaginal outlet obstruction [5]. In the case presented, the Müllerian ducts did not merge with the lower section of the vagina arising from the urogenital sinus. The uterine cavity was normal, and functional endometrial tissue was present.

Common physical examination findings of HMC include a pelvic mass and abdominal distension [6]. In cases with delayed diagnosis, urinary retention may lead to serious nephrological and infectious complications as well as life-threatening conditions such as respiratory distress, gastrointestinal obstructions, and cardiac comorbidities. A prompt diagnosis is of prime importance for the prevention of

such complications via surgical drainage and repair and the early diagnosis of additional anomalies [3]. In the case presented, an abdominopelvic cystic mass localized in the posterior bladder wall was detected on USG during the antenatal follow-up. Due to delayed presentation, the patient had developed grade 2-3 hydronephrosis on the left and grade 3 hydronephrosis on the right kidney, urosepsis due to urinary retention, and respiratory distress secondary to mass compression.

Hydrometrocolpos (HMC) can be diagnosed during the neonatal or pubertal period depending on the underlying etiology. Moreover, most cases reported in the literature are stillbirth and are diagnosed by autopsy. Currently, HMC can be diagnosed by USG during the antenatal period as well [1]. The differential diagnosis of HMC often includes a mesenteric cyst, enteric duplication cyst, ovarian cyst, ovarian tumors, rectal duplication, and bladder duplication [7]. In the case presented, the cyst was initially diagnosed as a mesenteric cyst on MRI and then a diagnosis of HMC was made intraoperatively. These findings implicate that the diagnosis of this extremely rare congenital malformation requires a high index of suspicion and awareness.

Although HMC typically presents as an isolated entity, it can be accompanied by urogenital/anogenital malformations and cardiac anomalies or can manifest as part of a syndrome [8]. In the case presented, no additional anomaly other than PAPVC was detected and thus a syndromic diagnosis was not assigned.

Vaginal atresia and the resultant HMC should be considered in the differential diagnosis of female infants with a cystic mass in the intrauterine period. Early diagnosis and intervention are of prime importance for the prevention of complications.

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