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Evaluation of the effect of dinoprostone vaginal ovule for cervical maturation and labor induction in term pregnancies on the duration of the third stage of labor and amount of postpartum bleeding

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The study was approved by Clinical Research Ethics Committee of the University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital (2011-KAEK7-25, 2020/09-02).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Postpartum bleeding is a leading preventable cause of maternal death. Prolonged 3rd stage duration of labor and induction agents can increase postpartum bleeding. This study evaluated the effect of using a dinoprostone (PGE2) vaginal insert, a cervical ripening and labor induction agent, on the 3rd stage duration of labor and the amount of postpartum bleeding.
Methods: This prospective cross-sectional study involved 301 patients with vaginal delivery between 01.10.2020 and 30.06.2021. Patients were separated into two groups: PGE2+oxytocin (Group A) and only oxytocin (Group B). They were compared in terms of prepartum and postpartum data, 3rd stage duration of labor, and the amount of blood loss in the first 18 h postpartum.
Results: The median 3rd stage duration of labor was 8 min in Group A and 7 min in Group B (P=0.009). No significant differences were found between the groups in the amount of postpartum blood loss, percentage changes in hemoglobin and hematocrit values, or when patients were analyzed based on 3rd stage duration of labor (≤10 vs. >10 min). Severe postpartum hemorrhage (≥1000 ml) was associated with decreased gravida, increased body mass index, longer oxytocin use, and prolonged 3rd stage duration of labor in all patients. In Group A, severe postpartum hemorrhage was associated with decreased gravida, increased body mass index, and longer duration of PGE2 use.
Conclusion: PGE2 prolonged the 3rd stage duration of labor, but this did not increase postpartum bleeding compared to oxytocin. However, an increase in the duration of PGE2 use was associated with postpartum hemorrhage. Therefore, shortening the duration may be considered in patients with additional risk for postpartum hemorrhage.

Keywords: dinoprostone, 3rd stage duration of labor, postpartum hemorrhage, labor induction and augmentation

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Introduction

Every year, hundreds of thousands of women worldwide die from mostly preventable complications related to pregnancy and childbirth. In 2017, 295,000 female deaths were reported due to such complications [1]. Unfortunately, most of these deaths occur in developing countries with limited resources, insufficiently experienced healthcare providers, and inadequate emergency delivery services [2].

Maternal mortality refers to the death of a woman during pregnancy or within 42 days after delivery due to the pregnancy itself or its management or caused by any reason that is aggravated by these, regardless of the duration and location of the pregnancy. While maternal mortality is a significant concern, maternal morbidity is a more common condition that is just as important. Women face acute or chronic morbidity, with sequelae that can impair their life functions, approximately 20–30 times the maternal mortality rate, due to pregnancy and childbirth complications [3]. These sequelae can negatively impact a woman's physical, mental, or sexual health, body image perception, and social and economic status [4].

Postpartum hemorrhage is the leading preventable cause of maternal mortality and morbidity worldwide. Despite modern medical advancements, approximately one-fifth of maternal deaths are still linked to postpartum hemorrhage, with an even higher incidence in low socio-economic countries. The World Health Organization (WHO) defines postpartum hemorrhage as 500 ml or more bleeding within the first 24 h after birth. If the bleeding is 1000 ml or more, it is categorized as severe postpartum bleeding [5]. The incidence of postpartum hemorrhage varies worldwide due to different diagnostic criteria and methods of measuring blood loss. Studies based on estimated blood loss report rates of postpartum hemorrhage between 1–3% [6,7], whereas those based on quantitative measurement indicate that the rate may be as high as 10% [8]. The 3rd stage of labor is a significant factor in postpartum bleeding, with longer durations increasing the risk of hemorrhage. The 3rd stage duration of labor varies between 6 and 30 min, with an average blood loss of approximately 150–250 ml [9]. Patients whose placenta separates within the first 10 min tend to experience the least bleeding [10].

Prevention and treatment of postpartum hemorrhage is a globally accepted necessity. Identifying patients at high risk for postpartum hemorrhage, interventions to prevent bleeding, early diagnosis in case of bleeding, and timely management with appropriate resources all play an essential role in preventing maternal mortality and morbidity.

Dinoprostone (PGE2) vaginal ovule is a commonly used pharmacological agent for cervical ripening and labor induction in pregnant women who require delivery but are not suitable for induction of labor with oxytocin due to a low Bishop score on vaginal examination. One of the causes of postpartum hemorrhage is the duration of the 3rd stage of labor, including prolongation of placental separation and the presence of residual placental tissue in the uterus. Literature studies have shown that the risk of postpartum hemorrhage increases as the duration of the 3rd stage of labor lengthens. This study aims to evaluate the effect of using PGE2 vaginal ovule for cervical ripening and labor induction in term pregnant women on the duration of the 3rd stage of labor and the amount of postpartum bleeding.

Materials and methods

This prospective, cross-sectional, and single-center study was initiated after obtaining approval from the Clinical Research Ethics Committee of the University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital (approval numbers: 2011-KAEK7-25 and 2020/09-02). The study included 301 pregnant patients aged between 18 and 45 years, with term pregnancy ranging from 37 to 42 weeks, who met the inclusion criteria and were admitted to the delivery room for labor induction or augmentation between October 1, 2020, and June 30, 2021, and delivered vaginally. The study group (Group A) comprised pregnant women who received oxytocin after applying and withdrawing PGE2 vaginal ovules, while the control group (Group B) comprised pregnant women who did not receive PGE2 vaginal ovules and only received oxytocin.

The study's exclusion criteria were pregnancy before 37 weeks, multiple pregnancies, absence of fetal head presentation, history of placental retention in previous deliveries, history of three or more curettages, history of previous cesarean section or uterine surgery, stillbirth due to in-utero ex fetus, diagnosis of hypertensive disorders of pregnancy in antenatal follow-ups, placental abruption, a vaginal or cervical laceration that could increase the amount of postpartum bleeding, hematological disease or drug use that could increase postpartum bleeding, and not having a vaginal delivery. Patients were informed about the study, and their consent was obtained.

The following information was recorded: age, gravida, gestational age (days), parity, weight, and height. Vaginal ovules containing 10 mg PGE2 (Prostaglandin E2) were administered to patients with a Bishop score ≤5, provided there were no contraindications. After sufficient cervical maturity was reached, labor began, or the maximum usage time was reached, the ovule was withdrawn, and oxytocin infusion was started 30 min to 1 h later. Patients who had vaginal delivery were included in the study group. Patients with a Bishop score >5 did not receive PGE2 vaginal ovules; only oxytocin infusion was applied. Patients who had vaginal delivery were included in the control group.

Oxytocin infusion was prepared by adding 5 units of oxytocin to 500 ml of Ringer's lactate, started as an intravenous infusion of 4 milliunits/min, and increased by 2 milliunits every 20 min until the adequate uterine contraction was achieved. The maximum dose was 20 milliunits/min. Oxytocin was started as an augmentation application for pregnant women who did not enter active labor and for pregnant women who were in active labor but did not have a sufficient uterine contraction.

The study and control groups' third-stage duration of labor, prenatal hemoglobin and hematocrit values, hemoglobin and hematocrit values at the 6th and 18th h after birth, baby gender, birth weight, 1st and 5th min APGAR scores, newborn intensive care hospitalization, need for erythrocyte transfusion, and postpartum curettage requirement was recorded. The third stage, duration of labor, is the period from the baby's delivery to the placenta's delivery. Controlled cord traction was not applied until signs of placental separation were observed during this period. When the spontaneously separated placenta came to the

vagina, it was removed with cord traction. Manual extraction was applied for the placentas that did not come out within the first 30 min. As postpartum bleeding prophylaxis, 10 U oxytocin infusion in 500 ml Ringer's lactate was administered after the baby's delivery, and 0.2 mg methylergonovine was intramuscularly administered after the delivery of the placenta.

The volume of blood loss at the postpartum 18th h was calculated in ml according to the postpartum blood loss calculation formula, using the patient's height, weight, and prenatal and postpartum 18th-h hematocrit values. Statistical methods were used to compare the data and results of both groups.

Statistical analysis

The distribution of variables was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. For normally distributed variables, independent samples t-tests were used to compare the two groups, and for non-normally distributed variables, the Mann-Whitney U test was used for independent samples, while paired samples t-tests and Wilcoxon signed-rank tests were used for normally and non-normally distributed dependent variables, respectively. Descriptive statistics were presented as mean (standard deviation) for normally distributed data and median (minimum-maximum) for non-normally distributed data. Categorical variables were reported as numbers (%), and comparisons between groups were made using Pearson's chi-square, Fisher's exact, and Fisher-Freeman-Halton tests. The Spearman rank correlation coefficient was used to examine the relationships between variables. The Backward method was employed in binary logistic regression analysis to identify risk factors. Percentage change values were calculated to compare the changes in hemoglobin and hematocrit levels at the 6th and 18th h relative to the first measurement between the groups [Percent change = (last measurement - first measurement) / first measurement]. All statistical analyses were performed using SPSS version 22.0, and a significance level of α=0.05 was used.

Results

Table 1 compares demographic data and postpartum findings between study participants. The duration of oxytocin use and the 3rd stage duration of labor showed statistically significant differences between the groups (P=0.048 and P=0.009, respectively). In Group A, the median duration of oxytocin use was shorter (130 min), while the median duration of the 3rd stage of labor was longer (8 min). No relationship was observed between the duration of PGE2 use and the amount of blood loss (r=0.102, P=0.215). No significant differences were observed between the groups for the other variables listed in Table 1.

For all patients, the median hemoglobin and hematocrit levels measured prepartum were higher than those measured at the 6th and 18th h postpartum (P<0.001 for each), as shown in Table 2. The prepartum hemoglobin and hematocrit levels in both groups were significantly higher than the postpartum 6th and 18th-h measurements (P<0.001 for each), as shown in Table 2.

Groups A and B were further divided into two subgroups based on the 3rd stage duration of labor, i.e., ≤10 min and >10 min. The subgroups were compared regarding the blood loss amount and percentage changes in hemoglobin and hematocrit levels at the 6th and 18th h postpartum. No significant differences were observed between Group A or B subgroups (Table 3).

Table 1: Comparison of demographic data and findings between groups

	Group A (n=151)	Group B (n=150)	*P*-value
Age (years)	26 (18:44)	25.5 (18:42)	0.596
Pregnancy period (weeks)	277 (259:294)	274 (259:290)	0.029
Gravida	2 (1:7)	2 (1:6)	0.706
Parity	1 (0:4)	1 (0:5)	0.383
BMI	29.21 (20.20:53.13)	28.18 (21.22:39.96)	0.243
Oxytocin usage time (min)	130 (20:985)	177.5 (15:1070)	0.048
3rd stage duration of birth (min)	8 (2:33)	7 (2:30)	0.009
3rd stage duration of birth (min)			
<=10 min	111 (73.5)	122 (81.3)	0.105
>10 min	40 (26.5)	28 (18.7)	
3rd stage duration of birth (min)			
0-10 min	111 (73.5)	122 (81.3)	0.234
11-20 min	37 (24.5)	25 (16.7)	
21 min and over	3 (2)	3 (2)	
Blood loss (ml)	486.2 (15:1657)	382.77 (26:1765)	0.054
Blood loss (ml)			
(0-500) ml	76 (50.3)	92 (61.3)	0.124
(500-1000) ml	57 (37.7)	47 (31.3)	
>=1000 ml	18 (11.9)	11 (7.3)	
Blood loss (ml)			
<1000 ml	133 (88.1)	139 (92.7)	0.249
>=1000 ml	18 (11.9)	11 (7.3)	
HGB-N6 n (%)*	-3.57 (-23.97:10.61)	-2.28 (-23.02:6.96)	0.465
HGB-N18 n (%)*	-4.02 (-25.14:12.66)	-2.71 (-22.08:7.58)	0.489
HCT-N6 n (%)*	-9.26 (-29.06:1.96)	-7.55 (-29.69:0)	0.107
HCT-N18 n (%)*	-8.77 (-28.13:-0.29)	-7.46 (-29.01:-0.47)	0.095
Baby gender n (%)			
Male	71 (47.3)	77 (51)	
Female	79 (52.7)	74 (49)	0.525
Birth weight (kg)	3243.9(374.65)	3168.44(409.68)	0.097
APGAR 1	9 (8:9)	9 (4:9)	0.161
APGAR 5	10 (7:10)	10 (8:10)	0.621
Blood transfusion n (%)			
No	150 (100)	150 (99.3)	
Yes	0 (0)	1 (0.7)	1.000
Postpartum intervention n (%)			
No	148 (98.6)	150 (99.3)	
Perform manual extraction	1 (0.7)	1 (0.7)	0.748
BUMM curettage	1 (0.7)	0 (0)	
NIC insertion n (%)			
No	146 (97.3)	139 (92.1)	0.074
Yes	4 (2.7)	12 (7.9)	

* In order to compare the groups, it was calculated by taking the percentage change of the measurements at the 6th and 18th h compared to the first measurement. Percent change = (last measurement-first measurement)/first measurement. BMI: Body Mass Index, n: number, HGB: Hemoglobin, HCT: Hematocrit, N: Newborn, NIC: Newborn Intensive Care

Table 2: Comparison of prepartum and postpartum hemoglobin and hematocrit values

	All Patients (n=301)		Group A (n=151)		Group B (n=150)	
		P-value		*P*-value		*P*-value
HGB (Prepartum)	11.9 (8.4:14.9)	<0.001	11.81(1.21)	<0.001	11.9 (8.4:14.1)	<0.001
HGB (Postpartum 6th h)	11.4 (7.7:14.60)		11.37(1.23)		11.5 (7.8:14.1)	
HGB (Prepartum)	11.9 (8.4:14.9)	<0.001	11.9 (8.4:14.9)	<0.001	11.9 (8.4:14.1)	<0.001
HGB (Postpartum 18th h)	10.8 (7.3:13.8)		10.8 (7.3:13.4)		10.6 (7.5:13.8)	
HCT (Prepartum)	35.9 (26.5:43.9)	<0.001	35.70(3.10)	<0.001	35.29(3.58)	<0.001
HCT (Postpartum 6th h)	34.5 (24.1:44)		34.33(3.32)		33.97(3.72)	
HCT (Prepartum)	35.9 (26.5:43.9)	<0.001	35.70(3.10)	<0.001	35.29(3.58)	<0.001
HCT (Postpartum 18th h)	32.3 (23.4:42.7)		32.17(3.25)		32.19(3.67)	

HGB: Hemoglobin, n: number, HCT: Hematocrit. The values given are given as mean (standard deviation) in normally distributed data or median (minimum:maximum) in non-normally distributed data, according to data distribution.

To identify factors associated with a risk of blood loss ≥1000 ml in all patients, a Binary Logistic Regression Analysis using the Backward method was conducted on the variables of the group, gravida, parity, body mass index (BMI), oxytocin duration, and the 3rd stage duration of labor (Table 4). Gravida, BMI, oxytocin duration, and the 3rd stage duration of labor were statistically significant. In all patients, a decrease of 1 unit in gravida was associated with a 2.141 (1/0.467) times higher risk of blood loss ≥1000 ml (P=0.002); an increase of 1 unit in BMI was associated with a 1.101 times higher risk of blood loss ≥1000 ml (P=0.017); an increase of 1 unit in oxytocin duration was associated with a 1.003 times higher risk of blood loss ≥1000 ml (P=0.002); and an increase of 1 unit in the 3rd stage duration of

labor was associated with a 1.094 times higher risk of blood loss ≥1000 ml (P=0.038).

To investigate the factors associated with a risk of blood loss ≥1000 ml in Group A, a Binary Logistic Regression Analysis using the Backward method was conducted on the variables of gravida, parity, BMI, oxytocin duration, PGE2 duration, and 3rd stage duration of labor. The gravida, BMI, and PGE2 duration variables were statistically significant (Table 4). In this group, a decrease of 1 unit in gravida was associated with a 2.762 (1/0.362) times higher risk of blood loss ≥1000 ml (P=0.008); an increase of 1 unit in BMI was associated with a 1.107 times higher risk of blood loss ≥1000 ml (P=0.040); and an increase of 1 unit in the duration of PGE2 use was associated with a 1.003 times higher risk of blood loss ≥1000 ml (P=0.019).

Table 3: Comparisons by duration of the 3rd stage of birth

	Group A (n=151)			Group B (n=150)		
	≤10 min (n=111)	>10 min (n=40)	*P*-value	≤10 min (n=111)	>10 min (n=40)	*P*-value
Amount of Blood Loss (ml)	483.12 (36.72:1657.57)	553.69 (15.22:1289.59)	0.505	375.79 (61.21:1765.09)	424.32 (26.11:1496.3)	0.616
HGB-Dec6 (%)*	-3.28(6.39)	-4.36(6.52)	0.365	-1.9 (-23.02:6.96)	-3.7 (-17.5:3.48)	0.143
HGB-Dec18 (%)*	-3.29(6.61)	-4.74(7.03)	0.244	-2.1 (-22.08:7.58)	-4.57 (-20:3.03)	0.082
HCT-Dec6 (%)*	-9.09 (-29.06:1.96)	-9.95 (-26.45:0)	0.403	-7.66 (-29.69:0)	-7.43 (-27.56:-1.65)	0.889
HCT-Dec18 (%)*	-8.68 (-28.13:-0.62)	-9.98 (-27.30:-0.29)	0.650	-7.22 (-26.49:-1.03)	-7.8 (-29.01:-0.47)	0.714

* In order to compare the groups, it was calculated by taking the percentage change of the measurements at the 6th and 18th h compared to the first measurement. [Percentage change = (last measurement-first measurement)/first measurement], **The values given are given as mean (standard deviation) in normally distributed data or median (minimum:maximum) in non-normally distributed data, according to data distribution. HGB: Hemoglobin, HCT: Hematocrit, n: number. Dec: Decline

Table 4: Evaluation of risk factors for severe postpartum bleeding (≥1000 ml) in all patients and dinoprostone+oxytocin group by binary logistic regression analysis

		P-value	HR	95% CI.	
All Patients	Gravida	0.002	0.467	0.288	0.756
	BMI	0.017	1.101	1.017	1.191
	Oxytocin time	0.002	1.003	1.001	1.005
	3rd stage of birth	0.038	1.094	1.005	1.191
Group A	Gravida	0.008	0.362	0.171	0.765
	BMI	0.040	1.107	1.005	1.219
	Oxytocin time	0.053	1.003	0.999	1.005
	Dinoprostone duration	0.019	1.003	1.000	1.005

Both Models: P<0.001, BMI: Body Mass Index, CI: Confidence Interval/Confidence Interval, HR: Hazard Ratio

Discussion

The PGE2 vaginal ovule is a pharmacological agent frequently used to induce labor in pregnant women admitted for induction due to low Bishop scores in the vaginal examination and unsuitability for induction with oxytocin. This study aimed to compare patients administered oxytocin infusion after PGE2 use with those given oxytocin infusion without PGE2 in terms of the 3rd stage duration of labor, postpartum blood loss, and postpartum hemoglobin and hematocrit values compared to prepartum measurements.

Although numerous studies have investigated PGE2 vaginal ovule, few have evaluated its effects on the duration of the 3rd stage of labor. Comb and Laros [11] evaluated 12,979 vaginal deliveries and found that the median duration of the 3rd stage of labor was 6 min, with placental separation occurring within the first 10 min in 75% of deliveries. The same study found that birth augmentation increased the 3rd stage duration of labor by 1.47 times. In a study by Mahboobeh Taebi et al. [12], which analyzed 1000 births, the median 3rd stage duration was 5 min, and labor induction increased the duration by 2.05 times. No previous study has shown a relationship between PGE2 vaginal ovule and the duration of the 3rd stage of labor. In our study, the median duration of the 3rd stage of labor was 8 min in Group A and 7 min in Group B, consistent with the literature. When the two groups were compared, the duration of the 3rd stage of labor was significantly higher in Group A. This finding suggests that further studies should investigate this relationship.

In a study by Eran Ashwal et al. [13], including 33,915 vaginal deliveries, labor induction was found to increase placental retention 1.84 times, and the labor induction rate with PGE2/prostaglandins was significantly higher in the group with placental retention compared to the group without. In a study by Favilli et al. [14], labor induction with prostaglandins was associated with a 4.29-fold increase in the risk of placental retention. However, our study found no significant difference between the groups regarding placental retention, which may be related to the small number of our patients. Although blood loss in the first 18 h postpartum was higher in Group A than in Group B in our study, this was insignificant. There was no difference between the two groups in the percentage changes of postpartum 6th and 18th-h hemoglobin and hematocrit values compared to prepartum values. In the study of Khireddin et al. [15], labor induction was associated with a higher risk of postpartum hemorrhage than spontaneous labor. According to the same study, oxytocin induction of labor increased the risk of postpartum hemorrhage 1.52 times, and prostaglandin induction increased the risk by 1.21 times. The risk of severe postpartum hemorrhage was 1.57 times higher with oxytocin induction and 1.42 times higher with prostaglandin induction. A meta-analysis comparing the use of intravenous oxytocin along with other methods for labor induction found no significant difference between the oxytocin group and the PGE2 vaginal ovule group regarding postpartum bleeding [16]. The findings of our study are consistent with the results of the meta-analysis.

In the literature, studies have shown that as the duration of the 3rd stage of labor increases, the amount and risk of postpartum hemorrhage also increase. In a study by Manon Van Ast et al. [10] that examined 7,203 single vaginal deliveries, the group with postpartum hemorrhage had a median duration of the 3rd stage of labor of 26 min, while the group without postpartum hemorrhage had a median duration of 10 min. There was a statistically significant difference between these values. The same study found that compared to the subgroup with a duration of the 3rd stage of labor <10 min, the incidence of postpartum hemorrhage increased 1.5 times in the subgroup with a duration of 10–19 min, 2.3 times with a duration of 20–29 min, 3.2 times in the subgroup with a duration of 30-39 min, and 4.6 times in the subgroup with a duration of 40–49 min. In the study of Frolova et al. [17], an increased risk of postpartum hemorrhage was found when the 3rd stage of labor was 20 min or more. In our study, we divided the duration of the 3rd stage of labor into two subgroups as ≤10 min and >10 min and compared them in terms of the amount of blood loss, percentage decreases of postpartum 6th and 18th-h hemoglobin and hematocrit values in both Group A and Group B. However, we did not find a significant difference between the subgroups.

Our study found that a prolonged 3rd stage of labor was associated with an increased risk of severe postpartum hemorrhage. This finding is consistent with previous studies that have reported an increased risk of postpartum hemorrhage with a longer 3rd stage duration of labor [10,17]. Additionally, our study found that an increase in BMI was associated with an increased risk of severe postpartum hemorrhage, which aligns with previous studies reporting obesity as a risk factor for postpartum hemorrhage [19]. Furthermore, we found that each unit increase in the duration of PGE2 use in Group A increased the risk of severe postpartum hemorrhage by 1.003 times. This result is consistent with a French study that found that repeated use of PGE2 vaginal ovule, especially over 30 h, was associated with postpartum hemorrhage [18]. Lastly, we found that a decrease in gravida was a risk factor for severe postpartum hemorrhage, whereas a study by Wetta et al. [19] found nulliparity as a risk factor for postpartum hemorrhage.

Since our study was conducted in a single center and the number of patients was limited, further studies with larger sample sizes are required to evaluate the effect of using PGE2 vaginal ovule in term pregnancies on the duration of the 3rd stage of labor and the amount of postpartum hemorrhage. However, given that PGE2 is commonly used, studies are scarce in the literature regarding its impact on the 3rd stage duration of labor and its correlation with postpartum hemorrhage. Hence, our study will provide valuable insights into this topic and contribute to the existing literature.

Conclusion

Our study suggests that using PGE2 prolongs the 3rd stage duration of labor. Given that prolonging the 3rd stage increases postpartum blood loss, active management of the 3rd stage of labor could be considered in pregnant women using PGE2. Additional interventions could accelerate the 3rd stage of labor in patients given PGE2 induction. However, due to the small number of patients in our study and the limited number of studies on this subject in the literature, definite recommendations cannot be made now. Nevertheless, the lack of a significant difference in blood loss between the groups suggests that PGE2 is a safe agent for cervical ripening and labor induction and does not increase the risk of postpartum hemorrhage. Clinicians and patients could benefit from additional precautions, and predicting that the risk of bleeding will increase in patients with risk factors such as decreased gravida, increased BMI, and prolonged induction time.

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An analysis of misoprostol effectiveness in second trimester pregnancy terminations

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Ethics Committee Approval
The study was approved by Erciyes University Clinical Research Ethics Committee (2016/18). 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.

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Abstract

Background/Aim: Misoprostol is frequently used as a single agent in pregnancy terminations. However, it increases the risk of uterine rupture in patients who have had previous uterine surgery and terminations due to stillbirths. Therefore, it is used with concern by clinicians. The aim of this study was to evaluate the clinical features of the groups that responded and did not respond to termination treatment with misoprostol in a tertiary center and to investigate its efficacy and safety.
Methods: The study design was comprised of a retrospective cohort study. A total of 114 second trimester pregnancies (between 13-24 weeks gestational age) were included in the study. These pregnancies were indicated for termination based on the prenatal diagnosis unit for fetal or maternal causes. According to the International Federation of Gynecology and Obstetrics (FIGO) directions, misoprostol was applied in the following dosages: for 13-17 weeks gestational ages, one tablet per 6 hours; for 18-26 gestational ages, ½ tablet per 6 hours; and for other indications 2 tablets per 3 hours were administered. If the patient had had a previous cesarean operation, all doses were halved. After the first 24 hours, the percentage and demographics results, such as age, body mass index (BMI), gravida, number of cesareans, number of curettages, cervical lengths, BISHOP scores, gestational age, amniotic fluid index, and fetal cardiac beat of the patients with miscarriage, were recorded.
Results: The number of cases resulting in miscarriage within 24 hours were 84 (73.7%) and within 48 hours were 14 (12.2%). The total of misoprostol doses used were 8 tablets of 200 mg, mean time until the complete abortion was 17 hours. Sixteen patients required additional treatment, of whom four required Foley catheterization, five required D&E, seven required resting, and no one required a hysterectomy. Uterine rupture occurred in two patients who needed laparotomic surgery. The maternal age (P=0.340), BMI (P=0.790), gravida (P=0.270), previous cesarean history (P=0.390), previous curettage number (P=0.520), cervical length (P=0.380), Bishop score (P=0.190), gestational age (P=0.072), amniotic fluid index (P=0.470) and presence of fetal cardiac beat (P=0.350) were similar between groups
Conclusion: Our results indicated that misoprostol is a safe, useful, and effective treatment option for second trimester medical terminations. Caution should be exercised in its use in patients with a history of uterine surgery.

Keywords: misoprostol, medical abortion, second trimester, pregnancy termination

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Introduction

One of the most important aims of obstetrics is to minimize the trauma experienced by the mother during childbirth and conclude the pregnancy with the birth of a healthy baby. However, it may be necessary to terminate at any time during pregnancy due to maternal or fetal reasons. There is no consensus yet on the most optimal method for termination of pregnancy in case of fetal anomaly or fetal death in second trimester pregnancies [1].

It was estimated that 42 million abortions were induced in 2003 worldwide. The induced abortion rate In 2003, the induced abortion rate was 29 per 1000 women aged 15–44 years. Second trimester abortions accounted for 10–15% of all induced abortions [1].

Nowadays prostaglandin-derived drugs (misoprostol) are frequently used to provide cervical maturity and induction of labor [2]. The main problem in the use of misoprostol is at which week of gestation, at which indication, and at which dose it should be administered, especially in patients having had previous uterine surgery. It is, therefore, important that procedures for the induction of second trimester abortion minimize long- and short-term morbidity.

The aim of this study to evaluate misoprostol according to the International Federation of Gynecology and Obstetrics's (FIGO) dose directions [3] in terms of efficacy, safety, and complications and to investigate clinical and demographic features between responders and nonresponders to misoprostol in the first 24 hours.

Materials and methods

The present study employs a prospective, non-randomized method conducted at the Department of Gynecology and Obstetrics at the Erciyes University Faculty of Medicine Hospital from December 2015 to May 2016. Informed consent was obtained from all patients participating in the study. The study was approved by the Erciyes University Clinical Research Ethics Committee (2016/18).

Patient selection

A total of 114 second trimester (between 13-24 weeks gestational age) pregnancies were included in the study indicated for pregnancy termination by prenatal diagnosis unit with fetal or maternal causes. Inclusion criteria consisted of the following: 13-24 weeks gestational age, singleton pregnancy, no regular uterine contractions, and no preterm premature rupture of membranes (PPROM).

Misoprostol application

The misoprostol to be used for the termination was applied vaginally at the appropriate dosage and time intervals according to the conditions specified in the FIGO dose directives. Accordingly, misoprostol was administered for intrauterine ex fetus between 13-17 weeks gestational at one tablet every 6 hours; for fetuses between 18-26 gestational ages; ½ tablet per 6 hours; and for other indications, 2 tablets per 3 hours. If the patient had had a previous cesarean operation, all doses were halved. FIGO recommended dosages are shown in Figure 1. Application of misoprostol was continued for 48 hours. If the abortion did not occur after 48 hours, other methods were administered, such as dilatation and evacuation (D&E), Foley catheterization, resting, or hysterectomy.

Figure 1: FIGO recommended dosages

<table>
<tr><th></th><th>1st Trimester</th><th>2nd Trimester</th><th>3rd Trimester</th><th>Postpartum</th></tr>
<tr><td rowspan="2">25 µg</td><td></td><td></td><td>Induction of labour 25µg pv 6 hourly or 25µg po 2 hourly</td><td></td></tr>
<tr><td></td><td></td><td>Intrauterin foetal death 25µg pv 6 hourly or 25µg po 2 hourly</td><td></td></tr>
<tr><td>100 µg</td><td></td><td>Intrauterin foetal death 13-17 weeks 100µg pv 6 hourly (max4)</td><td></td><td></td></tr>
<tr><td>200 µg</td><td></td><td>Intrauterin foetal death 13-17 weeks 100µg pv 6 hourly (max4)</td><td></td><td></td></tr>
<tr><td rowspan="2">400 µg</td><td>Cervical ripening pre-instrumentation 400µg pv 3 hours or sl 2-3 hrs before procedure</td><td>Induced abortion/Interruption of pregnancy 400µg pv or sl 3 hourly(max5)</td><td></td><td></td></tr>
<tr><td rowspan="3">Incomplete abortion 600µg po or 400µg sl single dose</td><td></td><td></td><td></td></tr>
<tr><td>600 µg</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">800 µg</td><td rowspan="2">Missed abortion 800µg pv 3 hourly (max2) or 600µg sl hrly(max2)</td><td></td><td></td><td>Postpartum hemorrhage prophylaxis 600µg po single dose</td></tr>
<tr><td></td><td></td><td>Postpartum hemorrhage treatment 800µg sl single dose</td></tr>
<tr><td></td><td>Induced abortion 800µg pv or sl 3 hourly(max3)</td><td></td><td></td><td></td></tr>
</table>

pv-vaginal,sl-under the longue,po-oral,µg-microgramme

References-FIGO misoprostol recommended Dosages 2012

After the first 24 hours, the percentage and demographic results, such as age, BMI, gravida, number of cesareans, number of curettages, cervical lengths, Bishop scores, gestational age, amniotic fluid index, and fetal cardiac beat of the patients with miscarriage were recorded.

Statistical analysis

Descriptive data of the study group were given as mean, median, standard deviation, quartile, minimum, and maximum values. The distributions of the variables were evaluated by the Kolmogorov-Smirnov test and histogram, mean and standard deviation for normal distributed variables, and median, quartile, and minimum-maximum values for variables not showing normal distribution. In the comparisons between the groups, the independent-sample t-test was used for the variables that showed normal distribution, and the Mann-Whitney U test was used for the variables that did not distribute normally. Categorical variables and percentages were evaluated using the chi-square test. Binary logistic regression analysis was used to determine the independent factors that affect the logistic termination within 24 hours. Statistical significance was determined as $P<0.05$ for all analyses. The R package program was used for statistical analysis.

Results

Of 114 patients, 45 were terminated due to in utero-fetal death, 11 were open NTD, 7 were cystic hygroma, 7 were with multiple anomalies, and 7 were anencephaly. The other termination indications were Down syndrome, HELLP syndrome, intrauterine growth restriction (IUGR), severe preeclampsia, encefalocel, hydrops fetalis, fetal bladder agenesis, partial mole pregnancy, acrania, omphalocel, cardiac and skeletal anomalies,

chisencephaly, inencephaly, holoprecencephaly, and pregnancy with abuse.

Demographics and clinical values of the patients are shown in Table 1. The mean maternal age was 28.5 (5.4), mean BMI was 27.1 (5.2), mean gravida was 3 (1-9), mean cervical length was 35.8 (8.8), mean Bishop score was 2 (0-5), mean gestational age was 124.2 (22.3), and mean amniotic fluid index was 9.1 (4.1).

Table 1: Demographics and clinical values of the patients

Variable	Mean (standard deviation) median (range)
Age (years)	28.5 (5.4)
BMI (kg/m2)	27.1 (5.2)
Gravida	3 (1-9)
Previous cesarean history	0 (0- 4)
Previous curettage number	0 (0-5)
Cervical length (cm)	35.8 (8.8)
BISHOP score	2 (0-5)
Gestational age (days)	124.2 (22.3)
Amniotic fluid index (cm)	9.1 (4.1)

Comparative data of cases with and without response to misoprostol within 24 hours are shown in Table 2. Maternal age (*P*=0.340), BMI (*P*=0.790), gravida (*P*=0.270), previous cesarean history (*P*=0.390), previous curettage number (*P*=0.520), cervical length (*P*=0.380), Bishop score (*P*=0.190), gestational age (*P*=0.072), amniotic fluid index (*P*=0.470), and presence of fetal cardiac beat (*P*=0.350) were similar between groups.

Table 2: Comparative data of cases with and without response to misoprostol within 24 hours

Variable	Responsive (n=84)	Unresponsive (n=30)	*P*-value
Maternal age (years)	28.5 (6.9)	29.9 (6.8)	0.340
BMI (kg/m^2)	27.2 (4.7)	26.88 (6.5)	0.790
Gravida	3 (1-9)	3 (1-7)	0.270
Previous cesarean history	0 (0-3)	0 (0-4)	0.390
Previous curettage number	0 (0-5)	0 (0-1)	0.520
Cervical Length (cm)	36.2 (9.4)	34.5 (7)	0.380
BISHOP score	2 (0-5)	2 (0-5)	0.190
Gestational age (days)	122 (22.8)	135 (25.8)	0.072
Amniotic fluid index(cm)	8.9-(3.8)	9.5 (4.9)	0.470
Presence of fetal cardiac beat	53 (63%)	16 (53%)	0.350

Binary logistic regression analysis to determine the independent factors affecting the termination variable within 24 hours are shown in Table 3. The maternal age OR was 0.97 (0.89-1.05); gestational age OR was 0.98 (0.96-1.0), when the number of gravida 1-4 OR was 0.95 (0.11-8.3), when the number of gravida >4 OR was 0.3 (0.7-1.5), when the previous curettage number was 1, OR was 0.001 (0.001-5.2) , when the previous curettage number >1 OR was 0.001 (0.001-4.3), BMI OR was 1.02 (0.93-1.1), presence of fetal cardiac beat OR was 0.55 (0.19-1.6), cervical length OR was 1.0 (0.96-1.07). The Bishop score OR was 0.88 (0.64-1.2), amniotic fluid index OR was 0.96 (0.85-1.0) and previous cesarean history >1 OR was 2.0 (0.4-9.8).

Table 3: Binary logistic regression analysis to determine the independent factors affecting the termination variable within 24 hours

	OR (95% CI)
Maternal age (years)	0.97 (0.89-1.05)
Gestational age (days)	0.98 (0.96-1.0)
Gravida	
1-4	0.95 (0.11-8.3)
>4	0.3 (0.7-1.5)
Previous curettage number	
1	0.001 (0.001-5.2)
>1	0.001 (0.001-4.3)
BMI (kg/m^2)	1.02 (0.93-1.1)
Presence of fetal cardiac beat	0.55 (0.19-1.6)
Cervical length (cm)	1.0 (0.96-1.07)
Bishop score	0.88 (0.64-1.2)
Amniotic fluid index (cm)	0.96 (0.85-1.0)
Previous cesarean history	
1	1.3 (0.3-5.7)
>1	2.0 (0.4-9.8)

Data's related to misoprostol application

The number of cases resulting in miscarriage within 24 hours were 84 (73.7%); the number within 48 hours were 14 (12.2%). Total misoprostol doses used were 8 tablets of 200 mg (5-10 tablets), and the mean time until complete abortion was 17 hours (12-26 hours). The number of patients requiring additional treatment were 16 (14%). Of those, four required Foley catheterization (3.5%), five required D&E (4.3%), seven required resting (6.1%), and no one required a hysterectomy. Uterine rupture occurred in two patients (1.7%) and needed a laparotomic operation. The first one was 16 weeks pregnant and terminated for anencephaly. The other case was with 20 weeks pregnant and terminated for intrauterine death fetus. Both had previously had two cesarean sections. The ruptures were at the previous incision shape. Seven patients needed curettage to remove the rest placenta (6.4%). During the first 24 hours, the response rate was 73.7%, and in 48 hours, it was 85.9%

Discussion

In the present study, we evaluated the effect of misoprostol application on termination of pregnancy during the second trimester. In order to maintain the current location of the regular obstetrics practice, and because obstetricians are often undecided on the dosages of misoprostol, application times, and individualization of patients according to these parameters, we decided to publish our experience with the application of misoprostol.

When it is decided to terminate the pregnancy, the cervix must be mature and given appropriate time to delivery [4]. It has been determined in the termination of first and second trimester pregnancies that the use of misoprostol is non-invasive, easy to apply, cost-effective, quick, and reliable [5]. The current literature indicates that prostaglandin E1- misoprostol may be used for delivery induction in the presence of an inappropriate cervix [6]. However, there is no consensus on the effective and safe administration and dosage of misoprostol [7]. Carbonella et al. [8], reported 85% complete abortion rates at 9-12 weeks of gestation and 80% complete abortion rates at 12-15 weeks gestation with misoprostol. In another study, given two vaginal misoprostol every three hours and applied a total of five times achieved 80% abortion rate in the first 24 hours and 95% abortion rate in the first 48 hours [9]. In our study, 84 (73.3%) patients had complete abortions in the first 24 hours, and 98 pregnancies terminations were provided (85.9%) in 48 hours.

There are many factors that affect abortion rate within the first 24 hours with misoprostol. In some studies, the Bishop score was found to be more significant than the cervix size [10], whereas in others, abortus time was correlated with cervical length [11]. While it was determined that the abortion time decreased as correlated with gestational age [12,13] and inversely correlated with parity [13], BMI was not found to be related to abortion time [14]. While it was suggested that previous surgery had no effect on abortion duration [15,16], in some studies, it was determined that the rate of bleeding and incomplete abortion increased [16]. In our study, no statistically significant results were obtained regarding the factors mentioned above.

At times, additional methods are needed to shorten the duration of abortion. Although Foley catheterization was one of

these methods, contradictory results were obtained in the studies. While in one study it was observed that Foley catheterization and misoprostol use decreased the term of termination compared to misoprostol alone [17], another study determined that the use of Foley catheterization with misoprostol did not make a significant difference in termination time [18]. In our study, use of the Foley catheter resulted in abortion in patients who failed with misoprostol.

Another important variable affecting abortion duration is fetal cardiac activity. In a study including 89 cases, at the 12th, 24th and 48th hours, while the rate of abortion success of patients with alive fetuses were 15%, 54% and 92%, respectively, of the patients with intrauterine death fetuses were 50%, 83% and 92%, respectively [19]. Dilbaz et al. [20], found that if the fetus was alive and gestational age >16 weeks, the abortion duration was prolonged. In another study, it was detected that misoprostol dose and termination intervals were shorter in pregnancy terminations by reason of intrauterine ex fetuses [21,22]. In our study, 84 of 114 cases responded to treatment in the first 24 hours. In 53 of the patients who received response to treatment, and in 16 of the 30 unresponsive patients, fetal cardiac activity was available. Although the ratio was higher in responding patients, it was not statistically significant. In a study by Vitner et al. [13], nulliparity, young mothers' ages, and advanced gestational age were associated with abortion duration. This was not the case in our study; however it was the result in another Turkish study [23]. This may be associated with the demographic characteristics of Turkey.

After the second trimester medical abortions, incomplete abortion or remaining placenta is an important problem and requires surgical intervention. In the first studies on this subject, more than 80% of patients after misoprostol required curettage [9,24]. It was observed that this rate decreased below 5% in later studies [5]. In our study, curettage was performed for misoprostol failure in five patients and in seven patients because of remaining placenta. Our curettage rate was 6.4%, and this rate was similar to other studies.

In this study, we investigated effect and complicates of misoprostol alone. In a study achieved by misoprostol alone, 54 of 55 pregnancies terminated. Mean abortion duration was 12.7 hours and only one patient needed curettage for rest placenta [26].

Both the mother and the obstetrician are concerned during the termination of pregnancy. It has been shown that the use of misoprostol in these weeks is safe. This situation before the treatment and the guarantee thereafter will guide the reduction of the slowdown with the family.

Limitations

One limitations of this study is that the surgeons who performed previous operations on pregnant women with previous cesarean section births was different, and they may have used different techniques. In our study, the rate of abortion in the first 24 hours was 73.7% and in 48 hours was 85%. The reason for the low success in our study compared to other studies, may be caused by the usage of low doses of misoprostol on patients who had experienced intrauterine fetal death and previous surgery history. The guidelines followed were in accordance with FIGO directions.

Conclusion

Our results indicated that misoprostol is a safe, useful, and effective treatment option for second trimester medical terminations. Caution should be exercised in its use in patients with a history of uterine surgery.

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Research article

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Treatment of iatrogenic pseudo-aneurysms with ultrasonography-guided percutaneous thrombin injection and compression

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Ethics Committee Approval
This study was approved by the ethics committee of Karadeniz Technical University Medicine School (Approval number: 24237859-135). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Recently, endovascular interventional procedures have become prevalent. Thus, complications due to arterial catheterization are frequent. The most common access site complications are pseudo-aneurysms (PSAs). The present study aimed to treat iatrogenic pseudo-aneurysm (PSA) with ultrasonography (US)-guided compression and percutaneous thrombin injection and to report these methods' effectiveness and short-term outcomes.

Methods: The study was designed as a retrospective cohort study. Two treatment techniques were performed. Forty-eight of 54 patients were included in the study. Forty patients were treated with US-guided percutaneous thrombin injection, and eight were treated with US-guided compression. Six of the 54 patients were excluded from the study. Two of these patients needed further surgical treatment. The other four patients needed no further intervention due to spontaneous thrombosis of PSA. The patient demographics, history of AC/AA drug use, indication for performing arterial catheterization, localization and size of PSAs, treatment method applied, the effectiveness of treatment, early outcomes, and the treatment complications were evaluated.

Results: In eight patients treated with US-guided compression, recurrent filling was not observed at the 24-h and first-month post-treatment follow-ups, and 100% success was achieved. Among the 40 patients treated with percutaneous thrombin injection for whom a second session was applied, recurrent filling was observed in six PSAs at the 24-h post-treatment follow-up. While the treatment success rate was 85% in the first session, it increased to 97.5% after the second session. A first-month follow-up could be made in 84.6% of the treated patients, and recurrence was observed in no patients.

Conclusion: US-guided thrombin injection for PSAs has a high success rate. It is practical, relatively rapid to perform, has low complication rates, and may be selected as the first treatment choice for PSA.

Keywords: iatrogenic pseudoaneurysms, US-guided compression, US-guided percutaneous thrombin injection

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Introduction

Pseudoaneurysms (PSAs) are hematomas developing from blood leakage from the vessel wall defect containing blood flow. The pseudo-lumen is associated with the injured artery through the neck. It is the most common complication developing after femoral artery catheterization and comprises 61% of all arterial access site complications. While the incidence of PSA is 0.1–1.1% in diagnostic procedures, it increases to 3.5–5.5% in therapeutic procedures [1-3].

While the primary treatment approach for PSA was surgical methods until the 1990s, minimally invasive methods have gained popularity in medical practices in recent years; compression, ultrasonography (US)-guided thrombin injection, endovascular modalities, and other methods have replaced surgery. These methods have grown in popularity because of their effectiveness and low morbidity and mortality rates [2,4,5].

The present study aimed to evaluate the effectiveness, short-term outcomes, and complication rates of iatrogenic PSAs treated with US-guided percutaneous thrombin injection and compression.

Materials and methods

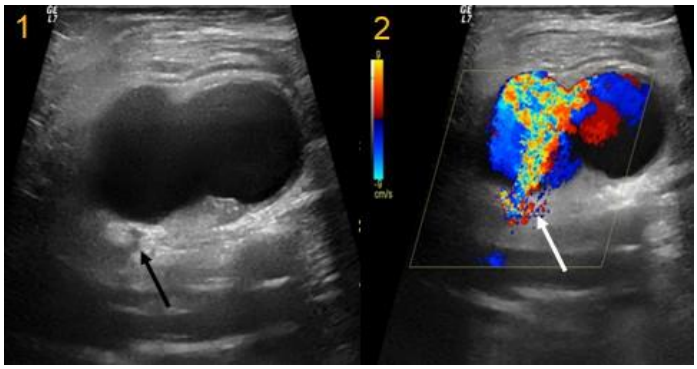
We retrospectively screened prospectively-collected data from 54 patients referred to the Karadeniz Technical University Medical Faculty Interventional Radiology Unit due to PSA developing after arterial catheterization between 2011 and 2018. The sample size could not be planned because iatrogenic PSA is an urgent condition that originates mostly from other clinics. Six of the 54 patients were excluded from the study. Two of these patients needed further surgical treatment, and the other four patients needed no further intervention due to spontaneous thrombosis of PSA. Therefore, 48 PSA patients treated with US-guided percutaneous thrombin injection and compression were included in the study. Features of PSAs (e.g., size, connecting artery) were evaluated with the grayscale and color Doppler US (CDUS) using a GE Voluson Expert US device (General Electric, Waukesha, Wisconsin) and 9-Mhz probe.

Patients with PSAs with the largest diameter of less than 20 mm and who were not using anticoagulant/antiaggregant (AC/AA) medications were treated with the compression method (Figure 1). Patients with PSAs larger than 20 mm were treated with US-guided percutaneous thrombin injections regardless of the history of AC/AA medication use. After treatment, all patients underwent compression dressing and inguinal compression with sandbag during the first 4 h and 24-h bed rest.

In US-guided compression treatment, the PSA neck was localized with the US, compression was applied to the PSA neck, and the blood flow in the neck region was completely interrupted. The flow was controlled every 15 min during compression. The procedure was terminated when thrombus formation was observed in the PSA sac, and flow was seen to be interrupted.

In patients treated with the US-guided thrombin injection method, surgical prophylaxis was provided by 1 g cephazolin given intravenously 30 min before the procedure, and anaphylaxis prophylaxis was provided by 40 mg methylprednisolone and 45.5 pheniramine maleate given by the intravenous route 1 h before the procedure. For all patients, human thrombin as TISSEEL (Baxter, Gurgaon, India) KIT 2/4 ml vials was provided following cold chain principles. The skin was sterilized with betadine (povidone-iodine). The PSA sac was entered from the most distant part of the neck part with a 27 gauge (G) dental needle. Following the injection, which lasted for approximately 30–60 s, the procedure was terminated when the PSA lumen was seen to be thrombosed. The flow in the PSA and related arteries were evaluated with CDUS. The patients were followed up for Color Doppler US 24 h and 1 month after the procedure. At the 24-h follow-up, patients who did not have recurrent filling and complaints were discharged. Those who had recurrent filling were re-treated.

Figure 1: Features of PSAs (e.g., size, neck, connecting artery). Neck of PSA with the gray scale (black arrow) and color Doppler US Aliasing artifact (white arrow) and "Ying-Yang" sign.



Statistical analysis

Data including patient demographics, the intervention that led to PSA, localization of PSA, treatment effectiveness, recurrence, and complications, were given as mean (standard deviation), frequency, and percentage values.

Results

The mean age of the patients was 61.5 (16.2) years (10–86); 39.6% of the patients were female, 60.4% were male, and 72.9% were using AC/AA medications. PSAs mostly originate from the femoral artery (Table 1). Of 48 patients, 83.3% (40 patients) were treated with US-guided percutaneous thrombin injection, and 16.7% (8 patients) were treated with the US-guided compression method.

Table 1: Demographic and clinical characteristics of the patients.

Parameter	Value
Age, mean (SD)	61.58 (16)
Gender	% (n)
Female	39.6 (19)
Male	60.4 (29)
Procedure	% (n)
Diagnostic coronary angiography	52.1 (25)
Percutaneous coronary intervention	27.1 (13)
Cerebral digital angiography	4.2 (2)
Cerebral aneurysm coil and stent	4.2
Renal AVF embolization	2.1 (1)
Ischemic stroke	2.1
External iliac artery stenting	2.1
Renal artery stenting	2.1
Abdominal aorta stenting-grafting	2.1
Coronary artery by-pass surgery	2.1
Vascular access site	% (n)
Main femoral artery	50 (24)
Superficial femoral artery	41.7 (20)
Deep femoral artery	2.1 (1)
Brachial artery	4.2 (2)
External iliac artery	2.1
AKG/AG history use	72.9 (35)

SD: standard deviation

The mean size of eight PSAs treated with US-guided compression was 18.3 (2.3) mm. For all patients, the duration of treatment varied between 15 and 30 min. The recurrent filling was not observed in patients with the grayscale and color Doppler US at the 24-h and 1-month post-treatment follow-ups.

Of the patients who underwent US-guided percutaneous thrombin injection, 87.5% were taking AC/AA medications. The mean size of PSAs was 35 (9.5) mm (range: 60–20 mm). The mean thrombin dose was 4 (1.7) diziems. At the 24-h post-treatment follow-up, recurrent filling was observed in six PSAs. One patient was treated surgically. Four patients underwent a second thrombin injection, one patient underwent US-guided 25 min compression, and the recurrent filling was not observed on color Doppler US performed at 48 h. While the success rate was 85% in the first injection in the US-guided percutaneous thrombin injection group, the success rate increased to 97.5% with the second procedure. At the first-month follow-up, one patient had died due to cardio-vascular reasons, and the follow-up of five (12.5%) patients were lost. Recurrent filling was not observed in 84.6% of the patients at the first-month follow-up (Table 2). Minor complications related to the procedure developed in three patients. A thrombus developed in the main femoral vein in one patient who had undergone a US-guided percutaneous thrombin injection. In two patients, numbness, sensation loss, swelling, and pain developed following the thrombin injection. The symptoms regressed in 24–48 h with medical treatment.

Table 2: RDUS characteristics of pseudo-aneurysms, treatment method and outcomes.

Parameter	Value
The largest diameter of the pseudo-aneurysm, mean (standard deviation)	32.7 (10.2)
PSA treatment method	%
US-guided compression	16.7
US-guided percutaneous thrombin injection	83.3
Treatment outcomes of all patients	%
24 h	87.5
48 h	98
1 month	87.2
Treatment outcomes of US-guided compression	%
24 h	100
1 month	100
Treatment outcomes of thrombin injection	%
24 h	85
48 h	97.5
1 month	84.6

* The values given are the rates of the patients whose 1-month control could be realized and in the controlled PSAs of whom no recurrence or residual filling was observed.

Discussion

While small PSAs may become thrombosed spontaneously, many require treatment. These may lead to more severe complications like rupture, skin necrosis, compression-related deep vein thrombosis, and neuropathy [6,7].

Until the 1990s, surgery was the primary treatment approach for PSAs. In 1991, Fellmeth et al. [6] first treated PSAs with compression. In 1986, Cope et al. [9] applied fluoroscopy-guided percutaneous thrombin injection; in 1997, Liau et al. [10] applied US-guided percutaneous thrombin injection. Gradually, surgical treatment was replaced by non-invasive and percutaneous treatment methods. These approaches reduced mortality and morbidity [2,5,6,8-10].

US-guided compression treatment is more successful than blind compression as it is applied by seeing the PSA neck; the rate of complications such as deep vein thrombosis is lower, and it is more comfortable due to the short duration of the procedure [11,12]. The success rate is affected by patient age, use of AC drugs, PSA size, being simple or complex, and the length and width of the PSA neck [8,13,14]. Time is the most important factor that restricts US-guided compression treatment. Longer duration induces thrombus. The patient may need analgesics and even narcotics for a prolonged time. It is also difficult for the practitioner to perform compression by keeping the position stable for a long time [11]. In our study, we performed compression treatment on patients whose PSA diameter was less than 2 cm and who were not using AC/AA medications. The duration of compression varied between 15 and 30 min. Hence, we did not encounter problems like pain intolerance and fatigue of the operator resulting from prolonged time. Thrombosis was provided in all patients, and no recurrence or complication was observed during the follow-ups. In the literature, we see a decrease in the success rates of US-guided compression treatment and an increase in the recurrence rates in patients who use AC drugs [13,15]. Studies also report that the PSA size and treatment success are inversely proportional [14,16]. As a result of these studies, we see that the small size of PSAs and the non-use of AC/AA by the patients increase the success rate of compression treatment. We see that US-guided compression treatment has some disadvantages, such as being uncomfortable for the patient and the operator, long duration of treatment, and a low success rate, particularly in patients who use AC/AA and have large PSAs. The history of AC/AA use and the PSA size (<2 cm) should be considered for achieving high success rates and eliminating technical disadvantages.

US-guided percutaneous thrombin injection is a preferred method due to its high success and low complication rates, not containing ionizing radiation, being easily applicable, having a short duration, and being well tolerated [17,18]. The results of our study indicate that US-guided thrombin injection is safe, practical, and successful. Recurrent filling was observed at the 24-h follow-up in 15% of the patients who had undergone US-guided percutaneous thrombin injection. However, the success rate increased to 97.5% with the second session of thrombin injection and US-guided compression method in one patient. Recurrent PSA was not observed at the follow-up 1 month later. In the literature, the success rate of US-guided percutaneous thrombin injection has been reported as 94–100% [5,10,17,19-21]. Previously, compression therapy was more frequently preferred in the treatment of iatrogenic PSAs. However, in the literature, when compared to thrombin injection therapy, success rates of 64–100% were reported, especially in PSA developing more than 2 weeks previously and in AC users. Complications are rare after US-guided percutaneous thrombin injection. According to the results of the studies, the incidence of complications has been reported to be 0–4% [1,8,20,22-25]. The most common complication is thrombin leakage into the arterial lumen associated with PSA and the development of distal embolism. Other complications are quite rare, including swine thrombin-related anaphylaxis-urticaria, infection-abscess, deep vein thrombosis, and coagulopathy due to the development of autoantibodies against factor V in recurrent swine thrombin injection [17,19,26,27]. We encountered two complications in our study: one patient developed a thrombus in the femoral vein; the other was the development of numbness and loss of sensation

in the leg, swelling and pain in the arm, which was thought to be due to the mass effect after thrombin injection in the superficial femoral and brachial artery, which regressed in the follow-up. In the literature, Weinman et al. [25] encountered sudden onset pain in two of 33 patients who underwent thrombin injection and skin infection in one patient. Pezzullo et al. [28] reported foot pain and temporary occlusion in the dorsalis pedis after paresthesia in 1 of 23 patients who underwent a thrombin injection.

Limitations

The relatively small number of cases, the evaluation of only the size of PSAs, and the inability to evaluate the parameters (such as the number of lobulations and neck diameter) are limitations of our study.

Conclusion

In our study, we observed that US-guided compression treatment was successful in selected patient groups. US-guided thrombin injection is a treatment method with a high success rate, and it is practical and relatively rapid to apply; it has low complication rates and may be selected as the first treatment choice for PSA.

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Research article

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The effects of mirabegron used for overactive bladder treatment on female sexual function

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Abstract

Background/Aim: Overactive bladder (OAB) is a common condition, especially in middle-aged women and can frequently have negative effects on female sexual function (FSD). The aim of the study was to assess the impact of mirabegron on female sexual dysfunction in women affected by OAB.

Methods: In this cross-sectional study, 42 women with OAB and FSD were retrospectively enrolled. Patients were evaluated based on a detailed history, physical examination, uroflowmetry and residual urine measurements, 3-day voiding diary, visual analog scale (VAS), and Female Sexual Function Index (FSFI) questionnaire before and 12 weeks after treatment with mirabegron (50 mg/day).

Results: At the 12-week follow-up, OAB symptoms improved significantly in all patients. The mean (standard deviation [SD]) FSFI total score significantly improved in 34/42 patients (80.9%) from 16.8 (1.3) to 26.9 (1.6); $P<0.001$. Mean (SD) scores significantly increased in domains of desire (from 2.1 [0.6] to 4.8 [0.2]), arousal (from 2.6 [0.3] to 4.3 [0.5]), lubrication (from 3.1 [0.6] to 4,1 [0.2]), orgasm (from 3.1 [0.2] to 4.3 [0.1]), and satisfaction (from 2.8 [0.4] to 4.1 [0.5]) after 12 weeks of treatment with mirabegron. Also, mean VAS scores significantly improved from 4.4 (1.4) to 8.8 (1.1); $P<0.001$.

Conclusion: Treatment of OAB with mirabegron yields positive effects on sexual function of OAB patients.

Keywords: female, sexual function, overactive bladder, mirabegron

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Ethics Committee Approval
The study was approved by Gulhane Ethical Committee Ankara (date: 2023/01/17, approval number: 2023-36).
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.

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Introduction

Overactive bladder (OAB) is defined as urinary urgency, frequency, and nocturia with or without urgency incontinence in the absence of any obvious pathologies [1]. OAB affects approximately 12% of men and women aged >40 years [2]. OAB negatively affects the quality of life (QoL) in both sexes. Female sexual function is important for overall health and well-being. Urinary incontinence (UI) contributes to the development of female sexual dysfunction (FSD) [3]. The association between OAB and FSD was evaluated previously [4–8]. The frequency of sexual intercourse may decrease in about 25% of women with OAB [4]. Also, these women report lack of enjoyment of sexual activity [5]. Treating OAB improves female sexual dysfunction [8]. Antimuscarinics or mirabegron (β3-agonist) are the first-line medical therapy for OAB. Mirabegron has an efficacy similar to antimuscarinics [9]. Data regarding the association between mirabegron used for the treatment of OAB and FSD are limited. The aim of this study was to describe the effect of mirabegron used for OAB treatment on sexual function in sexually active women.

Materials and methods

PAnkara Gulhane Training and Research Hospital Ethical Committee approved the study (date: 2023/01/17, approval number: 2023-36). Our outpatient database was retrospectively searched between 01 January 1, 2021 and January 30, 2023. Sexually active women with OAB for at least three months, who received mirabegron therapy, and who were >18 years old were enrolled into the study. OAB was defined as stated by the International Continence Society [1]: (1) urgency ± urgency urinary incontinence (UUI), (2) frequency, and (3) nocturia. Exclusion criteria included several parameters: (1) recurrent urinary tract infections (UTI ≥3 episodes/year), (2) post-void residual (PVR) urine volume >100 ml (3), stress urinary incontinence (SUI), (4) depressive symptoms, (5) urethral stricture, (6) pelvic or bladder tumors, (7) previous incontinence or pelvic surgery, (8) neurological disease, (9) uncontrolled systemic diseases (such as diabetes mellitus), (10) pelvic prolapse (Pelvic Organ Prolapse Quantification [POPQ] ≥ stage II), and/or (11) any previous OAB treatment..

Patients were evaluated based on a detailed medical and sexual history, urogynecological assessment to assess pelvic prolapse and SUI, urine culture, uroflowmetry, and PVR measurements. Visual analog scale (VAS) was used to score the impact of urinary symptoms on QoL (0=worse; 10=best). A 3-day voiding diary was used. Urgency, frequency, nocturia, UUI episodes, number of pads used, and voiding volume were recorded.

All patients completed the Turkish version of the Female Sexual Function Index (FSFI) questionnaire [10]. FSFI has been strongly recommended for assessing female sexual function [11]. FSFI contains several domains: (1) desire, (2) arousal, (3) lubrication, (4) orgasm, (5) satisfaction, and (6) pain. Higher scores are associated with better sexual function.

All patients underwent mirabegron (50 mg/day) treatment for 12 weeks. The 3-day voiding diary, uroflowmetry, PVR measurement, FSFI, and VAS were evaluated before and after the treatment.

Statistical analysis

The sample size required to achieve 90% power to detect post-treatment differences in FSFI scores, assuming an alpha of 0.05, was 40. SPSS 13.0 USA was used for statistical analysis. Continuous parametric and nonparametric variables were compared with Student's t- and the Mann–Whitney U tests. Continuous variables were reported as median and interquartile range (IQR) or mean (standard deviation [SD]). Relationships between differences in OAB parameters and FSFI were assessed using a Pearson's coefficient analysis. A *P*-value ≤0.05 was considered significant.

Results

Forty-two eligible patients were identified. Mean (SD) age was 43.5 (9.2) years. Patient characteristics are summarized in Table 1.

Table 1: Demographic characteristics of patients

	n=42
Age (years), (mean [SD])	43.5 (9.2)
Body mass index (BMI, kg/m^2), (mean [SD])	29.3 (4.3)
Postmenopausal, (n, %)	21 (50%)
Parity, (mean [SD])	2.9 (1.1)

SD: standard deviation; BMI: body mass index

Thirty-four out of forty-two patients (80.9%) reported significant improvements in sexual dysfunction as assessed by FSFI. The mean post-treatment FSFI score was significantly higher (26.9 [1.6]) compared to pre-treatment values (16.8 [1.3]) at *P*<0.001. All FSFI domains except pain improved after mirabegron treatment (Table 2). In addition, FSFI domains significantly improved both in continent and incontinent patients after treatment.

Table 2: FSFI domains in 42 female OAB + sexual dysfunction patients treated with oral mirabegron 50 mg/day

FSFI domains	Pre-treatment, Mean (SD)	12 weeks after treatment, Mean (SD)	*P*-value
Desire	2.1 (0.6)	4.8 (0.2)	<0.001
Arousal	2.6 (0.3)	4.3 (0.5)	<0.001
Lubrication	3.1 (0.6)	4.1 (0.2)	0.038
Orgasm	3.1 (0.2)	4.3 (0.1)	0.013
Satisfaction	2.8 (0.4)	4.1 (0.5)	0.021
Pain	2.7 (0.4)	3.1 (0.6)	0.51
Total	16.8 (1.3)	26.9 (1.6)	<0.001

FSFI: Female Sexual Function Index; OAB: overactive bladder

All patients had increased urinary frequency and urgency (100%), and 33 patients (78.5%) had UUI at baseline. Urinary symptoms improved significantly after treatment (Table 3). Seventeen (40.4%) patients were completely continent. A significant increase was found in mean (SD) VAS score (pre-treatment 4.4 [1.4], post-treatment 8.8 [1.1]; *P*<0.001). In addition, no side effects were reported during the treatment period.

Table 3: Urinary symptoms in 42 female OAB + sexual dysfunction patients treated with oral mirabegron 50 mg/day

Urinary symptoms	Pre treatment Mean (SD)	12 weeks after treatment Mean (SD)	*P*-value
Frequency/day	13.8 (2.7)	6.7 (1.5)	<0.001
Nocturia/day	1.9 (1.1)	0.7 (0.4)	<0.001
Urgency episodes/day	5.7 (2.5)	2.8 (2.1)	<0.001
Incontinence episodes/day	2.2 (0.8)	0.9 (0.8)	<0.001

OAB: overactive bladder

Discussion

In our study, we showed that mirabegron used for the treatment of OAB provided significant improvements in sexual dysfunction. FSD is seen more frequently in women with UI than in the general healthy population. Approximately half of OAB patients have FSD [12]. First-line medical treatment of OAB includes antimuscarinics and the β3-adrenoceptor agonist, mirabegron. Mirabegron has demonstrated similar efficacy and lower adverse events compared to antimuscarinics [9]. OAB treatment produces positive effects on sexual function in women with OAB [13].

Although all domains of sexual function are adversely affected in women with UI, the most common sexual complaints are decreased desire, vaginal dryness, and dyspareunia. OAB is associated with decreased sexual activity, more interruption of intercourse due to urinary symptoms, and decreased lubrication, more dyspareunia, and more orgasmic problems compared to other types of UI [14–16]. In OAB patients, the most important symptom that impairs sexual function is UUI [17]. UI in OAB patients is unpredictable and unavoidable and leads to distress and discomfort. In addition, OAB patients may need to go to the toilet during sexual intercourse or may leak urine during intercourse or orgasm. Interrupting intercourse to urinate or having UI during intercourse can be a cause of great embarrassment and therefore lead to a decrease in sexual interest [18]. OAB is associated with decreased sexual satisfaction, decreased desire, decreased lubrication, and orgasm problems [15,19].

In this study, we showed that mirabegron (50 mg/day) for 12 weeks produces an improvement in both urinary symptoms and sexual dysfunction. Impaired QoL of the OAB patients also improved significantly as assessed by VAS. Following mirabegron treatment, FSFI total scores significantly improved. The most improved FSFI domains are desire, arousal, satisfaction, lubrication, and orgasm. On the other hand, pain domain results did not changed significantly.

Gubbiotti et al. [20] conducted a study on the effect of mirabegron (50 mg/day) on sexual function. They reported that mirabegron treatment provided significant improvement in total FSFI score and in all FSFI domains except pain. Our data are similar to the data in Gubbiotti's study. The authors also found that continent women after mirabegron therapy showed higher improvements in FSFI scores compared to incontinent women [20]. However, in our study we found that improvements in FSFI scores were similar between continent and incontinent women following mirabegron therapy. We believe that this improvement in sexual dysfunction is mainly related to the improvements urgency levels.

In the literature, data are limited with regard to the effects of OAB treatment on FSD. Zachariou et al. [21] demonstrated that extended release (ER) tolterodine used for the treatment of OAB led to improvements in sexual dysfunction in women. In a randomized placebo controlled study by Rogers et al. [7], both OAB symptoms and sexual health scores improved with tolterodine ER in sexually active women with OAB. Balzarro et al. [22] treated 32 OAB patients with100 U of onabotulinumtoxin-A. They found that the total FSFI score showed a significant improvement, but desire and pain domains showed no significant improvements before and after treatment.

When the available data in the literature are examined, it is clear that a relationship between the improvement of OAB symptoms and the improvement of sexual function is apparent. We think that the positive effect of OAB treatment on sexual function may be indirectly associated with the improvement of urinary symptoms and QoL Mirabegron is a safe and effective treatment option for OAB patients without causing any significant side effects [9]. As we have shown in our study, mirabegron also produced a positive effect on sexual function.

The main limitations of our study are the retrospective design and the short-term follow-up.

Conclusion

Pharmacological therapy is the most important option for treating of OAB. Sexual dysfunction is an important health problem. Sexual dysfunction in women may negatively affect the relationship between couples and may also erode psychological well-being and overall health. According to our study, mirabegron (50 mg/day) treatment can leads to improvements both urinary symptoms and sexual function in sexually active women affected by OAB. This improvement is mainly due to the improvement in OAB symptoms and QoL. The potential benefits of mirabegron for OAB treatment may be explained to the patients. However, prospective trials with larger patient population should be conducted.

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Research article

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New biomarkers for differentiating renal neoplasms with eosinophilic cytoplasm: DARS2, reelin, and enkurin

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Ethics Committee Approval
The study was approved by Fırat University Non-Interventional Health Research Ethics Committee (date 01.12.2022 and number 2022/14-14). 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.

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Abstract

Background/Aim: Chromophobe renal cell carcinoma (CRCC), eosinophilic variant clear cell RCC, and oncocytomas are renal neoplasms with eosinophilic cytoplasm, and their differential diagnosis is challenging despite significant advances in molecular pathology. Although many biomarkers have been identified for the differential diagnosis of these neoplasms, specific markers have not yet been reported. No studies were found in the literature on the relationship between these tumors and the new molecules DARS2, reelin, and enkurin. This paper aims to determine the roles of these proteins in renal neoplasms with eosinophilic cytoplasm.

Methods: The study retrospectively analyzed 30 EC RCC, 30 CRCC, and 30 oncocytoma cases, evaluated among renal neoplasms with eosinophilic cytoplasm, independent of demographic characteristics, in the Fırat University Medical Pathology Laboratory between 2012 and 2022. The most representative samples of the tumor were selected for each group, and the expression of DARS2, reelin, and enkurin proteins was evaluated by the immunohistochemical method.

Results: The histoscore of DARS2 expression was highest in EC RCC and least in CRCC. DARS2 was seen to differentiate CRCC from oncocytoma and EC RCC. The histoscore of reelin and enkurin protein expression was highest in oncocytoma and lowest in ECRCC. The difference between the groups was statistically significant ($P<0.05$).

Conclusion: DARS2 can be a useful biomarker for differentiating CRCC from EC RCC and oncocytoma, and enkurin and reelin can differentiate among these three groups.

Keywords: chromophobe renal cell carcinoma, eosinophilic variant clear cell renal cell carcinoma, oncocytoma, DARS2, reelin, enkurin

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Introduction

Renal Cell Carcinoma (RCC) originates from the renal cortex epithelium, mostly the upper pole of the kidney, and is a common urological cancer with the highest mortality [1]. RCC constitutes approximately 85% of all parenchymal kidney tumors and 3% of adult solid tumors, with men aged 60–70 years being the most commonly affected group [2]. Several tumor-related prognostic factors, such as tumor stage, size, histological subtype, ISUP nuclear grading, lymphovascular invasion, and the presence of sarcomatoid differentiation, are present in RCC [1,2]. However, the most crucial prognostic factor is the pathological stage, and the 5-year survival rate of patients with Stage I or II cancer at the time of diagnosis ranges between 80% and 90% [1,2].

While tumors detected at an early stage have a high response to treatment, the treatment of advanced renal cancer is difficult, and the mortality rate is significantly high due to blood or lymphatic spread [3].

Eosinophilic Variant Clear Cell RCC (EC RCC) is a high-grade tumor with cells containing granular eosinophilic cytoplasm often seen around areas of hemorrhage and necrosis. EC RCCs commonly metastasize to the lungs, liver, soft tissue, and pleura, with an average of 45% of renal vein invasion [4].

Chromophobe RCCs (CRCCs) are malignant epithelial kidney tumors that originate from the intercalated cells of the collecting duct system and have a better prognosis compared to EC RCC but still have metastatic potential. Several ultrastructural studies have shown that numerous cytoplasmic microparticles characterize typical pale cells of CRCC due to defective mitochondrial development [5]. Conversely, oncocytomas are mitochondria-rich cells originating from intercalated similar to CRCC and are benign epithelial neoplasms consisting of large cells with large eosinophilic cytoplasm [6,7].

Oncocytomas are rare, predominantly benign neoplasms of the epithelium, causing respiratory defects and developing as a result of inactivating mutations in enzymes or control regions encoded by the mitochondrial genome, leading to the accumulation of defective mitochondria [8]. Despite their clinical differences and changes in their response to treatment, differential diagnosis of EC RCC, CRCC, and oncocytoma, which have similar histological structures, is one of pathology's most crucial and difficult aspects [9,10].

Although many immunohistochemical markers are used in differential diagnosis along with morphological findings, the inadequacy of these markers increases the need for an ideal single immunohistochemical marker or panel [10].

DARS2 is a mitochondrial protein with effects on tumorigenesis, and studies conducted on the relationships between mitochondrial dysfunctions and tumorigenesis made it valuable to examine mitochondrial proteins for many tumors [11]. Reelin is a protein that plays a significant role in regulating neuronal migration, dendritic growth/branching, dendritic spine formation, synaptogenesis, and synaptic plasticity in the brain, and it also affects the development of signaling pathways of lymphatic vessels, mammary glands, submaxillary glands, small intestine, cartilage, bone, and the immune system, liver fibrosis, and multiple cancers in adults [12]. Enkurin (canonical transient receptor potential) is a calcium-permeable cationic plasma membrane channel and was the subject of treatment-targeted studies for various cancer types. Enkurin binds to the oncogenic transcription factor (C-Jun) promoter, modulating many genes, and exerts anti-metastatic effects [13].

Here we examine the roles of DARS2, Reelin, and Enkurin proteins in the differential diagnosis of EC RCC, CRCC, and oncocytoma.

Materials and methods

Participants

We retrospectively re-evaluated all resection materials diagnosed as renal cell carcinoma at the Medical Pathology Laboratory of Fırat University between 2012 and 2022. Ethics approval was obtained from the Fırat University Non-Interventional Health Research Ethics Committee on 01.12.2022 (2022/14-14). We included 90 cases of renal cell carcinoma diagnosed with a renal cell carcinoma subtype and had their tumor tissue removed by total or partial nephrectomy. Cases diagnosed with needle biopsy and those in which the tumor subtype could not be determined excluded from the study. We studied 30 diagnosed cases of EC RCC, 30 Chromophobe RCC, and 30 oncocytoma cases. The patient's age, gender, type of surgery (total/subtotal resection), and pathological diagnosis were obtained from patient files and pathology reports.

Immunohistochemistry

For each disease group, up to ten Hematoxylin-Eosin stained sections were examined, and an immunohistochemical examination was performed by selecting the samples that best represented the tumor areas. The tissue samples of the groups were evaluated by a pathologist and a histologist blinded to the study.

Immunohistochemistry

Immunohistochemical procedures were performed as described by Kocaman and Artas [14]. Tissue microarray slides 3 µm thick were used for immunohistochemistry (IHC). We used the following antibodies: Anti-AspRS antibody (Sc-166535; Santa Cruz Biotechnology, Oregon, USA), anti-Reelin antibody (Sc; MyBioSource, Santa Cruz Biotechnology, Oregon, USA), and polyclonal anti-Enkurin Antibody (PA5-58028; ThermoFisher Waltham, Massachusetts, USA). Using indirect immunohistochemical staining, we calculated a histoscore to measure tissue levels of DARS2, Reelin, and Enkurin.

Microscopic evaluation of staining intensity

We used a scoring system to assess the distribution and intensity of staining, where the distribution was scored as 0.1 for <25%, 0.4 for 26-50%, 0.6 for 51-75%, and 0.9 for 76-100%. The intensity of staining was scored as 0 for no staining, 0.5 for very little staining, 1 for little staining, 2 for moderate staining, and 3 for very strong staining. We calculated a histoscore by multiplying the distribution and intensity scores [14].

Statistical analysis

We analyzed the data using the Statistical Package for Social Sciences for Windows version 22.0 (SPSS, Chicago, IL) program. Descriptive data were expressed as mean (standard error) and numbers. We evaluated the distribution of the data using the Shapiro-Wilk Test. We used the One-Way Analysis of Variance (ANOVA) Test and the Post-Hoc Dunn Test to

compare the data showing normal distribution. The significance level was set at $P<0.05$.

Results

General characteristics of the subjects

The demographic characteristics of the patients are given in Table 1. Thirty EC RCC, CRCC, and oncocytoma group patients were evaluated. In these cases, CRCC was more common in women, and EC CRCC and oncocytoma were more common in men. Among the tumor groups, the mean patient age in eosinophilic clear cell renal cell carcinoma cases was 59.00 years (min–max: 32–85); the mean age in chromophobe renal cell carcinoma cases was 60.60 years (min–max: 27–80); the mean age in oncocytoma was 63.70 years (min-max: 34–82); and no significant difference was detected between the groups in terms of age ($P=0.303$). When the groups were evaluated in terms of gender, a significant difference was detected ($P=0.009$).

Table 1: Summary of patients' clinical data

	Oncocytoma	CRCC	EC RCC	*P*-value
N (F/M)	30 (13/17)	30 (18/12)	30 (8/22)	0.009
Age	63.7 (34–82)	60.6 (27–80)	59 (32–85)	0.303

CRCC: Chromophobe renal cell carcinoma, EC RCC: Eosinophilic variant clear cell. Descriptives are expressed as median (min-max).

Histochemical findings

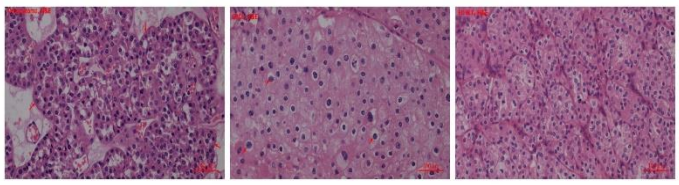
In the histopathological examination, oncocytoma sections showed tumors that consisted of solid cell nests in the loose edematous stroma, large granular eosinophilic cytoplasm, central nucleus, and uniform image. The CRCC sections showed tumors of cell layers with large eosinophilic reticular cytoplasm, significant cytoplasmic borders, clear perinuclear halo, and irregular hyperchromatic nuclei. For the EC RCC sections, we observed tumors with large pale eosinophilic cytoplasm, hyperchromatic nuclei in places, and slightly pleomorphic cell nests (Table 2, Figure 1).

Table 2: Histoscore of DARS2, reelin and enkurin for eosinophilic variant clear cell RCC, chromophobe renal cell carcinoma, oncocytoma

	EC RCC	CRCC	Oncocytoma
DARS2	2.40 (0.43)	1.06 (0.15)[a]	2.46 (0.40)[b]
Reelin	0.01 (0.02)	0.73 (0.17)[a]	1.15 (0.28)[ab]
Enkurin	0.02 (0.09)	0.33 (0.18)[a]	1.03 (0.17)[ab]

CRCC: Chromophobe renal cell carcinoma, EC RCC: Eosinophilic variant clear cell, a: compared with the EC RCC group, b: compared with the CRCC group

Figure 1: Hematoxylin-eosin image in eosinophilic variant clear cell RCC, chromophobe renal cell carcinoma, oncocytoma lesion areas



Immunohistochemical findings

Using immunohistochemistry, we stained the tissue samples of EC RCC, CRCC, and oncocytoma with DARS2, Reelin, and Enkurin. We formed a histoscore based on the extent and intensity of the staining. We compared the groups regarding DARS2, Reelin, and Enkurin expression. We evaluated and photographed the slides under a Zeiss Axio (Scope A1 Berlin, Germany) microscope ($P<0.05$) (Figures 1–4, Table 2).

DARS2, reelin, and enkurin immunoreactivity

DARS2, reelin, and enkurin cytoplasmic staining were performed in CRCC, EC RCC, and oncocytoma samples. We examined the immunohistochemical staining for DARS2 immunoreactivity under light microscopy and obtained the following findings. As shown in Table 2, DARS2 expression was detected in the EC RCC, CRCC, and oncocytoma groups. DARS2 expression was mostly observed in EC RCC and least in CRCC and oncocytoma. When we compared DARS2 expression between the groups, we found that it differentiated CRCC from oncocytoma and EC RCC, and the difference was statistically significant ($P<0.05$) (Figure 2, Table 2).

The expression of reelin and enkurin proteins was highest in oncocytoma, less in CRCC, and least in EC RCC. We found the difference in expression between the groups to be statistically significant ($P<0.05$) (Figures 3 and 4, Table 2).

Figure 2: Immunohistochemical reactivity (red arrow) of DARS2 protein at lesion sites in eosinophilic variant clear cell RCC, chromophobe renal cell carcinoma, oncocytoma.

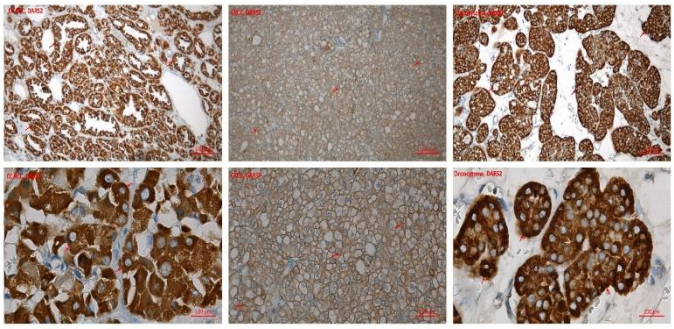


Figure 3: Immunohistochemical reactivity (red arrow) of reelin protein at lesion sites in eosinophilic variant clear cell RCC, chromophobe renal cell carcinoma, oncocytoma.

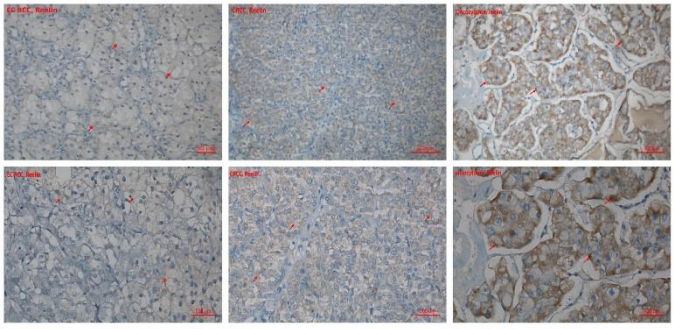
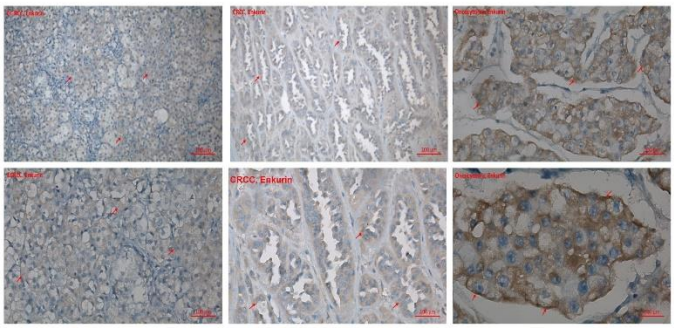


Figure 4: Immunohistochemical reactivity (red arrow) of enkurin protein at lesion sites in eosinophilic variant clear cell RCC, chromophobe renal cell carcinoma, oncocytoma.



Discussion

Immunohistochemistry is a valuable diagnostic tool in cases where RCCs with eosinophilic cytoplasm cannot be diagnosed based on morphological results, a current differential diagnosis problem [7]. The histopathological distinction of oncocytomas, Chromophobe RCC, and eosinophilic variant clear cell RCC is an important and frequently encountered challenge for pathologists. Tumoral structures with granular eosinophilic cytoplasm, hyperchromatic nuclei, and slightly pleomorphic cells are generally observed, making it difficult to diagnose histopathologically. Many molecules, such as kidney-specific cadherin, parvalbumin, claudin-7, and claudin-8, are sensitive

biomarkers for renal neoplasms, including Chromophobe RCC and oncocytoma [10]. However, previous studies have reported that many of the markers used are insufficient in the differential diagnosis, and it has become imperative to develop tumor-specific biomarkers. For example, CD117 is secreted from normal adult kidney parenchyma and can be used to differentiate classical RCC cases from other RCCs when it is negative. However, it is useless in differentiating oncocytoma from Chromophobe RCC because this marker is positive in both tumors [15].

No information was found in the literature regarding the relationship of DARS2, Reelin, and Enkurin proteins with EC RCC, CRCC, and oncocytoma. Aminoacyl-tRNA Synthetases (ARSs) are critical enzymes that synthesize proteins by catalyzing amino acids with tRNAs [16]. Aspartyl-tRNA Synthetase 2 (DARS2), encoded by the Class II aminoacyl-tRNA Synthetase family gene, is a mitochondrial enzyme specifically aminoacylates Aspartyl-tRNA and has been reported to be a novel biomarker for bladder cancer and acute leukemia [17-19]. Additionally, a previous study showed that DARS2 could be a biomarker to differentiate malignant mesothelioma from lung adenocarcinoma [20].

This study, DARS2 expression was detected in all groups, with the highest expression in EC RCC and oncocytoma. DARS2 expression differentiated CRCC from EC RCC but not from oncocytoma. These findings suggest that DARS2 may be associated with the tumorigenesis effect of EC RCC and oncocytoma. Overexpression of DARS2 has been previously shown to accelerate tumorigenesis in hepatocellular carcinoma [21]. In oncocytoma, the overexpression of DARS2 can be explained by the fact that this tumor is rich in mitochondria, and DARS2 is a mitochondrial protein [11]. The significantly lower expression of DARS2 in CRCC compared to oncocytoma may be due to more cells with pale eosinophilic cytoplasm, which are poorer in mitochondria [22]. Overall, DARS2 may be a potential biomarker for distinguishing between RCC subtypes.

The RELN gene encodes reelin, a large glycoprotein that functions in neuronal and non-neuronal tissues. Reelin is involved in developing various tissues, including the liver, kidney, and breast. Studies have shown that its expression is decreased in certain cancers such as breast, stomach, and pancreatic cancer [23]. In breast cancer, the RELN gene is epigenetically dysfunctional in the cancerous area, while normal tissues adjacent to the tumor continue to release reelin. Low reelin release has been linked to increased cancer cell migration, positive lymph node involvement, and poor prognosis. Conversely, increased reelin levels may have a suppressive effect on cancers [24,25].

Enkurin is a novel molecule with unresolved structure and function. It was first reported as an essential adapter in localizing a Ca2+ permeable ion channel in sperm [26]. Recent research has shown that Enkurin may act as a tumor suppressor in colorectal cancers and lung adenocarcinoma, inhibiting the proliferation, migration, and invasion of tumor cells. Epigenetic deficiency of Enkurin may accelerate tumor progression. These findings suggest that Enkurin could be an effective target for cancer therapy [27-29].

The expression of Reelin and Enkurin proteins was highest in oncocytoma, less in CRCC, and less in EC RCC, with statistically significant differences between the groups. Previous studies have shown that decreased secretion of these proteins is associated with increased cancer aggressiveness, possibly due to epigenetic deficiency. Conversely, higher levels in less aggressive and benign neoplasms may be due to their tumor suppressor roles [12,25]. Therefore, the low secretion of Reelin and Enkurin in EC RCC in this study may also contribute to the aggressiveness of this tumor, although further research is needed to confirm this finding.

When the cases were analyzed according to their demographic characteristics, no significant differences were found in age, but significant differences were observed in gender.

Limitations

The present study had some limitations, most notably its retrospective design and the absence of other prognostic parameters. More comprehensive studies incorporating clinical findings, pathological stage, and prognostic factors will greatly aid in understanding the relationship between these proteins and renal neoplasms with eosinophilic cytoplasm.

Conclusions

In conclusion, this study showed that DARS2, Reelin, and Enkurin proteins could be potentially effective and specific immunohistochemical markers for differentiating renal neoplasms with eosinophilic cytoplasm, which can be difficult to diagnose. Furthermore, the study suggests that Reelin and Enkurin proteins may hold promise in determining prognosis and developing targeted therapies for these neoplasms. However, further comprehensive studies are needed to explore the clinical implications of these findings and their potential for clinical application.

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Pediatric neuroanesthesia experiences: A single center retrospective cohort study

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Ethics Committee Approval
The study was approved by Gazi University Clinical Research Ethics Committee (date: 22.06.2021, number: 2022-095).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Pediatric neuroanesthesia is a special field that requires significant experience and infrastructure because of anatomical, neurological, and pharmacological differences in the pediatric patient population. Although technological improvements provide more effective and safer neuroanesthesiological management, the principles of neuroanesthesia, neurocognitive development, and the effects of anesthetic agents on central nervous system development are well-known. The majority of pediatric neuroanesthesia articles in the literature are reviews; however, retrospective/prospective case series and controlled research are limited. In this retrospective cohort study, we aimed to contribute to the existing literature by reviewing and analyzing our single-center 10-year experiences and results addressing pediatric neuroanesthesia management.

Methods: After ethical committee approval, anesthetic and surgical reports from 1165 pediatric neurosurgical cases over ten years were collected. Demographic data, intra-operative vascular management, anesthesia techniques, airway management, patient positions, analgesia methods, and complications were evaluated in this retrospective cohort study. The available surgical intervention, patient positions, intra-operative neuromonitorization (IONM), and intra-operative magnetic resonance imaging (IOMR) records were also analyzed.

Results: Six-hundred forty-six (55.4%) girls and 519 (44.5%) boys were included in the study. The median age was 60 (0–216) months. Cranial interventions were performed in 842 (72.3%) patients, and spinal interventions were performed in 323 (27.7%) patients. Patients' American Society of Anesthesiologists (ASA) physical scales grouped as I, II, III, and IV were 718 (61.6%), 360 (30.9%), 82 (7%), and 5 (0.4%), respectively. Sevoflurane (40.3%), propofol (37.2%), and sodium thiopental (2.5%) were used for anesthetic induction. Neuromuscular block was performed with rocuronium (56.7%) and atracurium (14.4%). Neuromuscular blocking agents were not used in 337 patients (28.9%). A blood transfusion was required in 120 patients (10.3%), and 40% of these patients underwent surgery for craniosynostosis. Two-hundred twenty-two (19.1%) were monitored with IONM, and IOMR was carried out in 124 (10.6%) of the cases. The anesthesia-related complication rate was 5.15% (60 patients).

Conclusion: Although pediatric neurosurgical interventions involve high risks, they are becoming increasingly common in our daily practice. Neuroanesthesiologists should know the procedures, techniques, and advances for safe and effective management of pediatric neurosurgical cases. We think that these data may be helpful as a guide for the anesthetic management of pediatric neurosurgical cases.

Keywords: anesthesia, neurosurgery, pediatric neuroanesthesia

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Introduction

Pediatric patients undergoing neurosurgical interventions are a unique group that require special care and attention in terms of anesthesia management and surgery. Pediatric neurosurgical interventions have become more common in our daily practice as a result of recent advances in neuromonitoring, neurointensive care, and more favorable surgical outcomes [1,2]. Furthermore, as better anesthesia equipment and medications have become available, neuroanesthesia applications in premature neonates cease to be dreaded procedures and have become routine operations [3].

Despite these developments, the goal of pediatric neuroanesthesia remains the same: (1) creating optimal surgical conditions, (2) reducing intracranial pressure, (3) preserving hemodynamic stability and venous return, (4) maintaining oxygenation with cerebral and spinal perfusion, (5) effective anesthesia–analgesia management, and (6) allowing for early neurological examination with rapid recovery in the post-operative period [4]. These steps require an understanding of not only pediatric neuroanesthesia principles but also normal neurocognitive development and the impact of anesthetics on the developing nervous system [5].

Many controversial issues in the literature about pediatric neuroanesthesia management exist. The majority of pediatric neuroanesthesia articles in the literature are case reviews, whereas retrospective/prospective case series and controlled research are limited. In this retrospective cohort study, 10 years of experience at a tertiary referral center for pediatric neurosurgery and neuroanesthesia, and 1165 patients were analyzed. This study may contribute to the literature as a guide for pediatric neuroanesthesia as it reflects the approaches and philosophy of an experienced team for quite a large population.

Materials and methods

After obtaining ethical approval from Gazi University Clinical Research Ethics Committee (Date: 22.06.2021, Number: 2022-095), a retrospective evaluation of records of pediatric patients undergoing cranial and spinal surgery between 2011 and 2020 was conducted. The data retained by the Departments of Anesthesiology, and the Department of Neurosurgery medical charts of the patients were reviewed.

Demographic characteristics, gender, age, body weight, American Society of Anesthesiologists (ASA) physical condition classification, emergency/elective surgery status, anesthesia and operation durations, and classification of surgical cases were evaluated. The patients were divided into six groups based on their age: (1) newborn (0–28 days), (2) infant (1–12 months), (3) toddler (1–3 years), (4) pre-school (3–5 years), (5) school-age (5–12 years), and (6) adolescent (12–18 years). Anesthesia duration was defined as the time interval between anesthesia induction and cessation of anesthetic agents. The surgical time was determined as the time between incision and closure of the skin. Due to the diversity of cases, the operations were classified under headings. An arteriovenous malformation was considered a supratentorial tumor if no related intracranial hemorrhage occurred, and if bleeding did occur, it was classified as a cranial trauma case. Similarly, all epilepsy surgeries, including amygdalo-hippocampectomy, were considered supratentorial tumors while vagal nerve stimulation implantation or other functional surgeries in addition to Arnold Chiari surgeries were considered " other " types of surgeries. Wound dehiscence, superficial infections requiring surgical management, and cerebral spinal fluid (CSF) fistulas due to index surgery were considered "minor surgeries". Excluding tumor resections and biopsies, all endoscopic ventricular surgeries (including suprasellar arachnoid cysts and Type III giant arachnoid cysts requiring surgery) were classified under "hydrocephalus/arachnoid cyst".

Intra-operative vascular management, anesthetic agents for induction and maintenance, preferred anesthesia techniques, airway management, patient positions, use of Mayfield head pins, post-operative analgesia strategies, intra-operative neuro-monitorization (IONM), and intra-operative magnetic resonance imaging (IOMR) applications and complications were analyzed. Patients with multiple surgeries and missing data were excluded from the study.

Statistical analysis

Statistical evaluation was completed using the Statistical Package For Social Sciences (SPSS Inc., Chicago, IL, USA) program version 23. Categorical variables are presented as numbers and percentages, while continuous variables are presented as mean (standard deviation). Mann–Whitney U and chi-squared tests were used for non-parametric data to search for differences and associations between groups of patients when appropriate. A *P*-value <0.05 was considered statistically significant.

Results

During the ten-year study period, 1442 patients underwent in the department of pediatric neurosurgery. The study excluded 175 patients who had multiple surgeries and 102 patients whose data could not be accessed. A retrospective analysis of 1165 pediatric patients was performed.

Five hundred nineteen (44.5%) of the cases were girls, and the boy/girl ratio was 1.24. Eighty-four cases underwent emergency surgery, and trauma was the most common indication in 24 (28.6%) patients. Eight-hundred forty-two patients (72.3%) underwent cranial surgery, and 323 patients (27.7%) underwent spinal surgery. The most frequently performed surgical procedures were performed for hydrocephalus/arachnoid cysts, supra/infratentorial tumors, and congenital spinal anomalies. These indications comprised 69.3% of the entire cohort (Table 1).

The youngest age group underwent congenital spinal surgery, and the longest duration of anesthesia was observed in supratentorial at 285.42 (108.64) min and infratentorial tumor cases at 271.63 (108.26) min.

Central venous catheterization (CVC) was performed in 92 patients, 38 of them were inserted after 2018 and accompanied by ultrasonography (USG). Three of the central catheters were subclavian, 21 were femoral, and 68 were internal jugular veins.

The most preferred agent for induction and maintenance was sevoflurane, and the most commonly used neuromuscular blocker (NMB) was rocuronium. The agents used in the intra-

operative period and the preferred anesthesia methods are summarized in Table 2.

Table 1: Demographic variables and surgery data

Gender, n (%)	
Female	519 (44.5)
Male	646 (55.5)
Age (months), mean (SD)	74.26 (65.23)
Age groups, n (%)	
Newborn	62 (5.3)
Infant	240 (20.6)
Toddler	184 (15.8)
Pre-school	102 (8.8)
School age	355 (30.5)
Adolescent	222 (19.1)
Body weight (kg), mean (SD) (min–max)	23.37 (18.42) (1.20-110)
ASA classification	
I	618 (53.05)
II	460 (39.5)
III	82 (7.04)
IV	5 (0.42)
Duration of anesthesia (min), mean (SD)	212.21 (96.98)
Duration of surgery (min), mean (SD)	157.48 (96.35)
Surgery planning, n (%)	
Elective	1081 (92.8)
Emergency	84 (7.2)
Types of surgery, n(%)	
Hydrocephalus/ arachnoid cyst	287 (24.6)
Supratentorial tumor	184 (15.8)
Infratentorial tumor	100 (8.6)
Craniosynocytosis	71 (6.1)
Cranial trauma	44 (3.8)
Head extracranial tumor	20 (1.7)
Cranial infection	13 (1.1)
Other	72 (6.2)
Minor surgery	72 (6.2)
Congenital spinal surgeries	237 (20.3)
Spinal tumors	40 (3.4)
Spinal trauma	18 (1.5)
Discopathies	5 (0.4)
Spinal infection	2 (0.2)

SD: standard deviation, ASA: American Society of Anesthesiologists

Table 2: Agents and methods used in the induction and maintenance of anesthesia

INDUCTION	
Anesthetic agent	
Propofol	433 (37.2)
Pentothal	262 (22.5)
Sevoflurane	470 (40.3)
Muscle relaxant	
Rocuronium	660 (56.7)
Atracurium	168 (14.4)
Not used	337 (28.9)
Analgesic	
Remifentanil	1103 (94.7)
Fentanyl	62 (5.3)
MAINTANENCE	
Anesthetic agent	
TIVA	269 (23.1)
Sevoflurane	896 (76.9)
Muscle relaxant	
Rocuronium	558 (47.9)
Atracurium	168 (14.4)
Not used	439 (37.7)
Analgesic	
Remifentanil	1133 (97.3)
Fentanyl	32 (2.7)

TIVA: total intravenous anesthesia

The airway was maintained by endotracheal intubation except for 39 (3.3%) laryngeal mask airway (LMA) patients. Six hundred seventy-three (57.8%) patients were operated on in the supine position and 7 (0.6%) in the sitting position (Table 3).

Table 3: Patient positions and airway management

	Supine	Prone	Sitting	Lateral decubitus	Total
ETT	530 (85.1)	86 (13.8)	-	7 (1.1)	623 (100)
Spiral ETT	105 (20.9)	391 (77.7)	7 (1.4)	-	503 (100)
LMA	38 (97.4)	-	-	1 (2.6)	39 (100)

ETT: endotracheal tube, LMA: laryngeal mask airway

In cranial and spinal surgeries, three Mayfield head pins were used in 207 children aged ≥3 years, and horseshoe gel pads were used in 24 children <3 years. No local anesthetic was applied to 51 patients who underwent neuronavigation monitoring, scalp block was applied to 49 patients, and local anesthetic infiltration was applied to 107 patients.

Paracetamol was administered in 794 (68.2%) patients, a non-steroid anti-inflammatory drug in 24 (2%) patients, morphine in 67 (5.8%) patients, a combination of paracetamol and morphine in 280 (24%) patients, and morphine patient-controlled analgesia in 52 patients for post-operative analgesia. Paracetamol was administered in the form of a suppository in 101 patients and intravenously in 973 patients.

Two hundred twenty-two (19.1%) patients were monitored with IONM, 179 (80.6%) underwent surgery for a congenital spinal anomaly, and 22 (9.9%) for spinal tumor indication. Propofol was preferred for induction in 147 (66.2%) patients, while sevoflurane was preferred in 75 (33.8%) IONM patients. Anesthesia was maintained with total intravenous anesthesia (TIVA) in all patients who had IONM. In 82.5% of the patients who had TIVA for maintenance of anesthesia, IONM was used. Neuromuscular blockers were not used in induction in 120 (54.1%) patients who underwent IONM, and rocuronium was used in 102 (45.9%) patients. Seventy-one (69.6%) of those who used NMBs were in the school-age group, and 31 (30.4%) were in the adolescent age group. In the maintenance of anesthesia, NMBs were not used.

Intra-operative magnetic resonance imaging was carried out in 124 (10.6%) of the cases, and all these cases were supratentorial malignancies. The average overall IOMR imaging time was 28 min.

Complications were investigated under two headings: (1) anesthesia-related complications (5.15%) and (2) surgical complications (1.1%). Anesthesia-related complications were found in 60 of 1165 cases in our study. The most common complication was airway related (2.4%) due to laryngospasm (17) and bronchospasm (11). As for cardiac complications, bradycardia was found in 13 (1.12%) patients and dysrhythmia in seven (0.6%). Other reported complications were allergic reactions, difficult intubation, and venous air embolism (VAE) observed in three (0.26%), eight (0.69%), and one (0.08%) patients, respectively. In 13 (1.1%) of the cases, we had intra-operative surgical complications, such as significant blood loss or VAE. Seven patients underwent surgery while in the sitting position in our study, and one of them developed VAE.

One hundred twenty-one (10.3%) cases required intra-operative blood transfusion, 48 (40%) were craniosynostosis and 42 (35%) were supra/infratentorial tumor cases. Blood transfusions were performed in 67.6% of all craniosynostosis surgeries. It was observed that those who received blood transfusions were statistically younger (45.97 [54.80] versus 78.06 [65.61] months) and had a lower body weight (15.88 [12.54] versus 24.38 [18.85] kg) compared to those who did not receive blood transfusions (P<0.01).

Discussion

The neuroaesthetics management of 1165 pediatric patients over 10 years was discussed in our study. According to the best of our knowledge, this study is one of the biggest retrospective series in the literature in the field of pediatric neuroanesthesia.

The innovations in pediatric neurosurgery have led to a dramatic reduction in mortality and morbidity rates in infants and children suffering from neurosurgical diseases. Since physiological and developmental variations in pediatric patients present difficulties for both neurosurgeons and anesthesiologists, most surgical and anesthetic improvements are first applied to adults. Pediatric neuroanesthesia articles are scarce in the literature, and the findings are primarily based on adult patient studies. Although it has been noted that the sex ratios in studies evaluating adult patients are close to each other, data on gender distribution are also limited since pediatric neuroanesthesia studies are rare [6].

Our study included 55.5% boys with a boy/girl ratio of 1.24 and a mean age of 6.2 years. Another study analyzing pediatric intracranial tumor surgery cases revealed a boy/girl ratio of 1.4 and a mean age of 8.2 years [7]. As per age distribution, the highest proportion of school-aged children (30.5%), infants (20.6%), and adolescents (19.1%) underwent surgery. The distribution of surgical procedures explains this issue. While cranial procedures are more common in older children (72.3%), spinal surgical procedures, particularly for congenital spinal defects, were more common in younger children (27.7%). While craniosynostosis surgery was conducted on 6% of the patients in our study, it was discovered that surgery for hydrocephalus/arachnoid cysts was the most frequently performed procedure (24.6%) in different age groups. This finding was an expected result as hydrocephalus is one of the most common neurological diseases in children.

Optimal pre-operative evaluation is essential in the management of pediatric neuroanesthesia. Age-related differences in neurophysiology and cranial development in addition to the neurosurgical illness spectrum affect the approach to the pediatric neurosurgery patient [8]. Pre-operative evaluation should focus on age-specific symptoms, signs of increasing intracranial pressure, the Glasgow Coma Scale, and airway examination results [3].

Vascular access can be challenging in pediatric patients, and multiple interventions may have unintended consequences, such as blood loss and hypothermia, in this patient population. Access to the child through sterile surgical drapes becomes limited in neurosurgery due to both the position required by the surgery and the patient's young age. As a result, it is even more critical to maintain the safety of the vascular access, which works well before the procedure and allows blood transfusion if necessary during surgery. In our clinical practice, two large-diameter venous cannulas were used in patients who had a craniotomy for tumors, craniosynostosis surgery, spinal tumor surgery, and/or trauma surgery. Failure of vascular access attempts, the risk of bleeding, and the need for parenteral nutrition during the critical care unit are our indications for a CVC. After 2018, CVCs were inserted with the aid of USG in the study. In the literature, it has been demonstrated that USG-guided CVC applications minimize the number of attempts and complication rates while allowing successful catheterization to be achieved in a shorter time [9]. Although our clinical practice confirms this observation, statistical analysis was not possible due to insufficient records.

Sevoflurane, propofol, and sodium thiopental, which are preferred for induction, are well-known agents for pediatric neuroanesthesia [10,11]. The use of these drugs in our study was organized based on the patient's age and surgical features. As in the literature, sevoflurane was preferred in the induction of patients without vascular access, particularly in the newborn group, and propofol was preferred in the induction of patients whose airway management was provided by a laryngeal mask airway (LMA) since it blocked the upper airway reflexes better than other anesthetic agents.

In adult neuroanesthesia, the superiority of inhalation anesthesia over TIVA in anesthesia maintenance is still debated. A meta-analysis comparing the efficacy and safety of remifentanil, sevoflurane, or propofol in the maintenance of anesthesia in craniotomies found that sevoflurane led to an increase in the incidence of intra-operative hypotension and brain edema in addition to post-operative nausea and vomiting, but no difference in recovery times was noted [12]. The effects of isoflurane, sevoflurane, and desflurane on early post-operative recovery outcome, intra-operative hemodynamics, and degree of brain swelling in addition to post-operative vomiting and shivering were evaluated in a study examining 60 pediatric cases who underwent supratentorial tumor surgery, and no difference among the agents was found in terms of intra-operative brain edema, hemodynamics, post-operative shivering, or vomiting. Desflurane and sevoflurane, on the other hand, provide faster emergence than isoflurane [13]. Sevoflurane has also been found to not affect cerebral blood flow in young patients, similar to adults, and is hence the best inhalation anesthetic for neuroanesthesia [14].

In elective craniotomies, propofol was found to lower intracranial pressure while causing an increase in cerebral perfusion pressure as compared to inhalation anesthesia [15]. Therefore, administration of propofol would be beneficial, particularly in cases of high intracranial pressure and midline shift [16]. In our analysis, TIVA was used in 222 of the 269 patients because of IONM and in 35 of 269 patients due to midline shift. In addition, regarding the carbon footprint, the use of TIVA and sevoflurane as inhalation anesthetics is supported by studies in the literature [17].

In our study, the administration of NMB was determined based on the patients' age, airway device, and monitoring features. It was not used, particularly in the newborn group, when LMA was preferred, and during short-term procedures. Totonchi et al. [18] found no significant positive effect of NMB use in LMA placement, contribution to airway pressures and oxygenation, or reduction airway problems in pediatric patients.

Intra-operative neuromonitorization is a very valuable technique that is one of the main adjuncts of neurosurgical cases and it is one of the unique concerns of NMB usage. This process not only prevents adverse neurological events but also protects the surgical team from medico-legal problems. Monitorization of motor evoked potentials (MEP) and somatosensory evoked potentials (SSEP) in cranial and spinal procedures is critical for assessing the intraoperative neurological condition and preventing problems [19–22]. Unfortunately, using the approach comes with a high cost due to the required anesthesiological

technology and anesthesiology time. The anesthesia team must be familiar with factors, such as blood pressure, hypoglycemia, body temperature, hematocrit, and acid-base balance, that may influence IONM responses [23].

During the anesthetic management of patients with IONM, preventing the unfavorable effects of anesthetic agents on IONM is extremely important [24]. The effects of anesthetic agents for induction have short-term effects which explains why typically IONM does not significantly affect the procedure. Maintenance anesthetic doses of TIVA can be safely used in IONM. However inhalational agents over 0.5 minimum alveolar concentrate are avoided as MEPs are highly sensitive to these agents. During maintenance, the anesthesiologist should be sure that the patient is not under a NMB-related effect [25].

The above-mentioned principles were performed in two different approaches in the presented series. These two approaches did not use NMB in induction or administer short-acting NMBs. The termination of the effect of NMBs is confirmed by the "train of four" monitorization. Sala et al. [22] reported that IONM procedures can be performed safely using propofol and fentanyl infusion (TIVA) and avoiding inhalational agents and NMBs after intubation. In the presented series the anesthetic management of cases with IONM was similar to the protocols described by Sala et al.

Airway management in our patients was provided by endotracheal tube (ETT) and LMA. Reinforced ETT was frequently used in the prone position because kinking of ETT due to neck flexion was reported in the literature [26,27]. The conventional ETT was used in the prone position only when appropriate size ETT was not available for newborns, premature patients, or the patients for whom IOMR is planned.

The different patient positions in neurosurgery present advantages and disadvantages. Before closing sterile surgical drapes, the patients should be carefully observed and checked. Dilmen et al. [28] detected VAE in 20.4% of adults and 26.3% of children who were in the sitting position in 692 cases. They also suggested CVC to aspirate the venous air embolism. In the presented series, VAE was detected in one of seven patients in the sitting position and managed with symptomatic approach.

Mayfield skull clamp was used in selected pediatric patients since it carries high risk under three years of age and may cause severe painful stimulation and major hemodynamic responses [29]. These principles were considered in the presented series also.

In pediatric cases, moderate or severe pain was previously reported [30]. Pain management in pediatric neurosurgery is extremely important and controversial. This type of pain may cause morbidity and mortality because it can lead to agitation, increased intracranial pressure, epileptic seizure, and post-operative hematoma. The pain and suppression of hemodynamic responses caused by Mayfield head fixation and post-craniotomy are important in patients with increased intracranial pressure and risk of subarachnoid hemorrhage [29,31].

In a randomized controlled study with 320 pediatric craniotomy cases, fentanyl, morphine, tramadol, and saline (placebo) were compared, and the authors found that the safest and the most effective post-operative analgesia was provided by the patient or nurse-controlled iv morphine. Although physicians do not frequently prefer opioid agents because of their adverse effects, post-operative pain can be managed without neurological impairment in pediatric neurosurgical cases [30]. Smyth et al. [32] concluded that a minor analgesia regimen (acetaminophen/ibuprofen) administered just after surgery and during the hospitalization in pediatric cases in whom suboccipital craniotomy was performed, significantly decreased the pain scores, hospitalization time, the need for narcotic and anti-emetic agents were found.

The complicated management of pain in pediatric neurosurgery requires multimodal strategies to effectively control the pain and avoid the side effects [33,34]. Scalp block is effectively used to control postoperative pain in pediatric patients with craniotomy as a part of multimodal analgesia similar to adult patients [35]. Festa et al. [36] reported that scalp block provides better pain control and limits the need for rescue analgesia when compared with conventional treatment in craniosynostosis surgery in patients under two years of age. Also, Ning et al. [37] showed that scalp block is associated with better postoperative pain control and intra-operative hemodynamic stability in comparison with the control group in pediatric craniotomy cases. Unfortunately, post-operative pain evaluation is not available in the presented study, so similar multimodal analgesia strategies based on studies in the literature were performed.

In the literature about pediatric neuroanesthesia, Van Lindert et al. [38] reported that the rate of anesthesia-related complications is 2.8%–9.6%. In our study, a rate of 5.15% was found to be consistent with the literature. Intra-operative airway complications are an important concern in pediatric neurosurgical procedures. The majority of anesthesia-related complications occur during maintenance, while airway-related complications are usually happening during the induction or extubation stages [39]. We think that difficult mask ventilation during induction and extra irritation due to head movements are the major causes of laryngospasm, which was the most frequently seen complication in our series. In our study, we observed that the second most common complication, bradycardia and dysrhythmia, occurred during brain retraction, and loss of blood and is secondary to intracranial pressure changes. Harrison et al. [40] reported 9.3% VAE in pediatric neurosurgery patients, and they concluded sitting position also applies to pediatric patients.

Seven patients underwent surgery while in a sitting position in our study, and one of them developed an air embolism. The reason for the lower ratio of air embolisms in the presented series is the very rare use of the sitting position by the surgical team. As a result, intra-operative complications could also occur in pediatric patients and are not common, but being aware of the situation is the first step to preventing it [38].

Limitations

The retrospective type of study is the major disadvantage of the presented research. The lack of post-operative pain records and evaluation is another pitfall in this study as it limited us to defining and suggesting better pain control methods. The management of pain in pediatric neuroanesthesia must be investigated prospectively.

Conclusion

We tried to explain our experience, methods, and results that were obtained from 1165 patients. We conclude that although retrospective cohort studies with complete and regular anesthesia and surgical records make a significant contribution to the literature and are helpful for better management of pediatric neuroanesthesia, prospective controlled studies are required to better define the standards and provide evidence-based guidelines.

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Effects of the COVID-19 pandemic on colorectal cancer surgery

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Ethics Committee Approval
The study was approved by the Research Ethics Committee of KTO Karatay University Faculty of Medicine (approval number: 2022/020, date: 22.12.2022).
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.

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Abstract

Background/Aim: In accordance with the guidelines published during the COVID-19 pandemic, cancer operations, except for emergencies, were postponed. However, the effect of postponed surgical treatment on the outcomes of cancer cases has not yet been determined. Therefore, this study aimed to compare the clinical data and outcomes of patients who underwent surgery for colorectal cancer before and during the pandemic.

Methods: This retrospective cohort study was conducted in the Department of General Surgery. Patients who underwent surgery for colorectal cancer during the pre-pandemic period (February 1, 2019-December 31, 2019) and pandemic period (August 1, 2020-June 30, 2021) were included. The patients' demographic data, clinical and laboratory findings, clinical presentation, operation type, complications, and pathology results were retrospectively obtained by screening the patient files.

Results: The study included a total of 183 patients, 91 in the pre-pandemic period and 92 in the pandemic period. During the pandemic period, the length of hospital stay was significantly shorter, but the rate of readmission after discharge was significantly higher ($P<0.001$, $P=0.04$). There was no significant difference between the two periods in terms of disease stage. During the pandemic period, the number of cases that underwent emergency surgery was significantly higher. The rates of mortality and postoperative complication rates were also significantly higher ($P=0.04$, $P<0.001$).

Conclusion: The pandemic had serious effects on colorectal cancer cases. There was an increase in mortality and morbidity due to the increase in complicated cases.

Keywords: COVID-19, colorectal cancer, effect, pandemic, surgery

Introduction

Coronavirus disease 2019 (COVID-19), which first appeared in China in December 2019, started to show its effects in Turkey as of March 2020, similar to many other countries across the world. During this process, many guidelines were published on how, when, and on whom surgical procedures should be performed [1-4]. A postponement of surgical operations other than emergencies was recommended. It has been reported that surgical interventions in patients with a diagnosis of COVID-19 have increased morbidity and mortality rates [5]. In a meta-analysis, the postoperative mortality rate in patients with COVID-19 was reported to be 20% [6]. The most important recommendation commonly included in all the guidelines concerning colorectal cancer was to avoid surgery in COVID-19-positive patients. Other recommendations included immediate surgery in emergency cases, such as obstruction and perforation; postponement of elective cases; and preference of non-surgical treatments in stage II/III rectal and metastatic colorectal cancer [3,4,7].

It has been reported that among gastric, pancreatic, and colorectal malignancy cases with postponed surgical treatments during the pandemic, colorectal cancer was the malignancy in which the survival of patients was most affected [8]. A meta-analysis showed that a 12-week delay in colorectal cancer operations was associated with reduced survival [9]. Therefore, it is recommended that surgery should not be delayed for more than 6 to 12 weeks in patients with early stage colorectal cancer, who have completed neoadjuvant therapy. There are also centers reporting that, provided that the pandemic measures included in published guidelines were strictly followed, the surgical treatment of malignancy cases was continued as in previous periods, with no additional problems being encountered in the postoperative period [10,11].

Despite the above-mentioned recommendations and studies, there is only limited research addressing the course, staging, and follow-up of colorectal cancer cases during the pandemic period. One of these studies undertaken in Korea reported that the rate of patients who did not undergo tumor resection and received neoadjuvant therapy was significantly higher compared to the pre-pandemic years [12]. In addition, during the pandemic period, minimally invasive approaches, especially laparoscopy, were less frequently applied, and compared to previous periods, more patients required multiple organ resections rather than the resection of only the organ with the tumor. The most important conclusion drawn from that study is that resectability decreased during the pandemic period, which could possibly affect long-term oncological outcomes [12].

Some studies have shown an increase in the number of colon cancer cases that presented to the hospital due to obstruction and underwent emergency surgery during the pandemic period compared to previous years [13,14]. In these studies, more T4 cancer cases were diagnosed during the pandemic period than in previous periods [13]. In another study, it was reported that patients admitted to the hospital under emergency conditions presented with more complications, and the rate of bowel resection increased [15]. In a Dutch-based study, it was determined that with the suspension of national cancer screening programs during the pandemic, there was a decrease in the diagnosis of early-stage colorectal cancer, but no change was observed in those with advanced stage cancer [16].

A study conducted in the UK also discussed the postoperative period in colorectal cancer surgery performed during the pandemic period, and reported no significant difference was detected in the rate of postoperative complications, length of hospital stay, readmission after discharge, tumor staging, and lymph node dissection success compared to the pre-pandemic period [17]. Similarly, in a study from China, It was found that the incidence of surgical complications did not differ during the pandemic. The length of hospital stays and the frequency of laparoscopies, however, increased during this time, according to the authors [18].

This study aimed to compare the demographic, clinical, and postoperative characteristics of patients who underwent surgery for colorectal cancer during and before the pandemic, and thus, examine the effects of the COVID-19 pandemic on colorectal cancer surgery.

Materials and methods

Trial design

After receiving approval from the Ethics Committee of KTO Karatay University Faculty of Medicine (approval number: 2022/020, date: December 22, 2022) and written informed consent from each participant, this study was retrospectively carried out at the General Surgery Department of Health Sciences University Konya City Hospital. The study was conducted in accordance with the Declaration of Helsinki.

Participants and eligibility criteria

Colorectal cancer operations performed in our clinic were retrospectively screened from the patient files. In Turkey, the first COVID-19 case was reported on March 11, 2020 (19). Therefore, we evaluated colorectal cancer operations performed between August 1, 2020, and June 30, 2021, as the pandemic period and those performed during the previous year (February 1, 2019-December 31, 2019) as the pre-pandemic period.

In our center, during the pandemic, the polymerase chain reaction (PCR) test for COVID-19 was routinely performed in patients scheduled for surgery. During this period, no patients with COVID-19 were followed up in our hospital or clinic. All the patients included in the study consisted of those confirmed to have no COVID-19 infection by the PCR test or thoracic computed tomography. Patients with incomplete data were not included in the study.

Inclusion criteria: over age 18 and having undergone emergency or elective surgery for colorectal cancer during the specified periods.

Exclusion criteria: under age 18, having undergone surgery for indications other than colorectal cancer, having undergone surgery for colorectal cancer outside the specified dates, diagnosed with COVID-19, and missing data.

Outcomes

Demographic data, such as age and gender, as well as tumor localization and TNM classification were recorded for all patients. In addition, information involving surgical procedures performed, whether surgery was performed under emergency or elective conditions, length of hospital stay, postoperative

complications (Clavien-Dindo classification), preoperative and postoperative white blood cell (WBC) count and C-reactive protein (CRP) values, presence of readmission and re-intervention, and rate of laparoscopy use were also recorded. These data were compared between the two periods.

Statistical analysis

In this study, the Statistical Package for the Social Sciences version 21.0 (SPSS, Chicago, IL, USA) was used for the statistical analyses of the data. As descriptive statistics, mean, standard deviation, median, minimum, and maximum values were used for continuous variables and number and percentage values for discrete variables. The Mann-Whitney U and chi-square tests were conducted for comparisons between two independent groups. The results were evaluated at the 95% confidence interval and P <0.05 indicated statistical significance.

Results

The study included a total of 183 patients, of whom 91 (36 women and 55 men) underwent surgery during the pre-pandemic and 92 (35 women and 57 men) during the pandemic. The mean age of the patients was 63.1 years for the pre-pandemic period and 63.7 years for the pandemic period. The demographic data of the patients are shown in Table 1.

When the preoperative and postoperative WBC count and CRP values of the patients were compared, only the preoperative CRP value was found to be significantly higher during the pandemic period *(P*=0.003). While the mean preoperative CRP value was 17.5 mg/L before the pandemic, it was 45.3 mg/L during the pandemic period. No significant difference was detected in the remaining laboratory values (Table 1).

When compared to the pre-pandemic period (12.1 days), the mean length of hospital stays significantly dropped during the pandemic (5.1 days) (*P*<0.001). The rate of patients undergoing surgery for emergency reasons, such as obstruction, perforation, and bleeding was significantly higher during the pandemic period (n=49/92, 26.7%) compared to the pre-pandemic period (n=32/91, 17.4% [*P*=0.01]) (Table 1).

It was also shown that the rates of morbidity and mortality were much greater during the pandemic *(P*<0.001, *P*=0.04). Mortality was observed in 13 (7.1%) patients during the pandemic and only 5 (2.7%) patients during the pre-pandemic period. According to the evaluation of postoperative complications with the Clavien-Dindo classification, the complication rate was significantly higher during the pandemic compared to the pre-pandemic period (*P*<0.001). There was no discernible difference between the pre-pandemic period (eight [4.3%]) and the pandemic (seven [3.8%]) in terms of the number of patients who experienced Grade I and II complications, which are considered minor. However, grade III, IV, and V complications, classified as severe, occurred in 11 (6.01%) patients in the pre-pandemic period and 37 (20.2%) patients during the pandemic period, indicating a significant increase in the latter (*P*<0.001) (Table 1).

Despite the fact that the rate of ostomies increased during the epidemic, this was not statistically significant (n=25, 30.83% vs n=37, 40.2%). The percentage of patients who received neo-adjuvant chemotherapy did not significantly differ between the two time periods (n=20, 21.9% vs n=22, 23.4%) (Table 1).

Table 1: Details of the patients' demographic and clinical data

	Pre-pandemic (n=91) (%)	Pandemic (n=92) (%)	*P*-value
Age, years (mean)	63.1	63.7	0.74
Gender			0.83
Male	36 (39.5%)	35 (38%)	
Female	55 (60.4%)	57 (61.9%)	
Clinical presentation			
Elective	59 (64.8%)	43 (46.7%)	0.01
Emergency	32 (35,1%)	49 (53.2%)	0.01
Bleeding	10 (10.9%)	13 (14.1%)	0.52
Obstruction	22 (24.2%)	30 (32.6%)	0.20
Perforation	0	6 (6.5%)	0.056
Surgical procedure			
Open surgery	78 (83.3%)	71 (77.1%)	0.14
Laparoscopy	13 (16.6%)	21 (22.8%)	0.14
Preoperative laboratory values			
White blood cell count (10^3/mm^3)	8.3	9	0.20
C-reactive protein (mg/l)	17.5	45.3	0.003
Postoperative laboratory values			
White blood cell count (10^3/mm^3)	11.8	11.5	0.68
C-reactive protein (mg/l)	116	133	0.24
Length of hospital stay (day)	12.1	5.1	<0.001
Re-admission	7 (7.7%)	17 (18.5%)	0.04
Re-intervention	5 (5.5%)	16 (17.4%)	0.02
Stoma Rate	25 (30.83 %)	37 (40.2 %)	0.07
Neoadjuvant treatment	20 (21.9%)	22 (23.4 %)	0.75
Postoperative complication (Clavien-Dindo, %)			
No complication	72 (79.1 %)	48 (52.2 %)	<0.001
Grade I	0	5 (5.4 %)	0.10
Grade II	8 (8.8 %)	2 (2.2 %)	0.04
Grade IIIA	1 (1.1 %)	4 (4.3 %)	0.18
Grade IIIB	5 (5.5 %)	10 (10.9 %)	0.18
Grade IVA	0	5 (5.4 %)	0.57
Grade IVB	0	5 (5.4 %)	0.10
Grade V	5 (5.5 %)	13 (14.1 %)	0.04

The rate of readmission was significantly higher during the pandemic period (n=7, 3.8% vs n=17, 9.2%) (*P*=0.04*)*. The rate of surgical interventions in readmitted cases was also significantly higher during this period (n=5, 2.7% vs n=16, 8.7% [*P*=0.02]). Despite the fact that laparoscopy was used more frequently during the epidemic period, there was no statistically significant change (n=13, 7.1% vs n=21, 11.4%) (Table 1). Last but not least, there were no appreciable differences in cancer pathological staging and T (tumor), N (lymph node), and M (metastasis) staging between the pre-pandemic and pandemic periods (Table 2).

Table 2: TNM staging of the patients

	Pre-pandemic (n=91) (%)	Pandemic (n=92) (%)	*P*-value
T (Primary tumor)			
T1	1 (1.1%)	3 (3.3%)	0.14
T2	10 (10.1%)	14 (15.2%)	
T3	39 (42.8%)	41 (44.6%)	
T4	41 (45%)	34 (36.7%)	
N (Lymph nodes)			
N0	40 (43.4%)	49 (53.3%)	0.17
N1	31 (34.1%)	23 (25%)	
N2	11 (12.1%)	19 (20.6%)	
N3	9 (9.9%)	1 (1.1%)	
M (Metastases)			
M0	80 /%87.8%)	72 (78.3%)	0.08
M1	11 (12.1%)	20 (21.8%)	

Discussion

Regarding the demographic information of the patients in this study, there was no discernible variation between the pandemic and pre-pandemic periods (mean age and gender distribution). Of the laboratory values of the patients, only preoperative CRP was found to be significantly higher during the pandemic period. As stated in the literature and recommended in relevant guidelines, surgery was performed in only complicated and emergency colorectal cancer cases during the pandemic, which explains the significantly higher CRP value in this period.

There is no clear information in the literature concerning the length of the hospital stay of patients undergoing colorectal cancer surgery during the pandemic. Some studies reported that the length of hospital stay was prolonged, while others did not indicate any change [17,18]. In the current study, the length of the hospital stay was significantly shorter during the pandemic period. This may be related to the willingness of both patients and surgeons to reduce the risk of COVID-19 transmission.

In this study, the rate of patients who underwent surgery for emergency reasons was found to be significantly higher during the pandemic period compared to the previous year. In the literature, there are studies confirming this finding [13-15]. It is known that patients tended to delay their hospital visits due to the risk of contracting COVID-19. In addition, with the healthcare personnel being affected by the pandemic, the number of outpatient clinics and endoscopy units were reduced, resulting in increased patient density in these settings. This can explain the higher rate of patients diagnosed for emergency reasons during the pandemic period.

Morbidity and mortality significantly increased with the increase in emergency operations. Despite the fact that there was no discernible difference in the rates of Clavien-Dindo Grade I and II complications, which were resolved with medical treatment without any interventional procedure, the rates of Grade III, IV, and V complication significantly increased during the pandemic period. At the same time, the mortality rate, classified as Grade V, significantly increased during this period, indicating that the cases surgically treated during the pandemic period were more complicated, as also stated in many previous studies [13-15]. Due to the increase in surgical operations performed under emergency conditions, severe complications, and thus associated mortality rates also increased.

In the literature, in addition to studies showing progression in cancer staging during the pandemic due to patients' delayed hospital visits to reduce the risk of COVID-19 transmission and the inability of outpatient-endoscopy units in hospitals to work at full capacity, there are also those reporting no significant change in staging during the pandemic [12,13,16]. In the current study, the number of patients with metastatic colorectal cancer was higher, but the difference was not statistically significant. In other words, there was no significant difference in pathological or clinical staging between the pre-pandemic and pandemic periods.

Rates of readmission and re-intervention after discharge from the hospital significantly increased throughout the epidemic period. This may have been due to the more complicated nature and emergency conditions of cases that underwent surgery and patients being discharged earlier during the pandemic. This finding should be supported by further studies with larger series.

Some authors have reported that COVID-19 spreads through not only droplets and contact but also fecal-oral route and aerosols. An international guideline on COVID-19 recommended that laparoscopy should be avoided due to the risk of aerosol formation and viral transmission [20]. Therefore, it was stated that laparoscopic operations should not be preferred, and even if they need to be performed, there is a need for careful management of laparoscopic gases, especially their evacuation process [21-23]. However, other studies have suggested that laparoscopic approaches can be used since there is no clear evidence yet indicating an increased risk of COVID-19 [24,25]. In a study examining the presence of COVID-19 in peritoneal fluid, the COVID-19 virus could not be detected in samples [26]. It has been argued that although laparoscopy may involve some risks for the surgical team, it does provide faster recovery and discharge for the patient [27]. In brief, there is no clear consensus on whether laparoscopy should be performed under pandemic conditions [25]. In our study, there was a numerical increase in the frequency of laparoscopy use compared to the previous year, but this was not statistically significant. We consider that this contributed to the faster recovery and discharge of our patients.

According to some studies, the rate of ostomies rose considerably during the pandemic period [28,29]. On the other hand, several authors claimed that there was no discernible change [30]. Although the rate of ostomies increased in our study during the pandemic, there was no statistically significant rise in this rate. The reason for this may be that ostomy was preferred more than anastomosis in infective conditions for emergency reasons during the pandemic period.

Limitations

Our article's retrospective approach and limited sample size are its two main limitations.

Conclusion

It is clear that the pandemic has had serious effects on colorectal cancer surgery. Our findings do not support the hypothesis that patients presented to the hospital with a more advanced cancer stage, which is one of the most commonly addressed issues in the literature. There was a significant increase in the number of patients operated for emergency indications, such as obstruction, perforation, and bleeding, and this had a significant effect on morbidity and mortality in the postoperative period. We attributed the higher readmission and re-intervention rates in the pandemic to the shorter length of hospital stay during this period.

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A retrospective analysis of the effects of femoral shortening osteotomy on clinical and radiologic outcomes in open reduction and Pemberton pericapsular osteotomy for Tonnis type 4 dysplasia of the hip

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Ethics Committee Approval
The study was approved by the Ataturk University Faculty of Medicine Clinical Research Ethics Committee (13.02.2019, No: B.30.2.ATA.0.01.00/).
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.

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Abstract

Background/Aim: Open reduction (OR) and Pemberton's periacetabular osteotomy (PPO) are efficient and reliable methods for treating late-diagnosed developmental dysplasia of the hip. However, various studies have reported an avascular necrosis (AVN) rate of up to 80% with this technique, which is increased in Tönnis type 4 hips. In this study, we hypothesized that femoral shortening osteotomy (FSO) would reduce the rates of AVN by decreasing the post-reduction pressure on the femoral head.
Methods: In this retrospective cohort study, we reviewed patients who had undergone OR and PPO between 2006 and 2016. Only hips with Tönnis type 4 dislocation were included. The subjects were divided into two groups: Group 1, who had undergone OR+PPO, and Group 2, who had undergone OR+PPO+FSO. The Kalamchi-MacEwen system was used for AVN classification. The groups were compared regarding the pre- and postoperative acetabular indices and the rate of AVN and other complications.
Results: We included 76 hips of 50 patients who met the inclusion criteria in the study. Group 1 consisted of 46 hips of 32 patients, and Group 2 consisted of 30 hips of 18 patients. The mean age of the patients was 31.5 months, and Group 1 (30 months) had a significantly lower mean age than Group 2 (34 months) (P=0.019). There were no statistically significant differences regarding the pre- and postoperative acetabular indices. In Group 1, 27 (58%) out of 46 hips had AVN, whereas the rate of AVN was ten (30%) out of 30 hips in Group 2. Out of the 27 hips with AVN in Group 1, 12 were type 1, five were type 2, and ten were type 3. Out of the 10 hips with AVN in Group 2, seven were type 1, two were type 2, and one was type 4. There was a statistically significant difference between the groups regarding the rates of AVN, with Group 2 having better outcomes not only in comparison to the rate of all AVNs (P=0.031) but also in comparison to high-grade AVNs (P=0.042) (Grade 3 and Grade 4).
Conclusion: Performing FSO with OR and PPO provides a significant decrease in the rate of AVN without altering acetabular development after surgery.

Keywords: developmental dislocation of the hip, femoral shortening, avascular necrosis, Pemberton's acetabuloplasty

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Introduction

Developmental dysplasia of the hip (DDH) is one of the most common congenital deformities [1]. The primary goal of treatment is to achieve and maintain a stable, concentric reduction to attain a pain-free, functional hip joint. The contemporary use of ultrasound (USG) screening for DDH facilitates early diagnosis and treatment. However, despite national screening programs, some patients are still diagnosed after they begin walking. Achieving reduction of the hip joint in late-diagnosed patients requires challenging surgical intervention. The soft tissue around the hip joint is contracted, the acetabulum is shallow due to the lack of reduction, the joint capsule is elongated, and there is an increase in femoral anteversion [2]. These issues are significant challenges in surgical treatment and may result in certain complications after treatment, such as soft tissue contractures, pain, aberrant gait, and early-onset osteoarthritis [3–5].

Two alternative options exist for relieving pressure on the femoral head in late-diagnosed, high hip dislocations. The first is preoperative skeletal traction. However, various studies report no improvement in outcomes with traction methods [6,7]. The second option is femoral shortening surgery (FSO), proposed by Hey Groves and Ombredanne in 1920 [8,9]. Many articles reported that femoral shortening in DDH improves outcomes [7,10–12]. The decision to perform femoral shortening is made during surgery when the reduction of the hip joint is forceful or the hip joint is under excessive tension after reduction [13–15]. Therefore, there is no specific indication for femoral shortening, and the decision mostly depends on the surgeon's experience. Certain studies aim to reveal the indications for femoral shortening, most of which conclude that it is required in late-diagnosed high hip dislocations [14–17].

Although femoral shortening is reported to improve outcomes, there is a limited number of comparative studies [13,14], and the results of these studies are conflicting. In this study, we hypothesized that femoral shortening would reduce the rates of avascular necrosis in late-diagnosed DDH cases with high-grade dislocations. To test this hypothesis, we compared the outcomes of patients who had undergone open reduction (OR) and Pemberton's periacetabular osteotomy (PPO) with those of patients who had undergone OR+PPO+FSO.

Materials and methods

The clinical ethical board of our institution approved the study (Ataturk University Faculty of Medicine Clinical Research Ethics Committee, approval date: February 13, 2019, protocol number: B.30.2.ATA.0.01.00/). We retrospectively reviewed patient data who had undergone OR and PPO between 2006 and 2016. To be eligible for the study, patients had to have undergone PPO and OR, be between 24-48 months of age, have Tönnis grade 4 dislocation, and have a follow-up period of at least 24 months [18]. Exclusion criteria included patients with neuromuscular or systemic disorders and teratologic hip dislocations, those with prior operative or non-operative interventions due to DDH, and those with insufficient radiologic follow-up data.

A total of 103 hips from 68 patients who were operated on between 2006 and 2016 at our department were initially eligible for the study. Seven patients with neuromuscular pathologies or teratologic hip dislocations were excluded, as were 11 patients with a follow-up period of fewer than 24 months. Ultimately, 76 hips from 50 patients met the inclusion criteria and were included in the study.

All patients were operated on via a Smith Petersen approach by the same senior surgeon experienced in DDH surgery. Separate approaches were used for femoral osteotomy and adductor tenotomy [19]. Open reduction was carried out with extensive soft tissue release and iliopsoas tenotomy at the level of the trochanter minor. A T-shaped incision was made on the joint capsule to facilitate capsulorraphy. Hypertrophic pulvinar, transverse acetabular ligament, and ligamentum teres were excised. Muscles were reflected from the inner and outer aspects of the ilium, and Pemberton osteotomy was performed [19]. An autogenous triangular iliac bone graft was inserted into the osteotomy line. Afterward, the hip joint was gently reduced. In cases of forceful reduction with excessive tension in the hip joint, FSO was performed. When reduction was achieved with excessive internal rotation and abduction, derotation and varus osteotomy were done. Semitubular titanium plates were used for fixation. Patients were kept in spica casts for 6–8 weeks, and an abduction orthosis was suggested afterward. Radiological results were evaluated using a digital PACS system with X-ray views of the patients taken before and after surgery and at their last follow-up.

The patients were divided into two groups: PPO+OR (Group 1) and PPO+OR+FSO (Group 2). Preoperative and postoperative acetabular indices and rates of avascular necrosis were recorded. The Kalamchi-MacEwen system was used to grade the severity of AVN [20].

Statistical analysis

IBM SPSS 20 software was used for statistical analysis. Data were presented as mean, median, minimum, maximum, standard deviation, percentage, and ratio. The normal distribution of continuous variables was calculated using the Shapiro-Wilk test if the sample size was greater than 50 and the Kolmogorov-Smirnov test if the sample size was less than 50. An independent samples t-test was used to compare two independent groups with a normal distribution, and if not, the Mann-Whitney U test was used. If the value of 2 × 2 comparisons between groups was more than 5, the Pearson chi-square test was used, and if it was less than 5, Fisher's exact test was used. A *P*-value less than 0.05 was considered statistically significant.

Results

A total of 76 hips from 50 patients with Tönnis grade 4 dislocations were included in the study, and the mean follow-up period was 44.1 months (range: 24–130 months). The mean age at the time of surgery was 31.5 months (range: 24–48 months), with ten male and 40 female patients. Group 1 consisted of 32 patients (46 hips) who had undergone PPO+OR (Figure 1), while group 2 consisted of 18 patients (30 hips) who had undergone OR+PPO+FSO (Figure 2).

Figure 1: A: 2.5 years female with bilateral Tönnis grade 4 dislocation. B: postoperative X-ray AP view. C: AP view 68th month postoperative X-ray view with bilateral type 3 avascular necrosis.

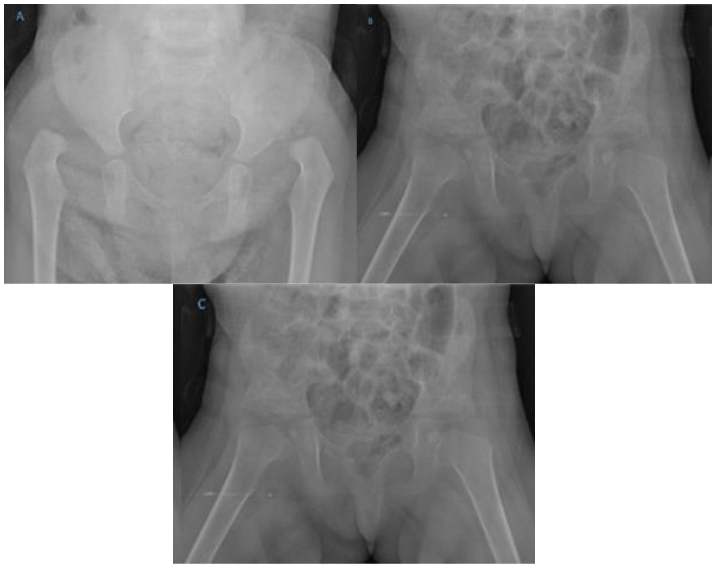
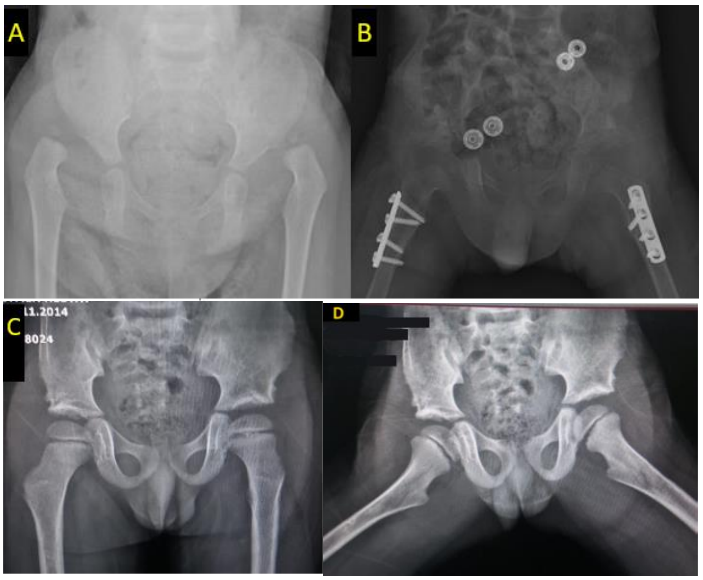


Figure 2: A: 33 months male with bilateral DDH. Plain X-ray AP view. B: Plain X-ray AP view two months after the operation, showing good containment of the femoral head. C, D: AP view 41st month postoperatively with an excellent radiographic outcome.



The mean preoperative acetabular index (AI) was 37 in group 1 and 39 in group 2, and there was no statistically significant difference between the groups (P=0.25). However, the mean age of patients in group 1 (30 months) was significantly lower than that in group 2 (34 months) at the time of operation (P=0.019) (Table 1).

Table 1: Summary of the clinical features of study subjects

Characteristics	All Hips	No femoral shortening	Femoral shortening	*P*-value
Patients(hips)	76	46	30	
Male	15	10	5	
Female	61	36	25	
Age	31.5	30	34	0.019
Preop AI	37.5	36.7	38.6	0.25

AI: Acetabular Index

In group 1, which did not have FSO, 27 out of 46 patients (58%) developed AVN. Among those with AVN, 12 had type 1, five had type 2, and ten had type 3, according to the Kalamchi-MacEwen classification. In group 2, which had FSO, ten out of 30 patients (33%) developed AVN, with seven having type 1, two having type 2, and one having type 4, according to the Kalamchi-MacEwen classification. Statistical comparison of both groups regarding AVN revealed significantly better outcomes for group 2 (P=0.031).

After excluding patients with grade 1 and grade 2 AVNs, group 1 had ten cases (22%), while group 2 had only one case (3%) of grade 3 or grade 4 AVNs. The group comparison also showed significantly better outcomes for group 2 (P=0.044) (Table 2).

Table 2: Result of the acetabular index and avascular necrosis.

Characteristics	All Hips	No femoral shortening	Femoral shortening	*P*-value
Postop AI	14,5	14.2	14,5	0.12
AVN	37 (48.7%)	27 (59%)	10 (33%)	0.031
Type 1	19	12	7	
Type 2	7	5	2	
Type 3	10	10	-	0.042
Type 4	1	-	1	

AI: Acetabular Index, AVN: Avascular Necrosis

Discussion

Treating developmental dysplasia of the hip (DDH) diagnosed after the walking age is challenging. Open reduction is the gold standard option for this condition, and in many cases, additional procedures such as acetabular and femoral osteotomies are necessary [14–16].

In a study by Gholve et al. [16] involving 49 hips with DDH in walking-age children, with a follow-up period of 9.7 years, only 12 patients did not require additional procedures after open reduction. Moreover, no patient younger than 18 months underwent femoral shortening, while all patients older than 36 months required PPO and FO. The study also reported better outcomes for patients who had undergone femoral osteotomies than those who had not.

In a study by Cordier et al. [21], 118 hips of patients who had undergone OR when less than 4 years old were evaluated and followed up for 10–21 years. Of these, 86 hips required additional procedures along with OR. The mean age of patients who underwent only OR was 7 months. The study reported no cases of AVN among those who had femoral shortening osteotomies in this series.

Most surgeons prefer to decide about femoral shortening osteotomy intraoperatively in cases of forceful reduction and excessive tension after reduction [13–15]. However, there is still no consensus on performing femoral shortening osteotomies. Reviewing the literature on this issue, the mean age of patients who underwent FSO was 36 months, and most had high dislocations [14,15,21]. FSO was usually not required for patients younger than 18 months of age [16,21]. To eliminate bias and have a homogenous group of patients, we included only patients between 24-48 months of age with Tönnis grade 4 dislocations.

Although numerous studies have investigated the outcomes of femoral shortening osteotomy, there is a limited number of studies focused on the requirement of FSO. Comparative studies have been criticized for having inappropriate control groups. For instance, Akgül et al. [13] studied the reliability of FSO with Dega osteotomy in 26 patients with Tönnis grade 3 and grade 4 dysplasia; they performed femoral shortening osteotomy on 13 patients and reported no significant difference in outcomes between the groups. However, the mean age of the group who had undergone FSO was 49 months, while the non-FSO group had a mean age of 27 months, which could have resulted in bias in comparing the groups. Many studies have reported worse outcomes with increasing age at the

time of treatment for DDH [11,22]. Therefore, we believe this study also had a significant bias in comparing the groups.

In our study, all of the patients had Tönnis grade 4 hips, and the mean age of the patients was similar (group 1, 30 years old; group 2, 34 years old). We only included patients who had PPO by the same senior surgeon to have homogenous groups who had undergone the same procedures at the same age, with a close number of subjects. So we aimed to clearly define the effect of femoral shortening osteotomy in this cohort of patients in this unique study

There was no significant difference between the two groups in terms of acetabular indices at follow-up, indicating that the central pressure point of the joint after reduction did not affect the development of the acetabulum. This finding is consistent with previous studies [13]. Due to the absence of redislocations in either group, we could not compare the groups in this regard [7], which is a limitation of our study. However, the AVN rate was significantly lower in the FSO group despite the higher mean age at surgery. Our findings suggest that femoral shortening osteotomies may be a valuable addition to OR and PAO in patients with DDH who are over 24 months of age.

Limitations

Despite having the most homogenous group of patients, our study had certain limitations, such as its retrospective design and limited follow-up period. Prospective studies with a larger cohort of patients could provide further insights into this issue.

Conclusion

A femoral osteotomy is an effective option for treating patients with high-grade dislocations who are over 24 months old and who have undergone open reduction and pelvic osteotomies to provide acetabular coverage. This procedure does not impede acetabular development and significantly reduces the rate of avascular necrosis.

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Research article

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Placenta accreta spectrum: Is placental invasion real?

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Ethics Committee Approval
The study was approved by the Institutional Review Board of Harran University's School of Medicine (HRU/21.18.24).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The description of placenta accreta spectrum disorder (PAS) has undergone significant changes. However, its association with obstetric morbidity and mortality has become even more important. Therefore, we aimed to assess the histopathologic evaluation of PAS patients who underwent a hysterectomy.

Methods: We conducted a retrospective study of all pathology reports from patients with peripartum hysterectomies at Sanliurfa Training and Research Hospital diagnosed with PAS. The study included 45 patients with a cesarean hysterectomy due to a preoperative placenta accreta spectrum disorder diagnosis. Hysterectomy specimens were evaluated based on placental invasion and myometrial defect at the site of the placenta.

Results: Out of 45 patients diagnosed with placenta accreta spectrum disorder who underwent a hysterectomy, only 17 (37.8%) had a histological diagnosis supporting the placental invasion. The histological diagnosis was consistent in 20 (44.4%) patients, indicating that the placenta protruded from a uterine wall defect without placental invasion. In eighth (17.8%) patients, the histopathological diagnosis was consistent with a histologically normal placenta.

Conclusion: The primary pathology of the disorder is variable, and the main issue is the association of the placenta with defective myometrium. Although a more alarming definition, such as invasion, should be avoided, PAS should not be underestimated due to its high mortality.

Keywords: adherent placenta, cesarean hysterectomy, placenta accreta

Introduction

Under a new definition, a class of placental adhesion anomalies is referred to as placenta accreta spectrum (PAS); the common feature of this class is the presence of a scar in the uterus, with the placenta attaching to this scar. However, the prognosis of these conditions varies considerably, making the most crucial feature of this class the differences in prognosis [1].

Over the past decade, there has been a significant increase in the diagnosis of PAS, with a tremendous increase in publications in this field [2]. Although the increase in cesarean rates has been cited as the primary cause, accepting this as the only factor is inaccurate. More than 90% of PAS cases are associated with placenta previa, with the combination of placenta previa on a previous cesarean section scar, and PAS is the leading factor of maternal morbidity and mortality due to massive peripartum hemorrhage [3]. However, Carusi et al. [4] reported their experience with PAS cases not associated with placenta previa in 2020 and found that these cases were less severe.

Ultrasonography and magnetic resonance imaging (MRI) are primarily used for the prenatal diagnosis of PAS. Findings described with both ultrasonography and MRI include placental "bulge", loss of the retroplacental clear or hypoechoic zone, imperceptible myometrium, and bladder wall interruption or irregularity. Vascular findings include sub-placental or ureterovesical hypervascularity and intraplacental abnormal vascularity or cavities [5].

In more than half of the literature on PAS, authors do not provide detailed information on the macroscopic clinical description at birth or histopathologic confirmation of the placenta accreta, even though hysterectomy is the primary treatment for PAS cases diagnosed prenatally or during labor [6]. In addition, very few studies differentiate these cases histopathologically from other adherent placentas.

This study evaluated cases diagnosed as PAS prenatally and who underwent a hysterectomy, including the histopathological results and the presence of placental invasion in the hysterectomy specimens. The primary aim was to determine whether the primary pathology in PAS cases is a placental invasion or another factor.

Materials and methods

We conducted a retrospective cohort study using Şanlıurfa Training and Research Hospital (Şanlıurfa, Turkey) and obtained Institutional Review Board approval from Harran University's School of Medicine (HRU/21.18.24). From May 2017 to September 2021, we included all patients who had undergone peripartum hysterectomy and were diagnosed with PAS. Preoperative diagnoses were made for all patients using sonography (Voluson E8, GE Healthcare, Milwaukee, WI) or MRI. Cases managed with uterine-sparing approaches that did not undergo hysterectomy were excluded from the study. Only cases with prior cesarean sections were included, and patients without any prior cesarean sections were excluded during patient selection. Patients provided verbal and written informed consent for using their data in studies in this area.

The antepartum diagnosis of PAS was made based on sonographic findings and, when necessary, MRI. Ultrasound examinations were performed centrally prenatally, and a single maternal-fetal medicine physician (Author 2: Ekmekci E.) confirmed all PAS findings. All patients were followed, and deliveries were planned electively at 35 weeks of gestation if there was no need for emergency delivery before that time. The same surgical team performed all elective deliveries, while several physicians at the same hospital performed emergent operations. Decisions regarding conservative management or hysterectomy were made based on multiple factors, such as disease severity, intraoperative surgical conditions, and patients' preferences. However, only subjects who underwent hysterectomy were included in the study, and these results did not affect our findings.

Collected outcome data included maternal age, gravidity, number of cesarean deliveries, gestational age at delivery, red blood cell unit transfusion, the occurrence of planned or incidental cystotomy, operation time, and the need for hospital readmission. The presence of placenta previa was also recorded. The final pathological diagnosis was determined from pathology reports, and a pathologist reevaluated the histopathologic diagnosis of all cases microscopically (Author 3/Coskun F.). Placental tissue invasion and myometrial tissue condition on the scar line were reevaluated. Trophoblastic tissue between myometrial fibers was defined as invasion and the loss of myometrial tissue, and the unrestricted presence of trophoblasts within the placental integrity was defined as placental protrusion.

Statistical analysis

The Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 22.0, IBM Corp., Armonk, NY, USA) was used for statistical analyses. The normality of distribution was assessed using the Kolmogorov-Smirnov test. Mean or median values were used to describe normally distributed data, while categorical data were presented as percentages. The chi-square and Fisher Exact tests were used for categorical data, and a t-test was used to determine two independent means. The significance level for all tests was set at $P<0.05$.

Results

Over 4 years, a retrospective analysis of medical records identified 45 cases of peripartum hysterectomy due to PAS. The average age of mothers was 35 years (range: 24–42), and all patients had a history of previous cesarean sections. No hysterectomy cases due to PAS were observed in patients without a prior cesarean section. On average, patients had undergone four previous cesarean sections (range: 3–7). Of the 45 pregnancies, 44 were singletons, and one was a twin pregnancy. Placenta previa was absent in only three cases, while 42 cases had total placenta previa. Only two cases had posteriorly located placentas, while 43 had placentas on the anterior uterine wall. Patient and pregnancy characteristics are presented in Table 1.

Table 1: Demographic characteristics of patients.

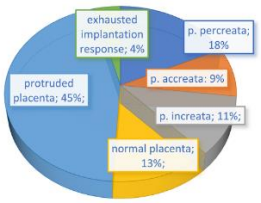
	n=45
Maternal age (years)	34.78 (3.63)
Previous cesarean section	3.96 (0.85)
Multiple gestations	1/45
Placenta previa	42/45
Placental localization	Anterior: 43
	Posterior: 2
Gestational age at delivery	35 (4.4) weeks
Mean operation time	137 (22) min
Red blood cell transfusion	4.6 (1.66) units

Thirty-four cases underwent elective surgery at 35–37 gestational weeks, with a median gestational age at the time of operation of 35 weeks (range: 21–37 weeks). Eleven cases underwent surgery before the 34th gestational week due to emergencies such as obstetrical hemorrhage or uterine rupture. Three cases underwent an emergency hysterectomy due to uterine rupture from a previous uterine scar, and eight (17.8%) underwent surgery for obstetrical hemorrhage.

The mean surgical time was 137 (22) min (range: 70–180). The median red blood cell transfusion was 4 units (range: 2–10), with seven cases requiring a transfusion of 5 or more units. Intraoperative cystotomy and bladder wall repair were required in seven cases. One maternal death occurred 36 h postoperatively due to disseminated intravascular coagulation induced by massive transfusion. After the operation, each patient was monitored in the hospital for 3 to 7 days before discharge, with no patient requiring hospital readmission after discharge.

Histopathology results are presented in Figure 1. Regarding invasion, materials with pathological diagnoses of placenta accreta, increta, and percreta were reevaluated. Of the 45 patients diagnosed with PAS who underwent a hysterectomy, only 17 (37.8%) had a histological diagnosis supporting placental invasion. Histological diagnosis was compatible with protrusion without invasion in 20 patients (44.4%), and eight patients (17.8%) had a histopathological diagnosis consistent with normal placentas.

Figure 1: Pathology reports of placenta.



In the histopathological examination, the mean surgical time of patients with normal placentas was 118.75 (29.97) min. In contrast, the mean surgical time was 139.51 (21.95) min in other patients, and the difference in operation time was significantly shorter in the group with normal placentas compared to the other groups (P=0.02). However, there was no significant difference in the amount of transfusion between the groups (P=0.05).

Upon examination of histopathology specimens, some specimens previously interpreted as placental invasion intraoperatively were evaluated as placental dehiscence or usual rather than invasion. The histopathological diagnosis of 12 (26.7%) of the 17 (37.8%) cases previously diagnosed as placental invasion was interpreted as an abnormal appearance consisting of a thinned or absent myometrium and a placenta located on abnormal decidua rather than placental invasion. These cases revealed that the previously considered placental invasion areas resulted from abnormal choriodecidual relations formed by the placement of the placenta on a damaged, insufficiently healed myometrium and decidua.

In the remaining five patients, a clear interpretation for the histopathological diagnosis was not made despite inadequate findings to describe placental invasion, as the presence of chorionic villi extending between myometrial fibers could not be distinguished from chorionic villi invasion or an inadequately healed myometrial defect (Figures 2 and 3).

Figure 2: Protrusion of placenta from the myometrial defect seen in cesarean section, Arrow: Protrusion of placenta out of the myometrial defect.

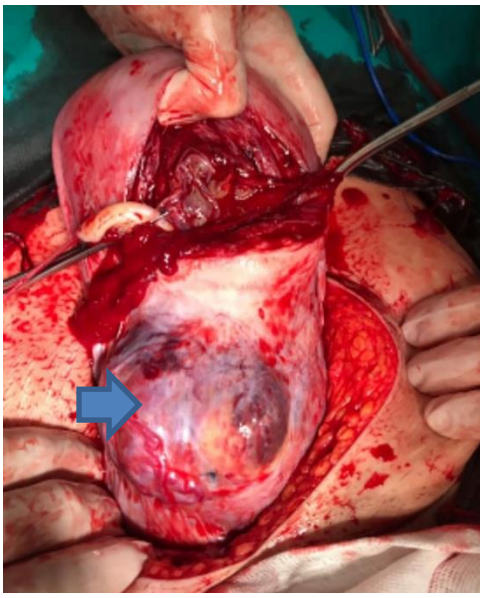
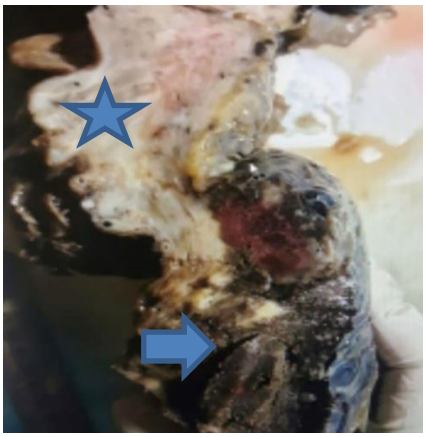


Figure 3: The macroscopic specimen of the hysterectomy material of placenta accreta spectrum, Asterisk: Macroscopic specimen of myometrial part, Arrow: Protrusion of placenta from the myometrial defect.



Discussion

Although risk factors for PAS are well-known, the underlying mechanisms that cause abnormal placentation remain unclear. Human placentation is a unique and highly invasive developmental process that occurs exclusively in the decidua and superficial myometrium of the uterus [7]. Several theories have been proposed to explain the aberrant placentation in placenta accreta. Initially, emphasis was placed on abnormal trophoblast function, leading to excessive invasion of the uterine myometrium [8]. Later, the other prevailing hypothesis suggested that abnormally deep trophoblastic infiltration results from the failure of decidua basalis formation in the uterine scar area [8,9]. Finally, localized hypoxia and abnormally vascularized scar tissue have been suggested to cause

decidualization disorder and increased trophoblastic invasion [10].

Tseng et al. [11] suggested that increased VEGF and EGFR expression from trophoblasts due to excessive angiogenesis are involved in the pathogenesis of PAS. Conversely, Earl et al. [12] argued that extravillous trophoblasts in PAS have the same immunophenotype as those in normal placentas and that overactive trophoblastic invasion is unlikely to be the cause of PAS. Instead, they emphasized that the absence of decidua plays a more significant role in the pathogenesis. Tantbirojn et al. [8] proposed that cracking and separation in the existing myometrial scar area in PAS are more likely to lead to trophoblastic invasion of the great vessels in the myometrial outer layer and serosa than trophoblastic growth defects or other immunologic factors. They presented the view in 2008 that anatomical factors, rather than immunohistochemical factors, are the main features in the pathophysiology of PAS.

Our results indicate that placental invasion was not detected in 40 (88.9%) of the 45 patients who underwent hysterectomy with a PAS diagnosis. Thus, the primary pathology was anatomical defects in the myometrium.

Although this study is retrospective, the antepartum diagnosis of the placenta accreta spectrum was confirmed by ultrasound in all included cases. All cases required a hysterectomy, indicating their severe and challenging nature. Therefore, subjective variations in diagnosing PAS were eliminated. However, only five (11.1%) cases showed evidence of placental invasion when pathological diagnoses were examined. In 20 (44.45%) cases, the pathological diagnosis was consistent with a normal placenta protruding from a uterine wall defect without invasion. In eight (17.8%) cases, both placenta and myometrial areas were histopathologically normal.

Maternal morbidity associated with PAS, such as massive transfusion, urinary tract injury, intensive care unit admission, hysterectomy, and maternal death, is linked to various factors. However, the results of our study do not align with the widely accepted notion that the severity of placental invasion is the primary factor associated with morbidity. The fact that 43 out of 45 cases had total placenta previa suggests that its presence is a critical factor in morbidity. Additionally, the size of the myometrial defect and the severity of the anatomical defect are also important factors related to morbidity.

In our histopathologically normal cases, the operation time was shorter than the remaining group, but there was no significant difference between the groups regarding transfusion units. The lack of significant difference in transfusion units between the groups may be due to the low preoperative hemoglobin counts of the patients, which could increase the need for blood. Additionally, the decision to perform a hysterectomy based on macroscopic appearance and previous surgeries may have increased the need for transfusion in patients with normal results. The use of hemostatic methods other than hysterectomy becomes controversial, as there is no reduction in blood use in normal cases. In our case series, the median history of previous cesarean sections was 4. A higher number of previous cesarean sections and more severe associated adhesions seem to be essential factors in morbidity.

Einerson et al. [4] identified the most critical factors associated with morbidity in cases of PAS, including the degree of uterine scar dehiscence, the degree and location of pelvic adhesions, and the extent of abnormal vasculature in and around hysterectomy planes.

Abnormal vasculature in and around the previous uterine scar area, particularly in the parametrial region, is a poor prognostic factor in PAS surgery. During the antepartum period, this abnormal vascularization appears as “lacunae” with irregular borders and low resistance flow in sonography. The presence of more lacunae is associated with a higher degree of difficulty in the operation. These cavities are often interpreted as evidence of placental invasion, but extravillous trophoblasts invading the uterine spiral arteries during normal placentation behave similarly in the case of an abnormal or damaged decidua. They penetrate the myometrium and access deep myometrial vessels, adhesions, and deeper pelvic vessels, causing dramatic uterine scar dehiscence. However, this trophoblastic behavior should not be considered an invasion of the placenta, such as in choriocarcinoma. Although cavities are associated with the severity of PAS cases, they should not be taken as an indicator of placental invasion. Placental lacunae are more common in placenta previa cases without a myometrial scar and are linked to postpartum bleeding, possibly due to insufficient decidual development in the lower uterine segment and the invasion of extravillous trophoblasts into deep myometrial arteries.

The first important factor related to the severity of the surgery is a defective decidual layer and pelvic hypervascularity resulting from the extension of extravillous trophoblasts into deep myometrial arteries. The second factor is the progressive scar dehiscence causing placental extension into the niche of the uterine scar in the first trimester and extending to the serosa as it progresses in later pregnancy. Cesarean scar pregnancy is considered a precursor of the placenta accreta spectrum, and the two conditions are histopathologically indistinguishable [14]. According to Timor-Tritsch et al. [14], the leading pathology and process of PAS is an abnormal attachment, abnormal recruitment of uterine vasculature, and slow progressive uterine scar dehiscence.

Limitations

The retrospective design of our study is a significant limitation. Furthermore, more data on conservatively managed PAS cases are necessary to improve our understanding of the condition. However, the advantage of our study is that all cases required a hysterectomy, indicating that we included cases with severe features. Additionally, the fact that the same physician diagnosed all cases during the antenatal period and the same pathologist evaluated all pathology materials prevented variations in diagnosis, which is advantageous for diagnostic accuracy.

Conclusion

While our findings suggest that anatomical defects and inadequate healing of the myometrium are the primary pathologies rather than placental invasion, it does not diminish the severity of PAS. It is crucial to always consider these cases’ as at high risk of morbidity and mortality and manage them individually.

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Research article

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Examining the relationship between patients who have undergone brain surgery and their fear of falling and pain, cognitive status, functional mobility, anxiety, and depression

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Ethics Committee Approval
The study was approved by Dokuz Eylul University Ethics Committee for Non-Interventional Clinical Research (Date:19.07.2018, Decision Number: 4142-GOA, 2018/18-06).
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.

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Abstract

Background/Aim: Patients who have undergone brain surgery are at risk of falling. Fear of falling causes an increase in the risk of falling and a decrease in movement and daily life activities. However, no previous research has investigated the fear of falling experienced by patients who have undergone brain surgery or the factors that affect it. This study aims to examine the relationship between fear of falling and pain, cognitive status, functional mobility, anxiety, depression, and socio-demographic and clinical characteristics in patients who have undergone brain surgery.

Methods: This cross-sectional study included 115 patients who had undergone brain surgery. The data were collected via a Patient Information Form, the Fear of Falling Scale, the Visual Analogue Scale, the Mini-Mental State Examination, the Itaki Fall Risk Scale, the Hospital Anxiety and Depression Scale, the Glasgow Coma Scale and the Timed Up and Go Test. IBM SPSS 22.0 software was used for descriptive statistics, correlation, and stepwise multiple linear regression analyses.

Results: Of the 115 patients, 73.1% were afraid of falling. Multiple linear regression analysis of the fear of falling in patients who had undergone brain surgery reveals that age (β=0.217, *P*=0.004), number of postoperative mobilizations (β=-0.141, *P*=0.031), a reported history of falling (β=0.155, *P*=0.032), the Timed Up and Go Test (β=0.372, *P*<0.001), and anxiety (β=0.358, *P*<0.001) were significant predictors of fear of falling. These variables explained 63% of the common variance.

Conclusion: Age, number of mobilizations, falling experience, functional mobility, and anxiety level can affect the fear of falling in patients after brain surgery. To mitigate this fear, it is important to plan care with reference to these variables from the time of the brain surgery until the patient is discharged. In addition, there is a need for further studies on falling and the fear of falling after brain surgery.

Keywords: fear of falling, brain surgery, pain, cognitive status, functional mobility, anxiety, depression

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Introduction

Fear of falling (FoF) is defined as anxiety related to falling that causes a person to avoid activities they can perform [1]. Studies have reported FoF in 56.5% to 71% of patients who have undergone surgery [1,2]. Falling and FoF are closely connected, and each is a risk factor for the other [1]. Research on the diseases that are most strongly associated with falling has indicated a direct relationship between falling and the lesion/pathology of the musculoskeletal system as well as an indirect connection with neurological and cardiac diseases [3]. Brain surgery patients often experience balance and gait problems, focal neurological disorders (e.g., hearing or visual impairment), epileptic seizures, motor strength and coordination deficiency, personality and emotional disorders, and changes in cognitive processes, which all pose a risk of falling [4–6]. Among patients who have undergone brain surgery, 82.9% have a high risk of falling [7]. Moreover, 40.6% to 74% of patients with cognitive changes exhibit FoF [8–11]. Studies have noted that an increase in cognitive impairment also heightens FoF [9–11].

The literature contains studies on FoF in patients with dementia, Alzheimer's, stroke, Parkinson's, and cognitive status changes [9,10]. However, no previous research has explored FoF in patients who have undergone brain surgery. Fear of falling in patients who have undergone major surgery, such as brain surgery, may result in limited activity levels, diminished balance, more frequent falls, less independence, an increase in hospital stay, the development of postoperative complications, heightened costs, restricted social participation, and deterioration in the quality of life [12–14]. This study examines the relationship between FoF and pain, cognitive status, functional mobility, anxiety, depression, and socio-demographic and clinical characteristics in patients who have undergone brain surgery.

Materials and methods

Study design

This research is of a cross-sectional type. The research was carried out in the neurosurgery clinic of a university hospital located in western Turkey between July 2018 and March 2020. In the clinic, the first mobilization of the patients after brain surgery was performed by a physiotherapist at the discretion of the surgeon. Subsequent mobilizations were facilitated by the physiotherapist, nurses, or caregivers. Patients were mobilized either on the first or second postoperative day, depending on the type of surgery and their general health status.

This study was approved by the Ethics Board for Non-Interventional Clinical Research and the University Hospital in West Turkey (Dokuz Eylul University Ethics Committee, Approval Number: 2018/18-06, 19.07.2018). All patients were informed of the aims and methods of the study. Oral and written informed consents were obtained from the participants, and written consent was acquired from the institution where the research was conducted.

Participants

The sample comprised 115 patients who had undergone brain surgery and consented to participate in the study. The sampling criteria for the patients included being at least 18 years old, having undergone brain surgery, being mobilized at least once, participating in the study voluntarily, understanding and speaking Turkish, having person, place, and time orientation, and having no hearing or speech impairment. Patients were excluded if they had a Mini-Mental test score of 23 or less, had been diagnosed with a psychiatric disorder (e.g., anxiety, depression, schizophrenic), or were immobile and unable to be mobilized. The sample size was calculated using G*Power v3. A post-hoc test was conducted for the power analysis, where the effect size was taken as 0.05 (P=0.05), the sample size was 115, and the number of predictor variables was 10. The research power was calculated as 0.81.

Data collection

The data were collected from patients who were hospitalized after brain surgery. The first step of the process was to identify patients who had made their first mobilization in physical therapy, subsequently mobilized on their own or with support, and met the inclusion criteria for the research sample. Each participating patient engaged in a face-to-face interview at an appropriate time when the patient's condition was stable (e.g., no severe pain). Immediately after each interview, the patient completed a Timed Up and Go Test. The research data were collected by one of the researchers involved in the study.

Measures

The data were obtained via the Patient Information Form, the Visual Analogue Scale (VAS), the Fear of Falling Scale, the Itaki Fall Risk Scale (IFRS), the Hospital Anxiety and Depression Scale, the Mini-Mental State Examination (MMSE), and the Timed Up and Go Test (TUG). The Patient Information Form, which was created by the researchers in line with the related literature, included questions about socio-demographic and clinical characteristics [8,11,15].

The VAS was developed to measure pain severity. This scale can be used either horizontally or vertically (0: no pain, 10: most severe pain). The horizontal version was used in this study. The patients were asked to indicate their pain severity by marking the corresponding point on a horizontal line.

The Fear of Falling Scale consists of a single-item Likert-type question that prompts patients to indicate their fear of falling based on a four-point scale (1: not afraid, 2: slightly afraid, 3: moderately afraid, 4: very afraid). Many studies of surgical patients have utilized this scale [2,16].

The IFRS was developed by the Turkish Ministry of Health and is used in all hospitals. The scale collects information about patient demographics, the time of the evaluation, the reason for its completion, and the major and minor risk factors. The scale was created for patients aged 17 years or older and had a total of 19 items. The scale score is established by adding the scores of all items. A total score between 0 and 4 points indicates a low risk of falling, while a total score of 5 or above denotes a high risk of falling. The psychometric properties of the scale have been evaluated by Barış et al. [17].

The HADS was developed by Zigmond and Snaith in 1983 and adapted to Turkish by Aydemir [18]. The scale is not intended to make a diagnosis but only to determine the risk of anxiety and depression in people with physical conditions. The scale consists of 14 items: seven investigate the symptoms of depression (HADS-D), while seven concern the symptoms of

anxiety (HADS-A). The cut-off points of the Turkish form are 10 for the anxiety subscale and 7 for the depression subscale.

The MMSE was devised by Folstein et al. [19] in 1983. This test can be easily administered to measure the degree of cognitive impairment. It contains sub-sections or dimensions that evaluate orientation, registration, attention calculation, recall, language, and structuring. Although various cut-off points have been used, scores of 23 or less are generally accepted as indicative of cognitive impairment. The highest possible score is 30. Turkish validity and reliability studies of the MMSE have been conducted by Güngen et al. [20].

The TUG was established by Podsiadlo et al. [21] in 1991. This test includes measurements of independent functional mobility, such as standing up from a chair, walking, turning, stopping, and sitting again. The individual is initially seated on a chair and then instructed to stand up, walk three meters, turn around, and sit on the chair again. Meanwhile, the elapsed time is recorded in seconds. The time to complete the test is related to the functional mobility level. For the TUG, scores above 13.5 signal a risk of falling.

Statistical analysis

Data analysis was performed with SPSS 22 statistical software. The correlation between FoF and socio-demographic and clinical features was assessed with a Pearson correlation analysis in which a *P*-value of less than 0.05 was considered significant. Multiple regression using a stepwise approach was conducted to determine which set of independent variables predicted the dependent variable (FoF). Before creating the regression model, standardized residual and multicollinearity were examined for the variables and independent variables, respectively.

Results

In the study sample, the 115 patients who had undergone brain surgery had an average age of 54.65 (14.07). Additionally, 52.2% were female, 82.6% were married, and 55.7% were primary and secondary school graduates. Sixty percent of the patients had a brain tumor, 17.4% had a pituitary tumor, and 22.6% experienced hemorrhage (intracranial, subarachnoid, or subdural). Furthermore, 24.4% had hypertension, 14.3% had diabetes mellitus, 5.2% had chronic heart failure, and 3.1% had another chronic disease. Fifteen percent were using oral diabetes medication, 25.6% were using antihypertensive drugs, 21.2% were using painkillers, and 4.1% were using another type of drug.

While 26.1% of participants reported a history of falling prior to their hospitalization, only 2.6% actually fell while in the hospital. However, 73.1% stated that they were afraid of falling. The average postoperative days of the patients was 4.66 (1.56). The average first mobilization day was 2.38 (1.14) days after the operation, and the average number of total mobilizations was 5.6 (3.9). After the postoperative process, the average scores of the patients were 2.72 (1.71) for the VAS, 14.30 (3.25) for the IFRS, 14.88 (0.31) for the GCS, 27.08 (2.43) for the MMSE, 14.66 (4.86) for the TUG (second time), 8.33 (3.72) (min=0, max=18) for the HADS-A, and 7.94 (3.63) for the HADS-D (Table 1).

Table 1: Socio-demographic and clinical features of participants

		n	%
Gender	Female	60	52.2
	Male	55	47.8
Marital status	Married	95	82.6
	Single	20	17.4
Educational status	Primary school and secondary school	64	55.7
	High school	46	40
	Undergraduate	5	4.3
Diagnosis	Tumor	69	60
	Pituitary tumor	20	17.4
	ICH*/SAH**/SDH***	26	22.6
Drugs used regularly	Yes	74	64.3
	No	41	35.7
Chronic disease	Yes	46	40
	No	69	60
Fall history	Yes	30	26.1
	No	85	73.9
Fall in hospital	Yes	3	2.6
	No	112	97.4
Fear of falling	Not afraid	31	27
	Slightly afraid	14	12.2
	Moderately afraid	44	38.3
	Very afraid	26	22.6
		mean (SD) (min-max)	
Age		54.65 (14.07) (18-83)	
Days after surgery		4.66 (1.56) (2-8)	
FoF		2.56 (1.11) (0-4)	
First mobilization (day)		2.38 (1.14) (1-5)	
Number of mobilizations		5.6 (3.9) (1-20)	
VAS		2.72 (1.71) (0-10)	
IFRS		14.30 (3.25) (0-22)	
GCS		14.88 (0.31) (14-15)	
MMSE		27.08 (2.43) (24-30)	
TUG (time)		14.66 (4.86) (8-28)	
HADS-A		8.33 (3.72) (0-18)	
HADS-D		7.94 (3.63) (0-14)	

ICH: Intracranial hemorrhage, SAH: Subarachnoid hemorrhage, SDH: Subdural hemorrhage, FoF: Fear of Falling Scale, VAS: Visual Analog Scale, IFRS: Itaki Fall Risk Scale, GCS: Glasgow Coma Scale, MMSE: Mini-Mental State Examination, TUG: Timed Up and Go Test, HADS-A: Hospital Anxiety and Depression Scale- Anxiety, HADS-D: Hospital Anxiety and Depression Scale- Depression

The results suggest a statistically significant positive relationship between FoF and age (r=0.419, P<0.001), constant use of medicine (r=0.199, P=0.016), chronic disease (r=0.287, P=0.001), history of falling (r=0.464, P<0.001), postoperative IFRS score (r=0.307, P<0.001), VAS score (r=0.357, P<0.001), TUG time (r=0.666, P<0.001), HADS-A score (r=0.497, P<0.001), and HADS-D score (r=0.260, P=0.012). In addition, as Table 2 indicates, there was a statistically significant negative r correlation between FoF in patients who had undergone brain surgery and male gender (r=-0.189, P=0.046), educational status (r=-0.197, P=0.032), number of postoperative mobilizations (r=-0.410, P<0.001), GKS score (r=-0.238, P=0.014), and MMSE score (r=-0.344, P<0.001).

Table 2: Relationship between clinical characteristics and fear of falling

	r	*P*-value
Age	0.404	<0.001
Gender	-0.189	0.066
Marital status	0.076	0.408
Education status	-0.197	0.032
Diagnosis	-0.001	0.823
Drugs used regularly	0.199	0.016
Chronic disease	0.287	0.001
First mobilization (day)	0.049	0.868
Number of mobilizations	-0.410	<0.001
Prior falls history	0.464	<0.001
Itaki Fall Risk Scale	0.307	<0.001
Visual Analog Scale	0.357	<0.001
Glasgow Coma Scale	-0.238	0.014
Mini-Mental State Examination	-.0344	<0.001
Timed Up and Go Test	0.666	<0.001
Hospital Anxiety and Depression Scale- Anxiety	0.497	<0.001
Hospital Anxiety and Depression Scale- Depression	0.260	0.012

Multiple linear regression analyses were performed to determine the contribution of factors related to FoF in patients who had undergone brain surgery. As Table 3 illustrates, a model was created for the predictors of FoF. According to an examination of FoF in patients who had undergone brain surgery

based on the model, age (β=0.217, *P*=0.004), number of postoperative mobilizations (β=-0.141, *P*=0.031), history of falling (β=0.155, *P*=0.032), TUG time (β=0.372, *P*<0.001), and HADS-A score (β=0.358, *P*<0.001) were significant predictors of FoF. These variables explained 63% of the common variance.

Table 3: Multiple regression analysis for variables predicting fear of falling (n=115)

Independent variables	Model		
	β	t	*P*-value
Age	0.217	2.929	0.004*
Chronic disease	0.008	0.116	0.908
Number of mobilizations	-0.141	-2.184	0.031*
Visual analog scale	-0.003	-0.047	0.963
Prior falls history	0.155	2.173	0.032*
IFRS	0.041	0.632	0.528
MMSE	-0.062	-0.923	0.358
TUG (time)	0.372	4.813	<0.001**
HADS-A	0.358	4.231	<0.001**
HADS-D	-0.033	-0.452	0.653
Adjusted R2	0.637		
F	9.512		
***P*-value**	<0.001*		

* *P*<0.05, ** *P*<0.001, VAS: Visual Analog Scale, IFRS: Itaki Fall Risk Scale, GCS: Glasgow Coma Scale, MMSE: Mini-Mental State Examination, TUG: Timed Up and Go Test, HADS-A: Hospital Anxiety and Depression Scale- Anxiety, HADS-D: Hospital Anxiety and Depression Scale- Depression

Discussion

The research results reflect that age, history of falling, number of mobilizations, TUG time, and anxiety were significant predictors of FoF in patients who had undergone brain surgery. Evidently, FoF increased with age. In previous research, FoF also increased with age [22,23], and the prevalence of FoF in older adults varied from 26% to 64% [16]. In a study on factors relating to the movement level of postoperative patients, difficulties with movement increased in parallel with age [24]. The literature further identifies old age, diminished physical health, "insomnia, dizziness, weakness, problems in walking and vision" increased dependence in daily life activities, poor health perception, chronic diseases, and use of medicine as factors relating to FoF [15,16,25]. In line with this information — and considering the risk factors for FoF — older patients are seemingly at a higher risk. Therefore, it is likely that the postoperative patients in this study experienced a stronger FoF due to more serious problems associated with old age, such as additional comorbidities, hearing impairment, and inactivity, as well as memory, cognitive, and neurological impairments resulting from the brain surgery.

In this study, FoF increased with anxiety in patients who had undergone brain surgery. This finding is consistent with earlier reports of higher anxiety in people with FoF [2,22]. Similarly, Polat et al. [23] have observed a negative effect of FoF on mood. The literature also highlights that neuroticism, which encompasses anxiety, worry, fear, and indecisiveness, is a risk factor for FoF [25]. Brain surgery is usually performed to treat diseases such as brain tumors, brain hemorrhages, or aneurysms, which significantly affect an individual's life and cause a high degree of stress. Previous research has revealed that 50% of patients experienced anxiety after brain surgery [5]. Furthermore, emotional, cognitive, sensory, and motor issues caused problems with mobility, and anxiety led to diminished physical functions in patients with brain tumors [12]. Anxiety can reduce patients' confidence in their physical health and cause them to develop more intense FoF [26]. During the perioperative process, anxiety in patients affects their coping, attention, concentration, learning ability, cooperation, and postoperative recovery process [5]. These findings imply that anxiety reduces patients' confidence in their health status and worsens their FoF by compromising their ability to cope with the process.

In the present study, FoF decreased as the number of mobilizations increased. Furthermore, FoF increased as the duration of the TUG increased. The results also reveal stronger FoF in patients who reported a history of falling. Another study with a different surgical sample group has found that patients experienced severe FoF during their first mobilization [2]. The literature identifies impaired physical performance as both a cause and a result of FoF [13,22]. In the present study, the average duration of the TUG was 16 s. Individuals with FoF often exhibit a more cautious gait (fearful gait) [12,14]. Since FoF negatively impacts an individual's confidence in performing daily life activities, it leads to a less active lifestyle, additional health problems (e.g. muscle weakness), and negative effects on subunits of life quality (e.g., mobility and energy) [23].

In previous research, difficulty with walking corresponded to stronger FoF [15], and individuals with FoF required more help with walking [22]. After brain surgery, many patients develop movement disorders and coordination problems. Patients with cognitive changes may experience mobility problems, such as a slow walking speed [4], and approximately 40% of falls occur when walking forward [27]. Research on another surgical group has found that improved physical activity in elderly patients was associated with faster walking, a shorter TUG time, and less FoF [28]. Meanwhile, in patients who had undergone spinal surgery, a longer TUG duration was related to greater dependence, more fragility, and negative postoperative outcomes [29]. The literature specifies a history of falling as a risk factor for falling [1,13] and a cause of more intense FoF [15]. Accordingly, patients who had problems with their movement while experiencing confusion and falling exhibited stronger FoF.

Limitations

The first limitation of this study was its exclusion of patients who had an MMSE score of less than 23 and who were not oriented to person, place, and time (i.e., confused). Confused patients are at a high risk of falling but may have less FoF. Further research could study both confused and unconfused groups of patients, including those who have undergone brain surgery. Another limitation was that the study included only postoperative brain surgery patients. Future studies could examine FoF in patients with diseases such as traumatic brain injuries, frontal, occipital, or other lobe injuries, or ruptured aneurysms, which can require follow-up without surgery.

Conclusions

The results of this study indicate that FoF increased with the duration of the TUG, the anxiety level, and age in patients with a history of falling who had undergone brain surgery. Furthermore, FoF decreased as the number of mobilizations increased. Health professionals are advised to adopt an individual approach that accounts for these variables when evaluating patients for FoF. Such factors are relevant to the mobilization process of patients and the development of strategies for fall prevention. Health professionals might be able to effectively mitigate FoF by allowing patients to express their feelings of anxiety after surgery as well as by evaluating their

psychosocial conditions and coping mechanisms. In addition, the provision of structured education about the surgery process and the post-surgery period prior to the surgery may be able to alleviate anxiety in patients. Since research on FoF in neurosurgery patients is limited, there is a need for further studies on this issue.

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Genetic alterations in azoospermia patients may reveal potential biomarkers for male infertility: A bioinformatic study

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This study was approved by the Local Ethics Committee of the Ankara University (Document number: 39-837).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Azoospermia is defined as the absence of sperm in semen and is one of the most common causes of male infertility, with a prevalence of 10-15% in infertile men. Conventional methods for semen analysis do not provide a clear understanding of the etiology of azoospermia. Although testicular biopsy may exclude obstructive cases, non-obstructive azoospermia (NOA) treatment is limited due to a limited understanding of the underlying molecular mechanisms. Analysis of genetic alterations in azoospermia patients compared to the fertile population may be a valuable tool for determining diagnostic biomarkers for male infertility. This study aims to use bioinformatic tools to determine the top candidates in certain pathways altered in azoospermia.

Methods: Expression data (GSE108886) of the differential testicular transcriptome in patients with NOA was selected from the Gene Expression Omnibus (GEO) database. Testicular RNA was harvested from azoospermia patients (n=11) and healthy controls (n=1, pooled sample). The differentially expressed genes (DEGs) were examined using GEO2R software. Biological pathways were identified through the Kyoto Encyclopedia of Genes and Genomes (KEGG). Construction of the protein network and detection of hub genes were conducted in the STRING database. Data validation was performed via ELISA assay for the FOXO3 gene in obstructive and NOA patients. Significance was set at *P*-value <0.05.

Results: In NOA patients, 2115 genes were upregulated, and 1753 genes were downregulated compared to the control group. Ninety-one genes involved in spermatogenesis were downregulated. KEGG analysis revealed that the glucagon signaling, AMPK signaling, insulin and estrogen signaling, and oocyte meiosis pathways were upregulated, while the regulation of actin cytoskeleton, MAPK signaling pathway, focal adhesion, and chemical carcinogenesis – reactive oxygen species pathways were downregulated. Downstream genes with the highest score were PSMA4, PSMA6, PSMC1, PSME4, and UBA52, which are responsible for the ubiquitin-dependent protein degradation. The top hub genes with increasing expression were RPS18, RPS2, and RPS4X

Conclusion: Although hub genes selected within the altering pathways may serve as a diagnostic tool for NOA, further validation of the presented data is necessary, as protein-protein interactions may not reflect alterations in gene expression *in vivo*.

Keywords: male infertility, azoospermia, bioinformatic analysis, GEO, microarray

Introduction

The inability of a male to impregnate a fertile female following regular sexual intercourse for 12 months or more is defined as male infertility [1]. While congenital, systemic, and environmental risk factors exist, conventional semen analysis does not always provide information on male fertility potential or etiology. Azoospermia, which is simply defined as the absence of sperm in the semen, affects 1% of the male population and 10–15% of infertile men [2]. Obstructive azoospermia (OA) results from a blockage or missing connection along the reproductive tract, while non-obstructive azoospermia (NOA) may be due to impaired spermatogenesis or testicular dysfunction caused by genetic disorders [3]. While OA can be treated by surgery, both the diagnosis and treatment of NOA are limited [4]. Therefore, identifying altered genes involved in NOA pathology as potential diagnostic biomarkers for novel treatment options is crucial.

Several genetic factors have been linked to NOA, including karyotype abnormalities such as Klinefelter syndrome, translocations, and deletions, including Y chromosome microdeletions of the AZFa, AZFb, and AZFc subregions [5]. Other genetic factors include but are not limited to, Kallmann syndrome [6], mild androgen insensitivity syndrome [7], and mutations in genes involved in spermatogenesis, such as TEX11 [8,9] and FSHR [10].

In mammals, spermatogenesis involves over 40 stages, where the morphology, cellular components, genetics, and epigenetics of the male germ cell undergo significant changes [11,12]. During these stages, different protein groups are organized for stage-specific cellular events through sensitive genetic adjustments. Conventional semen analysis does not always provide information on fertility potential or etiology in idiopathic cases [13]. Therefore, examining semen should include protein-protein interactions and alterations in protein-coding genes at all stages of spermatogenesis for NOA patients, highlighting the urgent need for diagnostic markers.

Recently, several genes coding for cell junction proteins, transcription factors, cytokines, proteases, and protease inhibitors have been proposed as markers of NOA in numerous animal studies [14]. Despite the guidance of these studies, the excessive number of proteins involved in spermatogenesis limits the prediction of target genes. Thus human studies have been limited [15-17]. In the last decade, bioinformatics has transformed the field of reproductive medicine by providing a powerful tool for analyzing and interpreting large-scale genomic data. This study aims to use bioinformatic tools to reveal genetic alterations in NOA patients and identify specific genes and pathways that may be involved in sperm production. Through this approach, potential biomarkers for male infertility may be identified for diagnosing and treating the disease.

Materials and methods

Data acquisition

The study was designed as a bioinformatic investigation to identify genetic alterations in azoospermia patients and determine potential biomarkers for male infertility. Total testicular transcriptome data was selected from the Gene Expression Omnibus (GEO) database for various types of azoospermia. The GSE108886 dataset was obtained by testicular biopsy, and total testicular RNA from 11 azoospermia patients and one pooled control testicular RNA sample were analyzed via Illumina HumanHT-12 V4.0 expression chip. The differentially expressed genes (DEGs) between groups were analyzed using the GEO2R online tool, and statistically significant DEGs (P<0.01, log2FC ≥0 or ≤0) were compared using the Venny program.

Functional enrichment analysis

The alterations in molecular pathways and biological processes in the dataset were analyzed using the DAVID (https://david.ncifcrf.gov/) online tool. Gene Ontology (GO) was determined for biological processes (BP), cellular components (CC), and molecular functions (MF) subgroups. The Kyoto Encyclopedia of Genes and Genomes (KEGG) was used to identify biological pathways for DEGs. Terms with P-value <0.01 were considered statistically significant.

Protein-protein interactions

The DEGs were imported into the STRING database to determine protein-protein interactions (PPI). A confidence limit of >0.4 was set for constructing the protein interaction network. The network's topological properties were analyzed using Cytoscape software (Cytoscape v3.9.2), and the most interacted proteins within the defined network were selected as the hub genes. Protein clusters were determined using MCODE analysis in highly interconnected regions.

Data validation

Data was confirmed via ELISA assay for testicular tissues from one obstructive and one NOA patient. Following diagnosis, signed consent forms were collected from each patient for the further use of the remaining testicular tissue. Ethical approval was granted by the Ankara University Local Ethics Committee (Document number: 39-837). Protein extraction was performed using tissue lysis buffer (Thermofisher Scientific, Waltham, MA, USA) on ice for 1 h. 100 µl of standard or samples were added to a 96-well plate and incubated for 90 min at 37°C. Following a brief wash and a 1-h incubation in biotinylated FOXO3 antibody (MyBioSource.com Inc., San Diego, CA, USA) at the same temperature, horseradish peroxidase (HRP) and substrate reagents were added. Absorbance was detected at 450 nm.

Statistical analysis

Normally distributed data were evaluated using a one-way ANOVA (Analysis of Variance) test, and non-parametric data were analyzed using Sidak's multiple comparisons test in GraphPad Prism Software version 9.0.0. A P-value of <0.01 was considered statistically significant.

Results

Identification and functional analysis of DEGs

The GSE108886 dataset was analyzed using GEO2R to calculate P and log2FC values for conditions where P<0.05 and log2FC values are ≥0 or ≤0, respectively. The results showed that 2115 genes were upregulated and 1753 genes were downregulated in azoospermia patients compared to the control group.

Additional analysis of DEGs was performed using the DAVID software to investigate pathway enrichment. The results revealed that the DEGs were significantly enriched in the 'Molecular Function (MF)' group, followed by the 'Biological Process (BP)' and 'Cellular Component (CC)' groups (P<0.01). Among the subgroups, the most notable changes in gene numbers were observed in the mitochondrion, spermatogenesis, cell differentiation, motile cilium, and microtubule. Table 1 shows the GO terms and the list of important genes that increased or decreased.

The KEGG pathway analysis identified 16 downregulated and 11 upregulated gene clusters. Among them, the regulation of the actin cytoskeleton, MAPK signaling, and glucagon signaling pathways showed the most significant changes (Table 2).

Table 1: GO analysis of altered genes in azoospermia patients.

Category	Term	Count
Downregulated genes		
Biological process	GO:0000398~mRNA splicing, via spliceosome	14
	GO:0002181~cytoplasmic translation	9
	GO:0030968~endoplasmic reticulum unfolded protein response	8
	GO:0006412~translation	13
	GO:0051496~positive regulation of stress fiber assembly	6
	GO:0045454~cell redox homeostasis	5
	GO:0030433~ubiquitin dependent ERAD pathway	6
Cellular component	GO:0005739~mitochondrion	58
	GO:0005681~spliceosomal complex	12
	GO:0005840~ribosome	13
	GO:0022627~cytosolic small ribosomal subunit	7
	GO:0022626~cytosolic ribosome	8
	GO:0005769~early endosome	16
	GO:0071013~catalytic step 2 spliceosome	8
	GO:0031234~extrinsic component of cytoplasmic side of plasma membrane	6
Molecular function	GO:0019843~rRNA binding	6
	GO:0003735~structural constituent of ribosome	12
	GO:0003779~actin binding	16
	GO:0051015~actin filament binding	12
Upregulated genes		
Biological process	GO:0007283~spermatogenesis	91
	GO:0030154~cell differentiation	72
	GO:0060285~cilium-dependent cell motility	11
	GO:0007018~microtubule-based movement	17
	GO:0060294~cilium movement involved in cell motility	7
	GO:0036158~outer dynein arm assembly	8
	GO:0008152~metabolic process	6
	GO:0018095~protein polyglutamylation	5
	GO:0061621~canonical glycolysis	5
	GO:0018105~peptidyl-serine phosphorylation	18
	GO:0006096~glycolytic process	7
	GO:0006457~protein folding	16
Cellular component	GO:0031514~motile cilium	50
	GO:0005858~axonemal dynein complex	9
	GO:0036157~outer dynein arm	8
	GO:0005874~microtubule	42
	GO:0030286~dynein complex	10
Molecular function	GO:0051959~dynein light intermediate chain binding	11
	GO:0008569~ATP-dependent microtubule motor activity, minus-end-directed	8
	GO:0003796~lysozyme activity	7
	GO:0045505~dynein intermediate chain binding	11
	GO:0003777~microtubule motor activity	12
	GO:0015631~tubulin binding	11
	GO:0004674~protein serine/threonine kinase activity	36
	GO:0051082~unfolded protein binding	15

GO: Gene ontology

Table 2: Altered KEGG pathways in azoospermia patients.

KEGG Pathway	Co	Downregulated genes
hsa04810:Regulation of actin cytoskeleton	17	ITGB1, CYFIP1, ROCK2, MSN, RHOA, SLC9A1, CRKL, CXCL12, ARPC3, PDGFC, GNA12, MYH9, PIP4K2A, RAC1, PFN1, RAF1, CRK
hsa04612:Antigen processing and presentation	9	HLA-DRB4, HSPA5, NFYC, PSME3, PSME1, RFXANK, CALR, B2M, LGMN
hsa04722:Neurotrophin signaling pathway	11	SHC1, ARHGDIB, GRB2, RAC1, FOXO3, RAF1, CAMK2G, CRK, RHOA, ATF4, CRKL
hsa03010:Ribosome	12	MRPL4, RPS4X, MRPL20, RPS4Y2, RPS18, RPLP1, RPL12, RPS3, RPL27, RPS2, RPS4Y1, RPL6
hsa04110:Cell cycle	10	CCND2, YWHAB, CDK4, GADD45A, MYC, SKP2, GADD45G, CDC25B, CDC14B, YWHAH
hsa04510:Focal adhesion	13	ITGB1, SHC1, ROCK2, CAV2, VEGFC, RHOA, CRKL, CCND2, PDGFC, GRB2, RAC1, RAF1, CRK
hsa04210:Apoptosis	10	CASP7, TUBA1A, GADD45A, CTSK, HTRA2, FADD, RAF1, LMNB2, GADD45G, ATF4
hsa04530:Tight junction	11	ITGB1, TUBA1A, ROCK2, CDK4, ARPC3, MYH9, PARD6G, MSN, RAC1, RHOA, AMOT
hsa05208:Chemical carcinogenesis - reactive oxygen species	13	COX7B, NDUFA6, NDUFA10, NDUFA1, AKR1A1, FOXO3, COX5B, COX7A1, UQCRH, GRB2, RAC1, RAF1, ACP1
hsa04218:Cellular senescence	10	PPP3CB, CCND2, TRAF3IP2, CDK4, GADD45A, MYC, FOXO3, RAF1, SQSTM1, GADD45G
hsa04012:ErbB signaling pathway	7	SHC1, MYC, GRB2, RAF1, CAMK2G, CRK, CRKL
hsa04010:MAPK signaling pathway	15	GADD45A, SRF, VEGFC, GADD45G, CDC25B, CRKL, PPP3CB, MYC, PDGFC, GNA12, GRB2, RAC1, RAF1, CRK, ATF4
hsa00010:Glycolysis/ Gluconeogenesis	6	LDHB, PDHA1, PGAM1, AKR1A1, PGK1, PGAM4
hsa04670:Leukocyte transendothelial migration	8	ITGB1, CXCL12, ROCK2, CTNNA1, MSN, RAC1, RHOA, RAPGEF4
hsa04062:Chemokine signaling pathway	11	GNG10, CXCL12, SHC1, ROCK2, GRB2, RAC1, FOXO3, RAF1, CRK, RHOA, CRKL
KEGG Pathway	**Co**	**Upregulated genes**
hsa04922:Glucagon signaling pathway	16	ATF2, PDHA2, PGAM2, CALML3, CPT1B, ACACA, LDHC, G6PC2, CREB1, PPP3CC, PPP3R2, PRKACG, PHKG2, AKT3, PFKP, PCK2
hsa00010:Glycolysis/ Gluconeogenesis	11	LDHC, GPI, HK3, PDHA2, G6PC2, PGAM2, GAPDHS, PGK2, PFKP, PCK2, HK1
hsa04152:AMPK signaling pathway	13	STRADA, CAB39L, TSC1, CPT1B, ACACA, G6PC2, CREB1, PPP2R1B, PPP2R3C, PPP2R2B, AKT3, PFKP, PCK2
hsa04066:HIF-1 signaling pathway	12	LDHC, HK3, PDHA2, FLT1, EGLN2, NOS2, NOS3, AKT3, CUL2, PGK2, PFKP, HK1
hsa04114:Oocyte meiosis	13	PLK1, CUL1, SPDYE4, CALML3, SPDYE6, PPP1CC, SPDYE2B, PPP3CC, PPP3R2, PLCZ1, PPP2R1B, PRKACG, PGR
hsa04910:Insulin signaling pathway	13	BRAF, CALML3, TSC1, ACACA, HK1, MAPK10, HK3, PPP1CC, G6PC2, PRKACG, PHKG2, AKT3, PCK2
hsa04915:Estrogen signaling pathway	13	ATF2, HSPA1L, NOS3, KRT23, KRT34, CALML3, KRT33A, CREB1, PRKACG, KRT15, AKT3, RARA, PGR
hsa04146:Peroxisome	9	NOS2, PEX11A, AGPS, ACSL6, FAR2, PEX11G, CRAT, PEX13, PAOX
hsa04920:Adipocytokine signaling pathway	8	MAPK10, G6PC2, AKT3, ACSL6, ACSBG2, CPT1B, PCK2, NFKBIB
hsa05230:Central carbon metabolism in cancer	8	LDHC, HK3, PDHA2, NTRK3, AKT3, PGAM2, PFKP, HK1
hsa03320:PPAR signaling pathway	8	GK, ACSL6, AQP7, DBI, ACSBG2, CPT1B, PCK2, GK2

Co: Count

PPI network analysis and identification of hub genes

The integrated PPI Network was analyzed using the STRING database, resulting in 60 nodes and 112 edges for decreasing genes and 58 nodes and 86 edges for increasing genes (P<0.01). The core genes were ranked according to their predicted scores using the network analyzer embedded in Cytoscape software. The hub genes were analyzed using cytoHubba, and the top 20 genes with the highest score for decreasing (Figure 1) and increasing (Figure 2) gene expressions were listed. The decreasing hub genes with the highest score were RPS18, RPS2, and RPS4X, while the increasing hub genes were PSMA4, PSMA6, PSMC1, PSME4, and UBA52. According to the GO analysis, the decreasing hub genes with the highest score were related to ribosomal translation, while the increasing hub genes were not enriched in a specific pathway.

Figure 1: Top 20 hub genes with the highest score according to STRING analysis within the identified PPI network for decreasing profiles (P<0.01). The scores decrease from red to yellow.

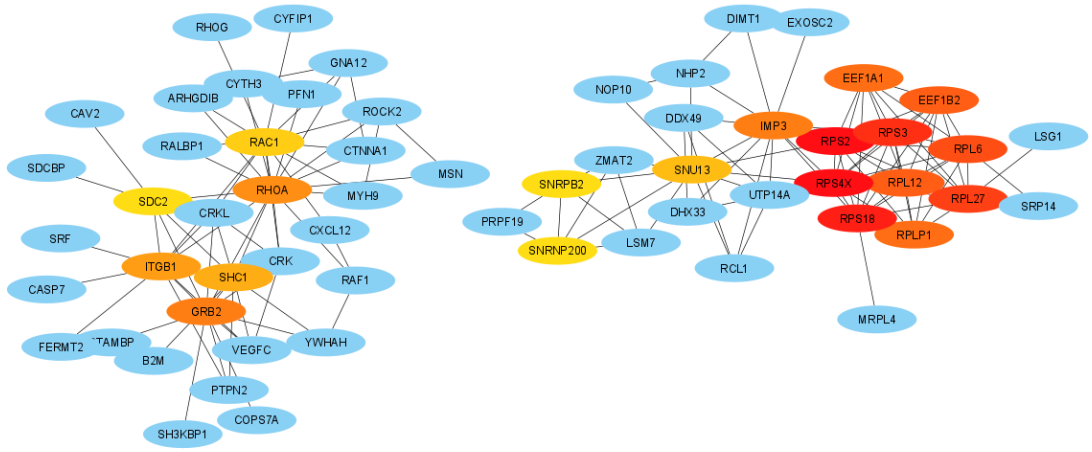
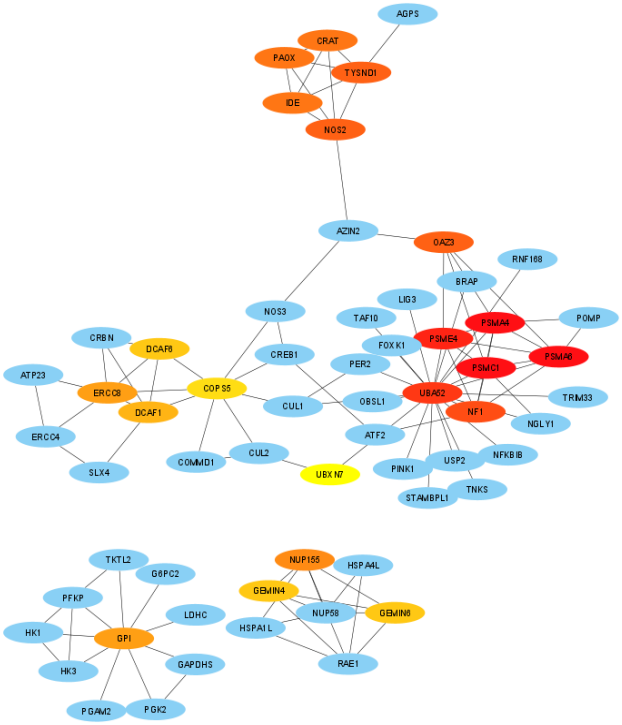


Figure 2: Top 20 hub genes with the highest score according to STRING analysis within the identified PPI network for increasing profiles [P<0.01]. The scores decrease from red to yellow.



Highly interconnected regions were analyzed with MCODE, and the cut-off score was set to 3 (Table 3). Protein clusters with the highest score included RPL12, RPS4X, RPL6, RPL27, RPLP1, RPS18, RPS3, EEF1A1, RPS2, and EEF1B2 for decreasing profiles, and PSME4, OAZ3, PSMA6, PSMC1, PSMA4, UBA52, and NF1 for increasing profiles, respectively.

Data validation

To validate the bioinformatic analyses, testes tissues from one obstructive and one NOA case were examined for the levels of FOXO3 protein. As predicted, the levels of FOXO3 protein were significantly decreased in the NOA sample (P=0.004).

Table 3: MCODE analysis for protein clusters in the identified PPI network.

Score	Nodes	Edges	Downregulated genes
9,778	10	44	RPL12, RPS4X, RPL6, RPL27, RPLP1, RPS18, RPS3, EEF1A1, RPS2, EEF1B2
5	5	10	SNRNP200, SNU13, ZMAT2, SNRPB2, LSM7
4	4	6	ITGB1, SDC2, RHOA, SHC1
3,6	6	9	NDUFA10, NDUFA6, ATP5H, ATP5L, NDUFA1, COX5B
3,333	4	5	RCL1, DHX33, DDX49, UTP14A
3,333	4	5	STX6, VAMP3, STX7, STX10
3,333	4	5	VCP, HSPA5, OS9, DERL1
3,333	7	10	COMMD7, COMMD6, COPS7A, COMMD10, GRB2, VEGFC, CRK
3	3	3	RGS19, RGS1, RGS10
3	7	9	THRA, PRDX5, PRDX1, NCOA1, RXRA, TXNRD1, TXN
3	3	3	HIST3H2A, MORF4L2, MEAF6
3	3	3	FOXO3, YWHAH, YWHAB
Score	**Nodes**	**Edges**	**Upregulated genes**
6,333	7	19	PSME4, OAZ3, PSMA6, PSMC1, PSMA4, UBA52, NF1
6	6	15	PLAT, F2, EDN1, PLAU, THBS1, VWF
5	5	10	PAOX, NOS2, IDE, TYSND1, CRAT
4,5	5	9	COPS5, DCAF6, DCAF1, ERCC8, CRBN
4	4	6	HK3, HK1, GPI, PFKP
4	4	6	CATSPERD, CATSPERB, CATSPER1, CATSPERG
3,333	4	5	GEMIN4, NUP58, RAE1, GEMIN6
3,333	4	5	POLR2I, GTF2A2, METTL14, POLR2D
3,333	4	5	SPA17, ROPN1L, ROPN1, AKAP3
3	3	3	UBE2V1, UBE2D3, UBE2U
3	3	3	SPAG6, SPAG16, MEIG1
3	3	3	TRAF3IP1, CLUAP1, TTC26
3	3	3	DNAH2, CFAP70, DNAH17
3	3	3	PPP2R1B, PPP2R2B, BRAF
3	3	3	BBIP1, BBS12, BBS5
3	3	3	ADSSL1, ASRGL1, IL4I1

Discussion

Spermatogenesis is a complex biological process that relies heavily on the genetic regulation of protein synthesis and degradation. While genome-wide analyses of testicular tissue have shed light on protein synthesis in male reproduction, little is known about protein degradation in spermatogenesis [18,19]. This study aimed to address this gap in knowledge by examining 91 genes involved in spermatogenesis and identifying hub genes through STRING analysis. Interestingly, the highest-scoring hub genes were PSMA4, PSMA6, PSMC1, PSME4, and UBA52, which have not previously been linked to protein degradation in spermatogenesis. This study is the first to highlight the potential role of these genes in this critical process.

The ubiquitination-proteasome system (UPS) regulates protein activity by facilitating protein degradation [20,21]. In this study, gene ontology (GO) analysis identified six altered genes in the ubiquitin-dependent endoplasmic reticulum-associated degradation (ERAD) pathway. In mammals, sperm quality is determined in the epididymis, where sperm mature to their final developmental stage. Abnormalities on the sperm surface are detected by ubiquitin secreted by epididymal cells. Ubiquitin, a 76-amino-acid polypeptide, tags substrate proteins for proteolytic destruction via proteasomes [22]. Interestingly, our study found that UBA52, which is responsible for ubiquitin conjugation through the regulation of translation [23], was upregulated in NOA patients compared to controls. These findings suggest that UBA52 may regulate protein degradation during spermatogenesis and warrant further investigation.

Recent studies have identified ubiquitin-related proteasomes in seminal plasma, suggesting that they may regulate sperm function by modifying surface proteins [24,25]. Mutations in the PSMA4 gene have also been associated with NOA [26]. Additionally, the PSME4 protein, a proteasome responsible for histone exchange during spermatogenesis, is highly expressed in human testis according to the Protein Atlas database and has been linked to male infertility in various animal studies [27]. Interestingly, our study found that the spermato-proteasomes mentioned above were upregulated with the highest scores according to STRING analysis. Conversely, PSMA6, another proteasome found in higher concentrations in the sperm of infertile bulls [28], was also upregulated in NOA patients compared to controls. Given the relationship between sperm ubiquitination and sperm DNA defects found in the literature, our study provides reliable candidates for diagnosing NOA patients, all involved in ubiquitin-dependent protein degradation during spermatogenesis.

Our study utilized KEGG analysis to identify upregulated pathways such as glucagon signaling, AMPK signaling, insulin and estrogen signaling, and oocyte meiosis pathways. In contrast, downregulated pathways included regulation of actin cytoskeleton, MAPK signaling pathway, focal adhesion, and chemical carcinogenesis/reactive oxygen species pathways. While these pathways play a crucial role in spermatogenesis and/or spermiogenesis, genetic screening for a particular pathway is not currently available in humans. Nonetheless, our findings provide important insights into the molecular mechanisms underlying NOA and may pave the way for future studies aimed at identifying potential therapeutic targets.

Limitations

It is important to note that further validation of the presented data is necessary, as protein-protein interactions identified through STRING analysis may not reflect alterations in gene expression *in vivo*. Additional studies incorporating other approaches, such as functional assays or animal models, are needed to confirm the potential roles of these candidate genes and pathways in NOA.

Conclusion

The study demonstrated the upregulation and downregulation of genes that play important roles in mammalian reproduction. The expression of 91 genes involved in spermatogenesis was found to be decreased in patients with azoospermia when compared to controls. The study also identified hub genes, including PSMA4, PSMA6, PSMC1, PSME4, UBA52, RPS18, RPS2, and RPS4X, which were particularly clustered in the ubiquitin-dependent protein degradation pathway in spermatogenesis. These hub genes may serve as a diagnostic tool for NOA.

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Research article

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An investigation of JAK2 mutation in patients with ulcerative colitis with a history of thrombosis

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Ethics Committee Approval
This study was approved by the Clinical Research Ethics Committee of Manisa Celal Bayar University (approval no. E: 31.05.2018-E.49233). Consent was obtained from the participants in this study. This consent form permits to use of participant's data in the studies
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: JAK2 is a gene that provides instructions for making a protein called Janus kinase 2, which is involved in the signaling process that regulates the growth and division of cells. Variations in the JAK2 gene have been associated with several different diseases, including certain blood disorders like myeloproliferative neoplasms (MPNs) and ulcerative colitis (UC). The exact reason for ulcerative colitis is not fully understood. This study aimed to examine the possible role of JAK2 V617F mutation in the etiopathogenesis of ulcerative colitis.
Methods: The included patients were selected with UC and with signs of thrombosis. The DNA isolation was carried out from peripheral blood for all included patients. RT-qPCR methods were used to find JAK2 V617F mutations in UC patients with signs of thrombosis.
Results: 73.3% of the included patients in this study had bloody diarrhea and 80% had abdominal pain. Also, the JAK2 V617F mutation rate was detected in 6.6% of the patients included in the study.
Conclusion: In this study, it was found that the V617F mutation was relatively rare in ulcerative colitis patients and there was no correlation with the JAK2 V617F mutation in most of the ulcerative colitis cases with thrombotic symptoms.

Keywords: ulcerative colitis, JAK2, thrombosis, V617F mutation

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Introduction

Ulcerative colitis is an inflammatory disorder of the gastrointestinal tract that an abnormal mucosal immune response and has a chronic and relapsing course [1]. It is defined by ulcerations starting from the rectum and spreading to the proximal colon [2].

The majority of symptoms of ulcerative colitis are abdominal distress and diarrhea with blood or mucus [3]. While its annual incidence in Europe and North America is approximately 25/100000 and 20/100000, respectively, the annual incidence rate in Asia is lower (6.3/100000). This difference is thought to arise from the variation in the level of industrialization [2]. While ulcerative colitis can occur at any age, it has a bimodal distribution pattern, with a tendency to occur between 15-30 years and 50-70 years of age. Although the etiopathogenesis of ulcerative colitis has not yet been fully clarified, it is thought to develop as a result of an interaction between genetic, immunoregulatory, and environmental factors [4]. Demonstration of high concordance of the disease in monozygotic twin studies, a 10-fold increased risk for the disease in the presence of a positive family history, and co-occurrence with several genetic syndromes suggest that genetic factors are also related to the pathogenesis of these diseases [5].

Inflammatory bowel disease (IBD), is a gastrointestinal disorder thought to be triggered by environmental factors in genetically predisposed individuals. As with many other inflammatory diseases, the near relation between thrombosis and inflammation also influences the course and intensity of IBD. Thrombocytosis occurs as both a primary disease (primary myeloproliferative diseases) and a secondary disease (reactive bone marrow diseases) [1]. Infections, neoplasms, severe iron deficiency, bleeding, inflammatory conditions, hemolysis splenectomy, and some medications also lead to reactive thrombocytosis [6]. Chronic myeloproliferative disorders (CMDs) progress by proliferation, differentiation, and maturation in one or more hematopoietic cell populations. These include essential thrombocytosis (ET), polycythemia vera (PV), chronic myeloid leukemia (CML), and primary myelofibrosis (PMF) [7,8].

Thromboses are frequently seen in the lower extremity veins and respiratory system, and less commonly in the portal vein, cerebrovascular field, retinal veins, mesenteric vein, and hepatic veins. The incidence of thrombosis in people with IBD ranges from 1% to 7%. In autopsy studies, this rate can be as high as 39-41%. The rate of thrombosis is higher than that of well-known extraintestinal signs. Spondyloarthropathies, with prevalence rates ranging from 12% to 23%, are the only extraintestinal signs seen more frequently than thrombosis. Important findings were also obtained from the cohort study which was carried out by Horsted et al. [9]., including 13,756 IBD patients performed by Horsted et al While the general risk for Venous Thromboembolism (VTE) was found to increase 3.6-fold in IBD patients compared with controls, this risk can increase up to 8.4-fold during acute attacks. Although the risk of VTE decreases during remission periods, it was still found to be 2,1-fold higher than in the normal population.

In a previous study that evaluated patients hospitalized for VTE, patients with IBD had a 2,1-fold increased mortality risk and stayed at the hospital longer than patients without IBD [10]. A study investigating factors associated with the recurrence of VTE detected that patients with IBD had a 2.5-fold increased risk for the recurrence of VTE attacks. Also, in a study by Miehsler et al. [11] that investigated whether the increased risk of thromboembolism was specific to IBD, it was found that the risk of thrombosis was not increased in cases of rheumatoid arthritis (as the control for inflammatory disease) and in cases of celiac disease (as the control for intestinal disease), but was increased 3.6-fold in cases of IBD.

Hereditary factors that predispose to thrombosis in inflammatory bowel disease play an important role. Therefore, patients with IBD should be evaluated in terms of susceptibility to thrombosis, family history, and use of prothrombotic drugs. Also, JAK 2 gene mutation is among the potential hereditary risk factors that remain unconfirmed due to insufficient evidence, and 48 IBD patients with thrombosis in an exemplary previous study were tested for the gene, but all of them tested negative. This mutation in the JAK2 gene has been demonstrated in some cases of myeloproliferative neoplasms (MPN) [12] and most commonly in those with ET (23%-57%), PV (65%-97%), and PMF (35%-57%). Also, it is seldom available in cases of chronic myelomonocytic leukemia, and myelodysplastic syndrome [13]. In cases with BCR/ABL-MPN, the presence of this mutation can be used as a marker to differentiate PV, PMF, and ET from reactive hematopoietic diseases [14].

The JAK2 gene encodes cytoplasmic tyrosine kinase, a protein that mediates growth factor receptor signaling. G>T transversion occurring in the 2343 nucleotide region of the JAK2 gene results in the V617F variation. As a result of this change, the amino acid phenylalanine replaces valine (V617F) in the JAK2 protein [15]. The mutant protein has increased kinase activity. As a result of this mutation in the JAK2 gene, PV progenitor cells may become hypersensitive to growth factors and cytokines.

This study aimed to explore the association between JAK2 mutation and ulcerative colitis and to investigate whether this is a risk factor for the development of ulcerative colitis.

Materials and methods

Patients

The study was approved by the Clinical Research Ethics Committee of Manisa Celal Bayar University (Manisa, Turkey), and written informed consent was obtained from all subjects (approval no. E: 31.05.2018-E.49233). Patients diagnosed with ulcerative colitis, who had an accompanying history of thromboembolic events such as pulmonary embolism, deep vein thrombosis, coronary artery disease, hepatic vein or portal vein thrombosis at Manisa Celal Bayar University Gastroenterology Clinic were included in the study. The inclusion criteria were as follows: 1. Age above 18 years, 2. A diagnosis of ulcerative colitis, 3. History of a concomitant thromboembolic event(s).

The exclusion criteria were as follows: 1. Diagnosis of mental retardation, psychotic disorder, or substance abuse disorder, 2. History of polycythemia, essential thrombosis, or myelofibrosis.

A total of 15 patients who met the inclusion criteria were identified, and 3 ml peripheral venous blood samples were collected in sterile gel tubes from each patient. Also, 15 healthy candidates of peripheral venous blood samples were used as a control.

DNA Isolation

Peripheral blood samples were obtained from the patients and control, which were collected in EDTA tubes. According to the instructions of the manufacturer, genomic DNA was extracted from the samples using a DNA isolation kit (Qiagen GmbH, Hilden, Germany) and kept at −20 °C until an RT–qPCR test could be performed.

Determination of the Amount and Purity of DNA Samples

After the isolation procedure, the DNA samples obtained for performing RT–qPCR testing were analyzed with a NanoDrop (NanoDrop ND-100) spectrophotometer.

RT–qPCR Analysis

To determine the JAK2 V617F mutation the DNA samples were analyzed with ipsogen JAK2 MutaQuant Kit (Qiagen GmbH, Hilden, Germany) according to the instructions of the manufacturer by quantitative RT–qPCR method (Table 1).

Table 1: DNA amounts obtained from patient tissue samples.

Patient	DNA amount (ng/ul)
Patient 1	87.61
Patient 2	92.51
Patient 3	121.02
Patient 4	92.52
Patient 5	155.01
Patient 6	192.09
Patient 7	163.61
Patient 8	345.33
Patient 9	92.12
Patient 10	149.57
Patient 11	264.61
Patient 12	15.25
Patient 13	251.48
Patient 14	169.57
Patient 15	213.63

Statistical Analysis

The significant differences between the patients and controls were evaluated with the ANOVA test (SPSS 23.0 statistical program) using Tukey post-hoc analysis. A *P*-value of <0.05 was considered statistically significant.

Results

Demographic and medical data

A total of 4 (26.6%) of the patients were female, and 11 (73.4%) were male. Of the cases included in the study, 73.3% had bloody diarrhea, 20% had joint findings, 80% had abdominal pain, 53.3% had weight loss, 26.6% had skin findings, 40% had liver-gall bladder findings and 33.3% had ocular findings (Table 2).

Table 2: Demographic and medical data of the patients

	Yes	No
Bloody diarrhea	4	11
Joint signs	3	12
Abdominal pain	12	3
Weight loss	8	7
Skin signs	4	11
Liver-gall bladder signs	6	9
Ocular signs	5	10

JAK 2 Mutation Analysis in Patient Groups

Mutations were detected in one of the 15 patients (6.6%) included in the study (*P*=0.378). A statistically significant association between JAK2 mutation and ulcerative colitis in patients with thrombotic findings was not found in this study (Table 3).

Table 3: Primer sequencing data of transcripts of housekeeping and JAK2 genes.

JAK2	F:5'TTCCTTAGTCTTTCTTTGAAGC3'
	R:5'GTGATCCTGAAACTGAATTTTCT3'
IL17A	F:5'ACAATCCCACGAAATCCAGGA3'
	R: 5'AAGGTGAGGTGGATCGGTTG3'
HPRT1	F: 5'-CGTCTTGCTCGAGATGTGAT3'
	R:5'TTCAGTGCTTTGATGTAATCCAG3'
B2M	F:5' TCTCTCTTTCTGGCCTGGA3'
	R:5'TGTCGGATGGATGAAACCC3'

Discussion

The JAK2 V617F mutation is known to reason an overactive JAK-STAT signaling pathway, which can cause abnormal immune responses and inflammation in the gut. This can contribute to the development of UC. For this reason, some research has shown that this variation is present in a small subset of UC individuals, and it is relied on to play a role in the development and progression of the disease [16-18]. It was shown in a study performed on Korean patients by Yang et al. [19] that JAK2 variants could act a role in the etiopathogenesis of ulcerative colitis. Prager et al. [20] found that JAK2 could influence the etiopathogenesis of ulcerative colitis by disrupting the integrity of the intestinal barrier. Another hand, similar to our study, Karimi et al. [21] examined the role of JAK2 mutation in 48 patients with the inflammatory disease who had thrombotic complications but did not find JAK2 V617F mutation in any of the study participants.

It is known that there may be regional variations in the prevalence of JAK2 V617F mutations depending on the population [19-21]. In a study performed by Can et al. [22] in Turkey, JAK2 mutation was shown to be a factor in the cause of inflammatory bowel disease in the Turkish population.

Limitations

The limitations of this study were the small number of the included patients due to the difficulty to find UC with signs of thrombosis. For this reason, a statistically significant association between JAK2 mutation and ulcerative colitis in patients with thrombotic events was not demonstrated found in this study. However, it is important to mark that the V617F mutation is relatively rare in ulcerative colitis cases, and the majority of cases of ulcerative colitis are not directly caused by JAK2 mutations. More research is needed to fully understand its causes and potential treatments.

Conclusion

As a result of JAK2 mutation analyses applied in patients who met the inclusion criteria of this study, which analyzed the role of the JAK2 V617F mutation in the etiopathogenesis of ulcerative colitis an autoinflammatory disease with an etiopathogenesis that has not yet been fully elucidated. A statistically significant conclusion could not be reached regarding if the JAK2 V617F mutation is a risk factor for ulcerative colitis. This study provides data to the literature on this topic, albeit limited because of the small sample size.

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Case report

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Application of a conventional paravertebral block on the thorax with a novel intrathoracic approach during the intraoperative period: Two case reports

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

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Abstract

Pain management significantly reduces mortality by aiding in the effective elimination of secretions after thoracic surgery. We present two cases requiring emergency surgical intervention due to major trauma. Both patients were provided pain control with an intrathoracic approach of the paravertebral block performed by a sterile-clothed anesthetist with a single-shot 20 ml injection of 0.25% bupivacaine from the inner surface to the superior costo-transverse ligament (SCTL). After extubation, the measured VAS score was no higher than 3–4, and the patients could breathe and cough comfortably. The intrathoracic approach may be an effective method to implement for postoperative acute pain.

Keywords: paravertebral space, intrathoracic approach, major thoracic trauma, superior costo-transverse ligament

Introduction

Pain management contributes to physical rehabilitation; therefore, it impacts mortality after major thoracic surgery by reducing the release of stress factors and inflammatory mediators. Pain management also reduces the incidence of atelectasis and pneumonia by enabling patients to eliminate secretions effectively with comfortable coughing [1].

Although epidural analgesia is considered the gold standard in pain management, it can be contraindicated or difficult to apply, leaving hemodynamically stable and unilateral paravertebral block (PVB) as an alternative choice [2]. PVB has been used for many years with the loss of resistance technique that forms after passing the superior costo-transverse ligament (SCTL) [3].

In cases of major trauma, the primary target of pain relief is to start the surgery and provide hemodynamics. Here, we present two patients whose pain control was ensured by intrathoracic application as an alternative to conventional PVB at the end of surgery.

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Case presentation

Case 1: A 37-year-old male patient with Chronic obstructive pulmonary disease (COPD) disease had severe thoracic trauma injury due to a traffic accident caused by a car rolling onto him from a high place. He experienced multiple rib fractures in many places, from the first rib to the tenth rib, haemopneumothorax, and extensive subcutaneous emphysema on the right side, as detected from thorax computed tomography (CT) scans (Figure 1a). The patient's preoperative hemodynamic values were a measured non-invasive brachial arterial pressure (BAP) of 64/36, SpO2 of 83% and heart rate (HR) of 151. In the induction phase, 1 mcg/kg fentanyl, 0.5 mg/kg ketamine, 0.5 mg/kg propofol, and 0.5 mg/kg rocuronium were administered. After double lumen intubation, the patient was placed in the decubitus position on the left lateral side and left radial arterial monitoring was achieved. After repair of the related traumas, thoracic integrity was established by applying six fixators (posterior of the 3rd, 4th, 5th, 6th and 7th ribs and anterior of the 4th rib) to the major rib fractures (Figure 1b). Before extubation, the patient's invasive radial arterial pressure (RAP), SpO2, and HR were measured as 130/71, 97% and 61, respectively.

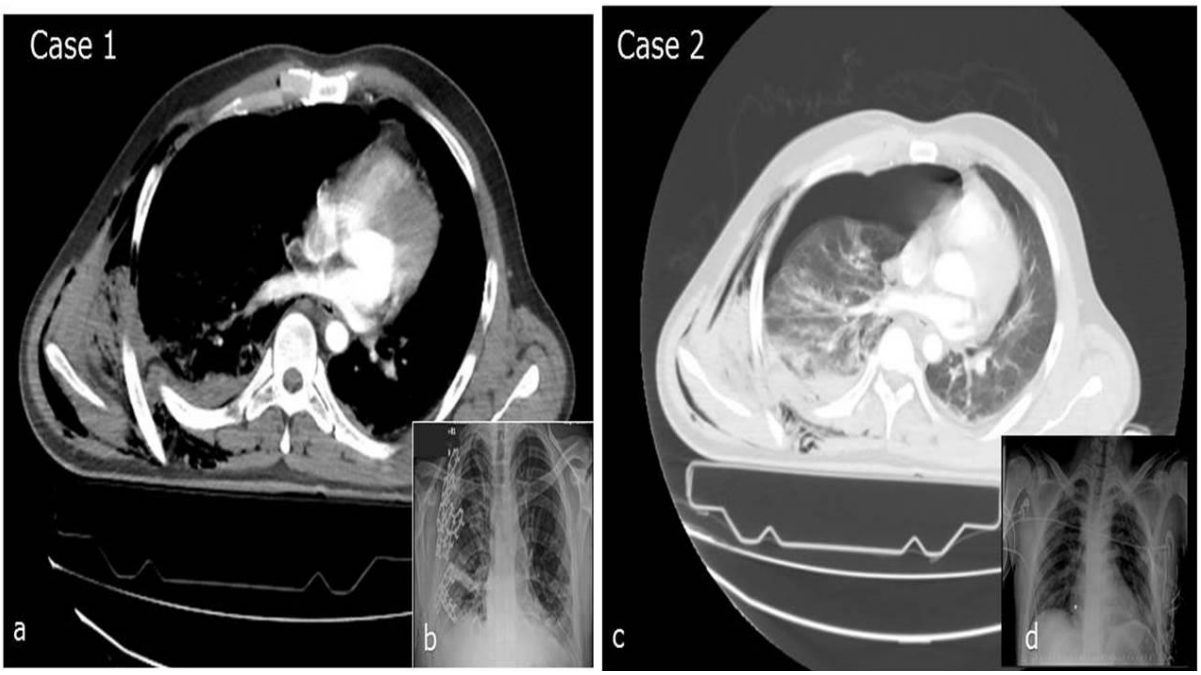
After extubation, the patient had extensive pulmonary secretions but was observed to breathe and cough easily and had a Visual Analog Scale (VAS) score of 3–4. The patient's invasive RAP, SpO2, and HR were 138/76, 92% and 83, respectively. The VAS score did not exceed 3–4 in the first 12 h. The patient received 100 mg of tramadol and 75 mg of diclofenac three times a day after 12 h as a routine pain treatment. The VAS score was assessed as 1–2 in the 24th hour. An intraspinal injection of 0.2 mg morphine was administered at L4-5 to the patient when he had difficulty coughing and discarding his secretions, and his VAS score increased to 3–4 in the 36th hour. After the injection, the VAS score decreased to 1–2, and the patient again began to cough easily and discard his secretions. He did not describe any chest pain in the 48th and 72nd hours. No additional problem was detected in the continuing follow-ups, and the patient was discharged on the 12th postoperative day.

Case 2: A 22-year-old male patient was brought into the emergency service due to a sharp object injury at 3.5 cm below the breast on the left mid-axillary line. Surgery was immediately performed on a massive haemothorax on the left side detected by thoracic CT (Figure 1c). The patient's preoperative hemodynamic values were measured as a non-invasive ABP of 83/41, SpO2 of 90%, and HR of 138. In the induction phase, 1 mcg/kg fentanyl, 0.5 mg/kg ketamine, 0.5 mg/kg propofol, and 0.5 mg/kg rocuronium were administered. After double lumen intubation, the patient was placed in the decubitus position on the right lateral side, and right radial arterial monitoring was achieved. The intercostal arterial hemorrhage and an approximately 2.5 cm laceration of the lung were repaired from the 5th intercostal space. Before extubation, the patient's invasive RAP, SpO2, and HR were measured as 121/65, 97%, and 97, respectively.

After the extubation, the patient had a VAS score of 3–4 and was breathing comfortably. Postoperative VAS scores ranged between 0 and 2, and no additional analgesia was required. No additional problems were detected in the continuing follow-ups, and the patient was discharged on the 3rd postoperative day (Figure 1d).

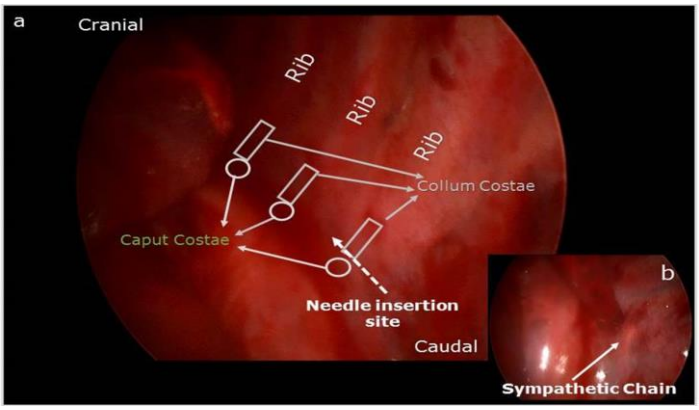
The blocks were performed just before the thoracotomy's closure and after the surgery's completion. The anesthetist wore sterile gear and was involved in the operative field from the posterior side of the patient in the lateral decubitus position. The costovertebral joint (the joint formed at the junction of the caput costae and vertebral corpus) was palpated on the inner surface of the thorax. The location of the collum costae was determined by proceeding laterally through the caput costae. The injection point was determined away from the intercostal neurovascular bundle, just above the base of the collum costae (Figure 2a), in the incision line and lateral to the sympathetic chain (Figure 2b). Our sterile medicine was connected to a 24-G blunt-ended needle and entered from the predetermined site. The needle was advanced with constant pressure, parallel to the ground, towards the SCTL. When resistance loss developed within the first 1 cm during needle orientation, and after confirming no blood or other fluids on negative aspiration, 20 mL of 0.25% bupivacaine was

Figure 1: Preoperative CT (a) and postoperative chest X-ray (b) images of Case 1. Preoperative CT (c) and postoperative chest X-ray (d) images of Case 2. CT: Computerized tomography.



administered at 1 mL per second as a single injection for postoperative analgesia. After the injection, the thoracotomy closure was routinely continued, and the surgery was terminated. At 15 min before the completion of the surgery, 100 mg of tramadol citrate was administered routinely. Extubation-induced pain in the extubated patients was prevented by administering 100 mcg of fentanyl citrate. The patient was transferred to the postoperative intensive care unit, and VAS scores were evaluated at 0, 1, 2, 4, 6, 12, 24, 36, 48, and 72 h after extubation.

Figure 2: Demonstration of the intrathoracic approach (a) and view of the sympathetic chain (b).



Discussion

Pain control and early extubation directly impact mortality, so effective pain management is important following major thoracic surgeries. However, regional approaches are difficult to apply in major traumas where the integrity of the thorax is impaired and emergency surgery is required. In these cases, alternative pain management approaches are needed [4].

One alternative site is the PVB area, which constitutes the first transition point of the peripheral nerves separated from the central nervous system and can therefore serve as an effective area for pain control. In the PVB, the SCTL is targeted as a reference point in both the conventional and ultrasound-guided (USG) approaches [5]. Our aim in this report was to present two cases in which we targeted the SCTL as an intrathoracic site for postoperative pain management.

In the PVB, fluctuation of the drug in the subpleural area is observed when targeting the anterior (or deep) regions of the SCTL. The posterior (or superficial) point of the SCTL is not a closed area, so the drug can spread to the effective cranio-caudal and pleural area via fenestras [6]. Today, the points on the posterior of the SCTL are targeted in variants (such as the Erector Spinae Plane Block [ESPB], retrolaminar and paraspinal blocks) defined to avoid the undesirable complications of the PVB [7]. The injection points at the posterior point of the SCTL are now used as the block names (ESPB, mid-transverse block, and costotransverse block) [8].

In the clinic, the applied approaches include intrathoracic approaches, intercostal blocks, pleural infiltrations or catheter application, and wound infiltration. The surgical team usually applies these approaches; however, they have disadvantages, such as a requirement for multiple injections, the possibility of catheter dislocation, the risk of infection or the formation of only a limited block in a specific area [9].

We came across only one clinical study that targeted the paravertebral area intrathoracically. In that study, the block was applied by passing the needle 5 mm at 1 cm lateral to the sympathetic chain and applying a subpleural fluctuation of 8 ml 0.5 ropivacaine at each injection, followed using two separate injection points [10]. In our study, the loss of resistance technique for the SCTL was targeted, and this is an approach that we have not encountered in any previous study. We aimed to increase the cranio-caudal spread by restricting the drug to a certain area.

A need for intubation did not develop in hemodynamically stable patients after surgery. No pulmonary pathology was observed in the ongoing recovery of patients who could actively cough and be mobilized.

Conclusion

This novel alternative method should be kept in mind because the paravertebral area is very close to the intrathoracic area and is easy to access compared to conventional approaches. In our opinion, this area deserves a multidisciplinary intrathoracic approach by the surgical-anesthetic team. Further studies are needed on the subject.

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Case report

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Diagnosis and treatment of spinal extradural arachnoid cysts: A chronic traumatic case report with review of the literature

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

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Abstract

Arachnoid cysts are formed by duplication of the arachnoid membrane between the arachnoid and the pia mater. Although it is very common in intracranial localization, those with spinal location are rare. Extradural arachnoid cysts of the spinal canal are extremely rare pathologies regarded as either congenital or acquired. These cysts, which can develop idiopathic, post-traumatic, and after arachnoiditis, are often detected incidentally. They present with weakness in the extremities, neuropathic pain, paresthesia, or myelopathy. Here we describe the case of a 17-year-old male patient with a history of chronic spinal trauma who attended our clinic with severe low back pain for 7 months.

Keywords: arachnoid cysts, spinal, extradural, trauma

Introduction

Spinal arachnoid cysts are rare lesions that are mostly idiopathic and congenital. Intradural arachnoid cysts are more common, although they can be seen in intra-dural or extradural localization [1]. They usually develop after arachnoid herniation through a small dural defect and progressively expand with increased cerebrospinal fluid (CSF) pressure. This increased wall tension causes counterpressure that contributes to the closure of the communication pedicle. Changes in the arachnoid trabecula after a trauma or arachnoiditis can also cause intradural spinal arachnoid cysts to appear [2-4].

Although spinal arachnoid cyst is mostly seen in the thoracic region, it can also be seen more rarely in the cervical and lumbar regions [5]. It is frequently seen in the middle and lower thoracic region and men. Although they are usually asymptomatic, the ones with anterior localization often present with weakness and myelopathy, and those with posterior localization are presented with neuropathic pain and paresthesia [6].

Spinal magnetic resonance imaging (MRI) is the method for detecting spinal arachnoid cysts that cannot be seen with conventional myelography due to their posterior localization [7]. Treatment involves surgical excision of the cyst. In cases that undergo early surgery, the prognosis is good [1]. Here we describe the case of a 17-year-old male patient who attended our clinic with a history of chronic spinal trauma, complaining of severe low back pain for 7 months.

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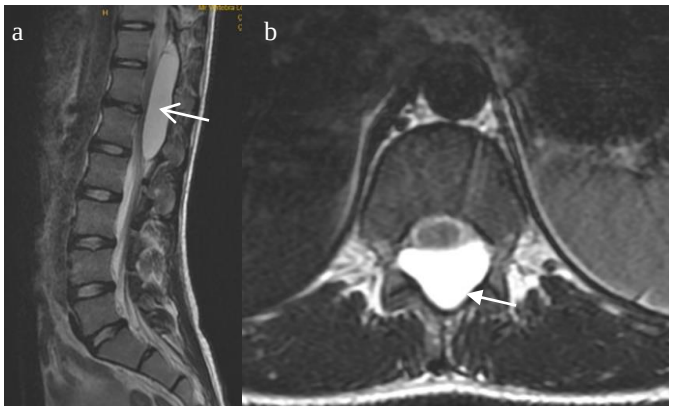
Case presentation

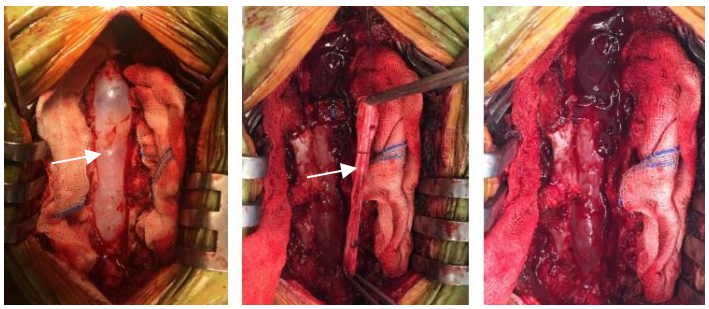
A 17-year-old male patient, whose written consent was obtained from his legal guardian before the surgical procedure, had complained of severe back and low back pain for 7 months. The patient, a professional football player, had no known diseases or history of infections, according to his medical history. In his neurological examination, his motor strength was normal, below T11 was hyposthenic, and the sphincter tonus was intact. On contrast-enhanced thoracolumbar MRI, an isointense cystic lesion of 18 × 32 × 90 mm in size at T11-L1 level was detected with CSF that did not show contrast enhancement. The cystic lesion in the epidural area at this level caused significant narrowing of the thecal sac, and the conus medullaris was pressed (Figure 1).

Figure 1: Preoperative thoracolumbar MRI, T2 contrast section, sagittal (a) and axial T2 (b) imaging; at the T11-L1 level, a cystic lesion (arrow) of 18 × 32 × 90 mm in size is located in the epidural area without contrast enhancement, and a marked narrowing of the lesion in the thecal sac, and compression of the conus medullaris are seen



The patient was taken into operation with intraoperative neuromonitorization. T11, T12, and L1 posterior elements bilateral end block were removed. On the dura, a cystic lesion was seen (Figure 2). Using bipolar biopsy forceps and a director in the craniocaudal plane, the cystic lesion seen from the cranial and caudal ends of the dura was then dissected and totally excised. A serial Valsalva maneuver was performed, and it was seen that there was no connection between the cyst and the subarachnoid space. T11, L1, and L2 laminoplasty was performed with the miniplate screw system after it was observed that the spinal cord was relieved from the posterior.

Figure 2: a, b: Cystic lesion (arrow) after laminectomy at T11-L1 level in the perioperative photograph, c: Intact appearance of the dura after en bloc removal of the cyst



Control thoracolumbar MRI was performed on the patient who was taken to the service without any postoperative deficit, and it was seen that the lesion was totally excised (Figure 3). The patient was mobilized on the first postoperative day and was discharged on the fourth day without any problems. No newly developed complaints or radiological findings were detected in the 1-year clinical follow-up of the patient whose histopathological examination was reported to be compatible with an arachnoid cyst (Figure 4).

Figure 3: Postoperative thoracolumbar MRI, contrast-enhanced T2 sagittal (a) and axial (b) imaging; it is seen that the extra-axial cystic mass (arrow) at the T11-L1 level was totally excised, and there was no evidence of residual/recurrence.

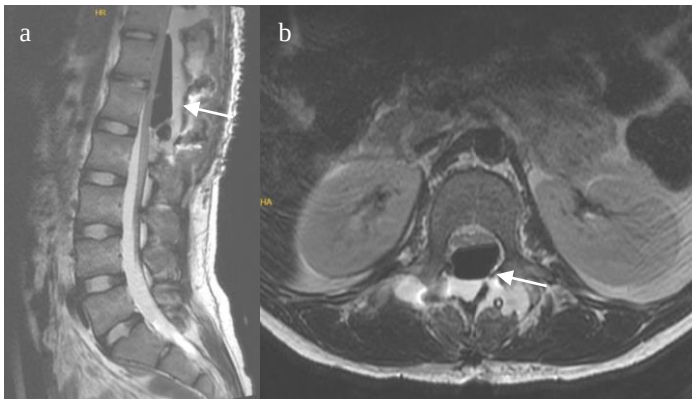


Figure 4: Postoperative 1st year, thoracolumbar X-ray; sagittal (a) and axial (b) imaging; deterioration of the patient's thoracolumbar axis and newly developed kyphotic deformity are not observed.

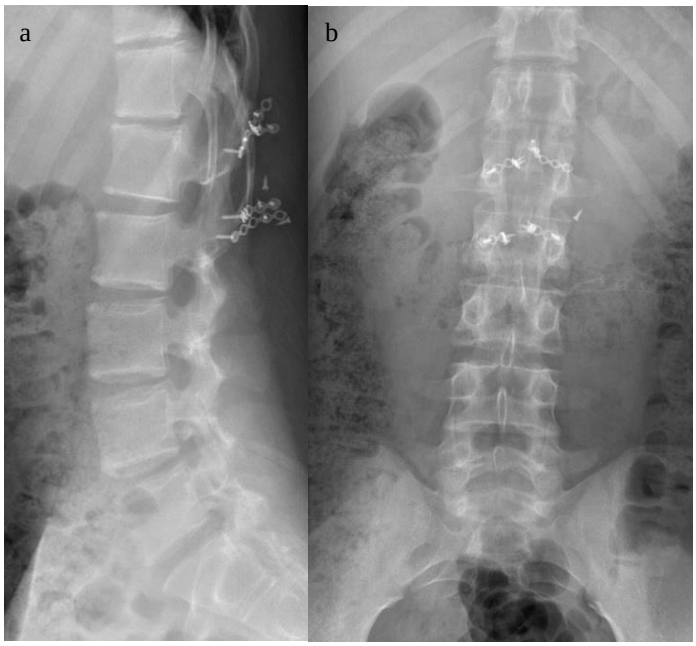


Table 1: Comparative data analysis of previous series reported in literature

Author& Year	No of Pts	Mean Age (yrs)	Female Sex	Presentation (% pts)	Imaging	Location	Surgical treatment (% pts)	Follow-up (months)	Outcome (%)
Wang et al., 2003 [6]	21	52	38%	Pain (76%), sphincter (24%), myelopathy (52%)	MRI only	10 dorsal thoracic, 4 ventral thoracic, 2 dorsal cervical, 2 ventral cervical, 3 dorsal lumbar	Laminectomy w / cyst fenestration & radical cyst wall resection, plus syrinx-subarachnoid shunting	17	No cyst recurrences during the FU period. Symptoms of weakness (100%), hyperreflexia (91%), & incontinence (80%) were more likely to improve than neuropathic pain (44%) & numbness (33%).
Bassiouni et al., 2004 [19]	12	43.6	52%	Pain (50%), myelopathy (62%)	MRI & CTM in 11 cases	12 dorsal thoracic	Laminectomy/laminoplasty w/ total excision of cysts <5 levels, otherwise generous fenestration	38.4	Follow-up MRI: no recurrence of the cyst was observed in any patient.
Netra R et al., 2011 [23]	18	34.6	22.2%	Post-traumatic back pain (10%)	MRI only	7 dorsal thoracic (one of them post traumatic patient), 8 dorsal thoraco lumbar, 3 dorsal lumbar	Unspecified	Unspecified	Unspecified
Funao et al., 2012 [18]	12	39.7	42%	Pain (42%), weakness (33%), gait ataxia (58%), paresthesia (67%), sphincter (50%)	CTM & cine MRI	12 dorsal thoraco lumbar	Laminectomy w/ total resection (58%), closure of dural defect w/o cyst, resection (42%)	56	No recurrence of the SEAC during the FU period. Improvement in the mJOA score.
Bond et., 2012 [22]	11	9.6	54.5%	Back pain (27%), loss of BLE function (36%), loss of sensation (18%), gait instability (27%), limited hip flexion (9%), incidental MRI finding (%9)	MRI only	3 dorsal thoracic, 4 dorsal thoraco lumbar, 1 dorsal lumbo sacral, 3 dorsal sacral	Total resection (100%)	19.1	No recurrence of the SEAC during the FU period
Kong et al., 2013 [14]	1	65	0%	Progressive paraparesis from 15 years following trauma, mild motor weakness of bilateral legs, urinary incontinence, muscle atrophy of both lower extremities	MRI only	Dorsal thoraco Lumbar	Laminectomy+ total resection	5	No recurrence of the SEAC during the FU period
Tokmak et al., 2015 [29]	10	50	60%	Hypoesthesia (20%), back pain (70%), post-traumatic back pain (10%), paraparesis (40%), radicular pain (20%), monoparesis (10%)	MRI only	7 dorsal thoracic, 1ventral thoracic, 2 dorsal thoraco lumbar (one of them post traumatic patient)	Hemilaminectomy/ total resection (30%), Laminectomy/ total resection (20%), Laminoplasty/ total resection (40%)	26.2	Follow-up MRI: no recurrence of the cyst was observed in any patient, incomplete recovery (20%)
Garg et al., 2016 [21]	9	29.7	22%	Weakness and sensory loss (44%), Urinary incontinence (33%), backache (55%), weakness and pain (33%)	MRI only	3 dorsal thoracic, 1 ventral thoracic, 3 dorsal thoraco lumbar, 1 ventral lumbo sacral, 1 ventral cervico lomber	Excision (88%), marsupialization (11%)	19.5	Follow-up MRI: no recurrence of the cyst was observed in any patient.
Viswanathan et al., 2017 [25]	14	52.1	36%	Weakness (79%), gait ataxia (100%), paresthesia (86%), sphincter (28.6%), myelopathy 71.4%	MRI only	12 dorsal thoracic, 1 dorsal cervico thoracic, 1 dorsal thoraco lumbar	Cyst wall fenestration & partial resection	22	Median improvement in mJOA score of 2.0 (1.3E3.0) (P<0.001) w/ respect to the preop scores.
French et al., 2017 [15]	10	60	66%	Pain (10%), gait ataxia (90%), paresthesia (60%), sphincter (20%)	MRI & cinemode bSSFP MRI in 3 pts	Unspecified	Fenestration (60%), complete excision (40%)	4.4	Follow-up MRI & subjective symptom assessment.
Fam et al., 2018 [20]	16	57	75%	Pain (63%), falls (31%), paresthesia (6%), weakness (44%), gait ataxia (50%)	MRI & CTM in 5 pts	10 dorsal thoracic, 2 ventral thoracic, 1 dorsal cervical, 1 ventral cervical, 1 dorsal lumbar, 1 ventral lumbar	Total cyst excision (79%), fenestration/marsupialization only (14%), fenestration & ligation (8%)	8.2	Improvement in SF-36 parameters across all quality-of-life parameters.
Singh et al., 2019 [24]	10	27.4	50%	Radiculopathy (60%)	MRI only	10 dorsal	Total cyst excision (80%), partial cyst excision (20%)	65.1	No one of the patients had clinical deterioration or radiological recurrence till last follow-up.
Our case	1	17	0%	Post traumatic back pain	MRI only	Dorsal thoraco lumbar	Laminectomy/ total cyst excision	12	Follow-up MRI: no recurrence of the cyst was observed in patient.

Pts: patients, FU: Follow-up

Discussion

Terminology and classification

Spinal arachnoid cysts were first identified by Schlesinger in 1893 and were first published by

Spiller et al. in 1903 [8]. In the literature, the terms "arachnoid diverticulum", "leptomeningeal cyst", "localized adhesive arachnoiditis", and "serous spinal meningitis" have been used by various authors to define SAC based on different pathological components [9]. Nabors classifies extradural spinal arachnoid cysts as type IA spinal meningeal cysts [10]. Dorsal cysts are more common than ventral cysts. The cyst localization was 120 dorsal and 14 ventral in the 134 patients presented in the literature (Table 1). Our case was also located dorsally, which is compatible with the literature.

Pathogenesis

Various theories have been proposed that claim that the formation mechanism of spinal arachnoid cysts is multifocal. Elsberg et al., who presented the first theory, suggested that spinal arachnoid cysts develop after arachnoid membrane herniation from a congenital diverticulum or congenital dural defect. Neural tube defects further support this theory, and a familial disposition has been noted in some patients.

According to certain theories, the reasons stated in most cases lead to a defect in the meninges membranes, which results in the herniation of the arachnoid membrane [11]. It is thought that if the cysts are associated with the subarachnoid space, they expand with the "valve-like" mechanism, and if not, they expand with H_2O osmosis from the cyst wall or active fluid secretion from the epithelial cells lining the cyst and eventually become symptomatic [9,11]. Most cases of spinal arachnoid cysts are idiopathic, but those of traumatic origin are particularly rare.

Regardless of the etiology, the underlying pathology results from herniation of the arachnoid through a defective or fragile dura mater. In traumatic cases, the defect is frequently found on the dorsal plane of the dura. When the literature was reviewed, we found that only four of the 144 cases presented had a history of trauma (Table 1). In these four cases of extradural arachnoid cysts that developed after trauma, the cyst localization was on the dorsal surface.

The fact that our case was a professional football player made us think of chronic trauma exposure, and the patient was evaluated as having a case of a post-traumatic arachnoid cyst. Additionally, consistent with the literature, the cyst location was on the dorsal surface.

Localization

It has been reported that cystic lesions are mostly in the thoracic regions (69–80%), followed by the cervical region (15–20%) and lumbar region (5–7%) [12]. Most patients with spinal arachnoid cysts of congenital origin present clinically in adolescence or early adulthood, and diverticula tend to be located in central regions. Cysts that extend along several vertebral segments and connect with the subarachnoid space via a small space are often located in the thoracic region [1,6]. Our case was also a young man, consistent with the literature. The lesion was in the form of a thoracic arachnoid cyst connected to the subarachnoid space in several areas.

Clinical presentation

In the pediatric age group, symptomatic spinal arachnoid cysts are rare lesions. Cysts that appear are frequently seen together with neural tube defects, such as meningomyelocele and diastometomyelia [13]. The mean age in the literature is 41.3 years (Table 1). Kong et al. [14] presented a case of a dorsal thoracolumbar spinal extradural arachnoid cyst that developed after a trauma at 65 years old, which is the most advanced age case in the literature. It is frequently seen in the middle and lower thoracic region and men. The literature shows an average of 59.2% male dominance (Table 1). Consistent with the literature, our case was a 17-year-old male patient. Although spinal arachnoid cysts are often asymptomatic, symptomatic cases present with slowly developing myelopathy findings [6]. The most common findings, according to research, are pain and myelopathic symptoms. Other common findings are radiculopathy, weakness, ataxia, and urinary incontinence. Post-traumatic back and low back pain is the most common symptom in patients with a history of trauma (Table 1). French et al. reported the incidence of pain as 10% in a study of 11 patients, which is contrary to the literature [15]. Kong et al. [14] presented a case with progressive paraparesis that developed after trauma from 15 years ago in addition to back pain. The only symptom seen in other post-traumatic cases presented in the literature, including our case, is back pain.

Imaging findings

As seen in most series, spinal extradural arachnoid cysts are more common than intradural cysts [16]. In the diagnosis, myelography, post-contrast computed tomography (CT), and MRI, a non-invasive and effective method, provide sufficient information about the lesion's width, volume, and structure [17]. MRI shows characteristic CSF-like density in both T1WI and T2WI (Figure 2). Additionally, it may highlight surrounding bone changes and the association of the cord or cauda with spinal extradural arachnoid cysts. The signal within the cyst may appear hyperintense compared with the CSF in the spinal canal due to the higher protein content of the cyst fluid. Contrast series is recommended to see if there is healing in the cyst wall. With the progress in MRI series, the size, number, and even the exact level of the dural defect can now be determined. Other rare features to look for in MRI include the absence of extradural fat, cord atrophy, and myelomalacia. Other imaging methods used in diagnosis include myelography, CT myelography, and cinematic MRI [15,18-20]. These imaging methods can show the location of the communication zone between the dura and the cyst cavity. Parasitic cysts, including cysticercosis or echinococcal cyst, should be included in the differential diagnosis, especially in patients from Anatolia.

Spinal extradural arachnoid cysts are often located in the thoracic area. In the literature, Wang et al. [6] reported 17 extradural and four intradural cyst cases in their series of 21 patients. In the series of Fam et al. [20], 12 of 16 patients had extradural cysts, and only four had intradural cysts. However, the same situation may not be true in children, as seen in several pediatric patients with intradural cysts in 58% of patients [21]. The authors suggest that this may be due to the high incidence of associated congenital central nervous system malformation in children in their series, known to be associated with intradural cysts [22]. In the reviewed articles, none of the patients had

intramedullary cysts described in the literature, albeit rare. In our case, thoracic MRI was used because it is a non-invasive method to define the lesion, and a dorsal cystic lesion with an isointense mass effect without contrast enhancement was detected.

The thoracic region is the most common site of spinal extradural arachnoid cysts [6,19,20,23-25]. In our case, similar findings were observed with thoracolumbar involvement. This could be because the dorsal column is the longest segment and/or because arachnoid cysts in the spinal extradural of the dorsal region are almost always symptomatic due to the narrow dorsal spinal canal.

Treatment and outcomes

There is no standard treatment protocol for the management of spinal arachnoid cysts. The usual practice is the excision of the cyst with the closure of the dural defect in extradural cysts, especially in symptomatic cases. Fenestration of the cyst is usually performed in intradural cysts, particularly ventral to the cord. Other surgical treatments include shunting the cyst to the peritoneum, pleural space, and right atrium with wide fenestration. Patients who undergo surgery before experiencing neurological symptoms have a better postoperative prognosis [1]. Wang et al. [6] recommend total cyst excision for spinal intradural arachnoid cysts. Simple cyst aspiration is not recommended because it does not meet adequate treatment. Despite a dural defect, some surgeons have also performed partial excision of the cyst wall. Hatashita et al. [26] stated that if the cyst is excised, it is not important whether there is a dural defect or not. This conclusion is based on cases when the dural defect area is sometimes not found or where there is no CSF accumulation if the entire cyst is removed without closure of the dural defect.

The large laminectomy required for complete cyst wall excision can cause complications, such as kyphosis and instability. To prevent these complications, laminoplasty is increasingly recommended instead of total laminectomy. In addition, another approach aims to limit the required laminectomy distance by closing only the dural connection instead of excision of the entire cyst wall [18,27,28]. To limit the size of laminectomy to maximum levels, Endo et al. advocate using endoscopes in spinal extradural arachnoid cyst management [28]. After partial hemilaminectomy/laminectomy, an endoscope is inserted into the cyst cavity after partial resection of the cyst wall through the bony window and moved cranially and caudally for fenestration of the cyst wall. Thus, communication of the cyst cavity with the subarachnoid space is ensured. It was observed that cyst recurrence rates were not higher in patients who underwent partial cyst excision after partial laminectomy and endoscope use than in patients who underwent radical laminectomy and complete cyst excision. However, kyphotic changes were observed in the spine in two patients in the total laminectomy group, while kyphosis did not develop in any patient in the partial laminectomy group, but this was not statistically significant.

A limitation of the study was that the mean follow-up time in the limited laminectomy group was significantly lower than the other group. Neurological improvement in these patients was the same as in patients with complete excision of the cyst without recurrence at a mean follow-up of 4.7 years. However, the degree of postoperative kyphosis in patients where only the dural connection is closed was significantly less than in patients who underwent a wide laminectomy to completely excise the cyst wall.

To prevent total cyst excision and possible kyphotic deformity, we applied T11-L2 laminoplasty on our patient, who had no other active complaints other than chronic back pain, and whose neurological examination was normal. No new complaints or radiological findings were detected in the follow-up of the patient, who was discharged without any postoperative neurological deficit or additional complaints.

Conclusion

The etiology, pathogenesis, and treatment of spinal extradural arachnoid cysts are not well defined. Neurological recovery appears to depend on the size of the cyst and the degree and duration of spinal cord compression. They are benign cysts that can show complete improvement in neurological findings when diagnosed with necessary radiological examinations and treated with early appropriate surgical methods before compression findings occur. Although early surgery is satisfactory, the rate of neurologic recovery decreases as the duration increases.

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Case report

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A rare cause of acute abdomen: Ovarian torsion due to dermoid cyst

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Abstract

Dermoid cysts are one of the most common causes of ovarian torsion. The causes of acute abdominal pain are mostly caused by the diagnosis of acute appendicitis, acute pancreatitis, and mesenteric ischemia, and the incidence of ovarian torsion is not known exactly. Although ovarian torsion is very rare, it ranks first among the indications for gynecological emergency surgery. A rare case of a non-ruptured dermoid cyst causing ovarian torsion in the emergency room is presented.

Keywords: dermoid cyst, ovarian torsion, acute abdomen

Introduction

Dermoid cysts are mostly seen in the reproductive period and unilaterally [1]. Dermoid cysts are one of the most common causes of ovarian torsion [2]. The causes of acute abdominal pain are mostly caused by the diagnosis of acute appendicitis, acute pancreatitis, and mesenteric ischemia, and the incidence of ovarian torsion is not known exactly [3,4]. In our case report, we aimed to report the association between non-ruptured dermoid cysts and ovarian torsion, which we rarely encounter in the emergency department.

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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.

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Case presentation

A 26-year-old female patient applied to the emergency department with a complaint of abdominal pain that had persisted for 2 h. The general condition of the patient was moderate, cooperative, and oriented, and vital signs were within normal limits. In the physical examination of the patient, who had no known chronic disease, there was widespread tenderness in the abdomen and signs of defense. There were no complaints of diarrhea or constipation. Laboratory tests results were as follows; white blood cells: 9.56 K/µL, hemoglobin: 13 g/dl, platelet: 177 K/µL, lymphocyte: 0.74 K/µL, glucose: 108 mg/dl, urea: 19.7 mg/dl, creatinine: 0.7 mg/dl, CRP: 0.8mg/dl. Aspartate aminotransferase, alanine aminotransferase, and serum electrolytes were within normal limits. No major pathology was observed in the complete urinalysis. In the abdominal ultrasonography image, 1 cm of fluid was observed in the abdomen, a dermoid cyst of 4 cm in diameter with hyperechoic areas in the right ovary was detected, and it was observed that there was no blood flow in the right ovary. Abdominal computed tomography revealed a 55 mm diameter hypodense lesion with calcification and fat densities in the posterior of the uterus (Figures 1 and 2). There was minimal free fluid in the pelvic region. The patient, who consulted with the obstetrics and gynecology department, was operated on at the 6th hour of her application. It was found that the right ovary was torsioned, and the ovaries and tubes were edematous. The ovary was detorsioned with the tuba, and blood supply to the right ovary was restored. The cystic structure was removed and evaluated as a dermoid cyst in the pathological assessment. The patient was discharged after being followed up in the hospital service for 2 d. There were no complications or recurrences during the outpatient clinic follow-ups. The consent of the patient was obtained for the case report.

Figure 1: Coronal CT image of dermoid cyst (arrow)

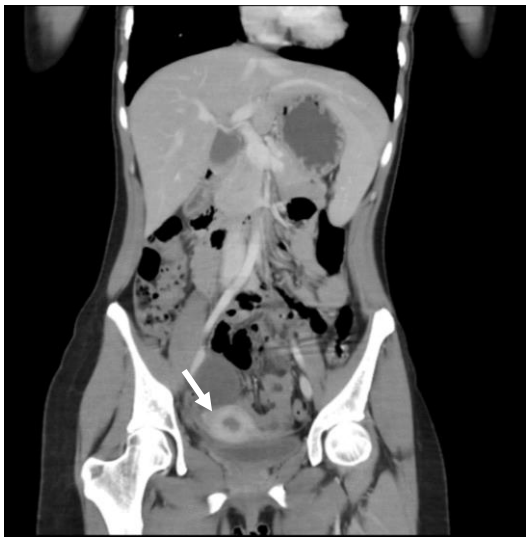
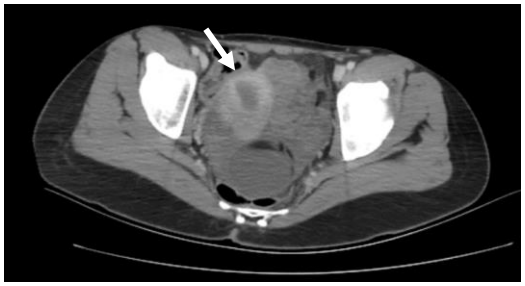


Figure 2: Axial CT image of dermoid cyst (arrow)



Discussion

Although ovarian torsion is very rare, it ranks first among the indications for gynecological emergency surgery. Half of the patients present with sudden onset of pelvic pain and accompanying nausea and vomiting symptoms, and the definitive treatment is laparoscopy or laparotomy [4,5]. In our case report, diffuse abdominal pain was present and widespread defense was detected on physical examination. No pathological changes were found in inflammatory parameters in laboratory examinations. Because of the absence of gastroenteritis-like clinical findings, an ultrasound examination was requested. There were no complications or recurrences during the outpatient clinic follow-ups. In a study, the risk of torsion was found to be 1–2% higher in pregnant women with dermoid cysts of 4 cm or more [6]. Our patient had a cyst of approximately 4 cm in diameter and was not pregnant. Despite this, it was observed that there were three rounds of torsion in laparoscopy.

The rarity of dermoid cysts and the rare occurrence of ovarian torsion as a complication have led to studies in the literature in which all ovarian pathologies are present. In a study in which 223 cases were examined in five years, dermoid cysts were evaluated as the most common ovarian pathology, and dermoid cysts were observed to be the most common ovarian pathology causing ovarian torsion [7].

Different reports have identified cases of torsion due to dermoid cysts in the fetus or in the premenarchal period [8, 9]. Although our case was of reproductive age and complained of abdominal pain, the operation of the teratoma immediately after torsion develops is a situation that needs special attention in services where the number of patients is high, such as the emergency department.

Although ovarian torsion takes the first place among the indications for gynecological emergency surgery, the period that will pose a risk for the development of ischemia is not yet known exactly. While this period may be extended up to 36 h in pediatric patients, it has been reported that adult patients who are operated on after more than 24 h will not be successful [10]. It has also been reported in various studies that a mean time of 16 h or 15 h may be sufficient [11,12]. Our patient was operated on within 6 h in accordance with the literature and was discharged after 2 d of follow-up.

Conclusion

Ovarian torsion is a clinical condition that should be considered because it is rare and can present with nonspecific clinical findings. Especially patients with acute abdomen should be followed carefully, and diagnosed cases of ovarian torsion should be operated on as soon as possible. Although a dermoid cyst is a rare cause of acute abdomen, it requires urgent surgery. Delays in diagnosis can lead to serious complications and poor prognosis.

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