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Comparison of the Effects of Thoracic Epidural Analgesia in Different Levels on Intraoperative Hemodynamics in Abdominal Surgery: A Prospective Randomized Trial

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Abstract: Our aim was to investigate the effect of thoracic epidural anesthesia (TEA) at different levels on hemodynamic parameters in elderly patients undergoing upper abdominal surgery. This randomized study was conducted on 60 patients aged 65 or above undergoing upper abdominal surgery. The patients were randomized into T6-7 and T9-10 groups, with epidural catheters placed at respective intervertebral spaces. Heart rate, systolic and diastolic blood pressure, mean arterial pressure, were recorded every 5 minutes for 30 minutes after TEA and every 10 minutes intraoperatively. Confirming adequate analgesia and 30 minutes after placement of a thoracic epidural catheter, general anesthesia was induced. Postoperative respiratory function tests, time to ambulation, gastrointestinal motility and length of stay were assessed. Systolic blood pressure (SBP) was statistically lower at minutes 5,80, and 90 in group T9-10 ($p=0.003$, $p=0.007$, $p=0.013$ respectively). At the same minutes, diastolic blood pressure (DBP) ($p<0.001$) and mean arterial pressure (MAP) ($p=0.009$, $p<0.001$ and $p<0.001$, respectively) significantly lower in group T9-10. A difference was observed for heart rate at minutes 10, 60, 80, and 90 ($p<0.001$, $p=0.005$, $p=0.003$ and $p<0.001$, respectively). Groups were different for highest and lowest dermatome with block, return of gastrointestinal motility, and length of stay. ($p=0.003$, $p=0.023$, $p=0.003$, $p=0.009$, respectively). Higher TEA provides more stable hemodynamics, respiratory functions, gastrointestinal motility and shorter length of stay compared to lower TEA. Therefore, we recommend high TEA in upper abdominal surgery. ©2024 NTMS.
Keywords: Upper abdominal surgery; thoracic epidural anesthesia; hemodynamics.

1. Introduction

General anesthesia (GA) and thoracic epidural analgesia (TEA) combination is one of the commonly used anesthesia methods in upper abdominal surgeries [1]. In these patients is provided by thoracic epidural analgesia gold standard for pain relief [2].
Elderly patients should use less drug dosage for

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thoracic epidural analgesia because more segments are blocked in the elderly compared to younger patients with the same drug dose. This is one of the reasons for increased hemodynamic instability in elderly patients [3]. Epidural local anesthetic administration creates autonomic denervation and thus causes vasodilation in the vessels [4]. The reduced cardiac reserve in the elderly, as well as structural alteration in the autonomic nervous system and the arterioles, may contribute to the impaired cardiovascular response to TEA [5].

There are studies evaluating various parameters such as cardiac index, stroke volume index, central venous pressure, and central venous oxygen saturation in high TEA [6]. There are studies in the literature of different levels of epidural analgesia in pigs. However, this study compared lumbar and thoracic epidural analgesia [7]. Different levels of thoracic epidural analgesia are performed in upper abdominal surgery. We noticed that there are not enough studies in the literature on thoracic epidural level selection. For this reason, we wanted to investigate the various effects of different levels of thoracic epidural analgesia.

The aim of this study was to investigate the effect of epidural analgesia at different levels on hemodynamic parameters in elderly patients undergoing upper abdominal surgery. The change in systolic blood pressure between the two groups in the intraoperative period was the primary outcome in this study. Secondary aim was to evaluate the extent of spinal segments blocked, respiratory parameters, time to discharge, and gastrointestinal motility with respect to the level of TEA.

2. Material and Methods

This randomized prospective study was performed on 60 patients aged 65 and above, with American Society of Anaesthesiologists (ASA) scores of I, II, and III, undergoing upper abdominal surgery. Approval of in this study was from the local ethics committe. All participants provided written informed consent.

2.1. Patients

Patients with a history of hypersensitivity or allergy to amide-type local anesthetics, vertebral surgery, cervical or thoracic vertebra arthritis, contraindication of epidural anesthesia (local infection at the site of epidural puncture, nervous system diseases, bleeding diathesis, use of an antiplatelet or anticoagulant agent etc.), uncontrolled hypertension. severe cardiac, respiratory, hepatic, or renal disease, diabetes mellitus, pregnant women, difficulty with communication epidural catheter couldn't be inserted, inadequate epidural analgesia, dural puncture, patients unable to decide or unwilling to participate in the study, weight above 110kg, and height below 150 cm, were excluded. Patients were separated into Group $T_{6\text{-}7}$ and Group $T_{9\text{-}10}$ according to a computer-generated randomization list. 30 patients were assigned to each group.

2.2. Premedication and Anesthesia

The patients were monitored using the ASA standart protocol. All patients were premedicated with 0.05 mg/kg of midazolam and were given 2 L/min of oxygen via a face mask during epidural catheterization. 18 or 20 gauge intravenous (iv) catheters were placed on left and right arms for fluid and drug administration. 10 ml/kg of colloid infusion was initiated prior to catheterization for to prevent hypotension.

Epidural catheters were placed in the T6-7 and T9-10 intervertebral spaces. For this, midline approach and loss of resistance technique were used in sitting position in each group. Intravertebral spaces were examined with palpation to locate T_7 from where target intervertebral spaces were counted up or down. The skin was sterilized and draped in accordance with asepsis-antisepsis principals. Following skin infiltration with %1 lidocaine, an 18-gauge Tuohy epidural needle was progressed with the open bevel facing the cranial direction and a 20-gauge epidural catheter was progressed in cranial direction with 4 cm remaining in the epidural space.

A test dose of 1:200000 epinephrine and 2 ml of 1.5% lidocaine was administered, confirming no drug delivered into intrathecal or intravascular spaces. 10 ml of a solution of 0.1% of bupivacaine + 2.5 μg/kg fentanyl (4cc %0.5 Bupivacaine, 50 mcg Fentanyl, 15cc saline) was given in 1 ml doses every 10 seconds. Sensorial block was assessed by pinprick or cold/hot differentiation test. Analgesia was defined as loss of sensation of a pinprick or the cold of ice.

Lower extremity motor block was evaluated with the Bromage scale (0= no block, 1=able to move ankle and knees, no hip movement 2=able to move only ankle, no movement in hips or knees, 3= complete block). Upper extremity motor block was evaluated with finger grip movement (C_8/T_1), wrist (C_8/C_7) and elbow flexion (C_6/C_5) (ESSAM score 0= all three movements normal, 1= no finger grip but can perform other movements, 2= only elbow flexion elbow, 3=no movement).

Evaluations were repeated every 5 minutes after the first 30 minutes following TEA. Sensory block of T_6T_7 dermatomes was adequate for induction of surgical analgesia. Analgesia at these dermatomes was evaluated every minute until sensory block was established. The above-mentioned solution was given in 5ml aliquots every 5 minutes until block was achieved in these dermatomes.

ESSAM and Bromage scores, extent of the sensory block were recorded.

2.3. Hemodynamic Parameters

Mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, and SPO_2 were recorded before TEA. These recordings were repeated every 5 minutes after 30 minutes of TEA and every 10 minutes after sedation.

5 mg of iv ephedrine was given if a drop of more than

30% in SBP was observed or if SBP was < 90 mmHg. 1 mg of iv atropine was given if heart rate was<55 bpm. Following adequate block and 30 minutes after placement of a thoracic epidural catheter, anesthesia was induced with 0.3 mg/kg etomidate, 0.6 mg/kg rocuronium bromide and 2 μg/kg fentanyl. Anesthesia was maintained with %6 desflurane, %50 oxygen of dry air and 5 ml of the above-mentioned solution. All patients underwent pulmonary function tests with a hand spirometer 30 minutes before surgery (T_0) and at postoperative 6th (T1) and 24th hours (T2) in a sitting position. The pulmonary function tests (Forced vital capacity (FVC), expiratory volume at 1 second (FEV1), forced and FEV1 / FVC (FEV1 %)) were recorded. Testing was concluded in case of patient exhaustion, unwillingness to continue the test or unsuccessful testing after 8 attempts. Postoperative analgesia was achieved with a 15 cc solution with 3 mg of morphine, 50 mcg of fentanyl, and 11 cc of saline. Any postoperative complications of nausea, vomiting, or itching were recorded, as well as time to ambulation, recovery of gastrointestinal motility, and length of hospital stay.

2.4. Statistical Analysis

Sample size was calculated by G -* power that 29 patients should be included in the study at 80% power and 95% confidence interval in order to find a significant 15% decrease in systolic blood pressure between the two groups.

Statistical analysis was carried out with IBM SPSS version 20 software. Descriptive statistics with mean, median, standard deviation, minimum-maximum, number, and percentages were presented. Normal distribution of continuous variables was tested with the Shapiro-Wilk test. Comparison of two independent groups was carried out with independent samples t-test for normal distributions and Mann Whitney U test otherwise. For 2x2 categorical variables with expected values > 5 Pearson Chi-squared, with expected values 3-5 Chi-squared with Yates correction, and with expected values <3 Fisher's Exact test was applied. P values <0.05 were accepted as statistically significant.

3. Results

In total, 60 patients were included into the study (30 parturients in each group) (Figure 1).Demographic and operative data of patients and their ASA scores are presented in Table 1. The two groups were not statistically different for their demographic and operative properties. (p>0.05). Distribution of patients by type of operation is shown in Table 2.

Table 1: Demographic and operative data of patients.

	Group T6-7 (n=30)	Group T9-10 (n=30)	p
Age	69±4	68±3	0.817
Weight (kg)	71±11	70±10	0.763
Height (cm)	164±8	166±5	0.510
Gender (M/F)	16/14	15/15	0.796
BMI	25.68±3.33	25.28±4.37	0.273
ASA Score (I/II)	10/20	12/18	0.592
Operative Time (min)	175±39	199±48	0.140

All values are presented as mean ± standard deviation (SD) or numerical values. M:Male, F:Female, ASA: American Society of Anesthesiologists, BMI: Body Mass Index p>0.05.

Table 2: Distribution of patients by operation type.

	Group T6-7 (n=30)	Group T9-10 (n=30)		p
Stomach Cancer (n)	13	11	0.167	0.683
Cholecystectomy(n)	8	10	0.222	0.637
Choledocolithiasis(n)	2	3	0.200	0.655
Liver Hydatid Disease (n)	3	2	0.200	0.655
Liver Mass (n)	2	1	0.333	0.564
Cholangiocellular Canser (n)	1	1	0.000	1.000
Operative time (min)	1	2	0.333	0.564

All values are numerical values p>0.05.

Table 3: Highest and lowest dermatome level of analgesia and number of segments with block, and time to recovery of bowel sounds, time to ambulation and length of hospital stay.

	Group T6-7 (n=30)	Group T9-10 (n=30)	P
Highest dermatomal level with analgesia	T3 (T1-T5)	T4 (T1-T5)	0.033*
Lowest dermatomal level with analgesia	T12 (T9-L1)	L1 (T10-L2)	0.023*
Number of segments with block	9±3	9±2	0.517
Time to recovery of bowel sounds (h)	25.00 (12.00-62.00)	36.00 (23.00-96.00)	0.003*
Time to ambulation (h)	20.00 (8.00-48.00)	23.00 (11.00-48.00)	0.480
Length of hospital stay (days)	14.50 (14.50-27.00)	16.00 (5.00-39.00)	0.009*

All values are presented as mean±standard deviation (SD) or numerical values. *p<0.05 between T6-7 and T9- 10 groups.

Table 4: Respiratory Function Test results at different measurement times.

		Group T6-7 (n=30)	Group T9-10 (n=30)	p
FVC (L)	T0	2.30 (1.77-3.39)	2.15 (1.15-4.09)	0.515
	T1	1.36 (0.91-2.33)	1.25 (0.25-2.32)	0.028*
	T2	1.72 (1.32-3.26)	1.72 (0.97-2.92)	0.066
FEV_1(L)	T0	2.01(1.46-3.01)	1.81(1.06-3.67)	0.314
	T1	1.01(0.63-1.50)	1.04(0.20-1.38)	0.280
	T2	1.49 (0.93-2.25)	1.38 (0.62-2.41)	0.006*
FEV_1/FVC(%)	T0	88.50 (75.00-97.00)	87.00 (71.00-92.00)	0.312
	T1	77.00 (40.00-79.00)	79 (65.00-99.00)	0.004*
	T2	82.00 (70.00-98.00)	80.00 (63.00-85.00)	0.002*

All values are presented as median (min-max). T_0; Preoperative base value, T_1;Postoperative 6 hours T_2; Postoperative 24 hours. FVC: Forced Vital Capacity. FEV_1: Forced expiratory volume at 1 second. FEV_1/FVC(%): FEV percentage at 1 second *p<0.05 between T6-7 and T9-10 groups.

3.1 Hemodynamic findings

SBP, DBP, MAP, and heart rate of patients across time are graphed in Figures 2, 3, 4, and 5. SBP at 5th, 80th, and 90th minutes showed statistically significantly higer for T6-7 group compared T9-10 group (p=0.003, p=0.007, and p=0.013, respectively). At the same minute, DBP and MAP were statistically significantly higer in the T6-T7 group (p<0.001, p<0.001, p<0.001 and p=0.009, p<0.001, p<0.001, respectively) Heart rate was statistically significantly lower at 10th minutes (p<0.001) and statistically significantly higer at 60th, 80th, and 90th minutes (p<0.001, p=0.005, p=0.003, p<0.001 respectively) for T6-7 group than T9-10 group. No significant difference was detected for hemodynamic variables at other measurement points.

3.2. Dermatomal Spread

Highest and lowest dermatome levels and the number of segments with block are presented in Table 3. The groups did not differ in terms of the number of segments with block. (p>0.05). However, the groups differed significantly for highest and lowest dermatome levels with analgesia. (p=0.003 and p=0.023, respectively).

Table 5: ESSAM and BROMAGE scores of groups.

	Scores	Group T6-7 (n=30)	Group T9-10 (n=30)
ESSAM Score	0	30 (%100)	30 (%100)
	1	0(% 0)	0(% 0)
	2	0(% 0)	0(% 0)
	3	0(% 0)	0(% 0)
BROMAGE Score	0	30 (%100)	30 (%100)
	1	0(% 0)	0(% 0)
	2	0(% 0)	0(% 0)

Table 6: Nausea, Vomiting, and Itching in Study Groups.

		Group T6-7 (n=30)	Group T9-10 (n=30)	p
Nausea	Yes	18 (60.0%)	9 (30.0%)	0.020*
	No	12 (40.0%)	21 (70.0%)	
Vomiting	Yes	31 (0.0%)	9 (30.0%)	0.053
	No	27 (90.0%)	21 (70.0%)	
Itching	Yes	0 (0.0%)	4 (13.3%)	0.161
	No	30 (100.0%)	26 (86.7%)	

All values are presented as number and percentage. * p<0.05 significant between groups.

3.3. Time to Recovery of Gastrointestinal Motility, Time to Ambulation, and Length of Hospital Stay

Comparison of groups for time to recovery of bowel sounds, time to ambulation and length of hospital stay is given in Table 3. No statistically significant difference was observed for time to ambulation, (p>0.05) while time to recovery of gastrointestinal motility and length of hospital stay were statistically significantly shorter in the T6-7 group than other group (p=0.003 and p=0.009, respectively).

3.4. Pulmonary Function Test Results

Results of pulmonary function tests across groups are shown in Table 4. FVC did not differ between groups at T0 and T2 (p>0.05) while was statistically significantly higer for T6-7 group than T9-10 group at T1 (p=0.028). FEV1 did not differ between groups at T0 and T1 (p>0.05), while was statistically significantly higer at T2 in the T6-7 group (p=0.006). FEV1/FVC did not differ between groups at T0 (p>0.05) while was statistically significantly lower at T1 and statistically significantly higer at T2 in the T6-7 group than T9-10 group (p=0.004 and p=0.002, respectively).

3.5. ESSAM and BROMAGE Scores

ESSAM and BROMAGE scores of cases are summarized in Table 5. No motor block developed in either of the groups.

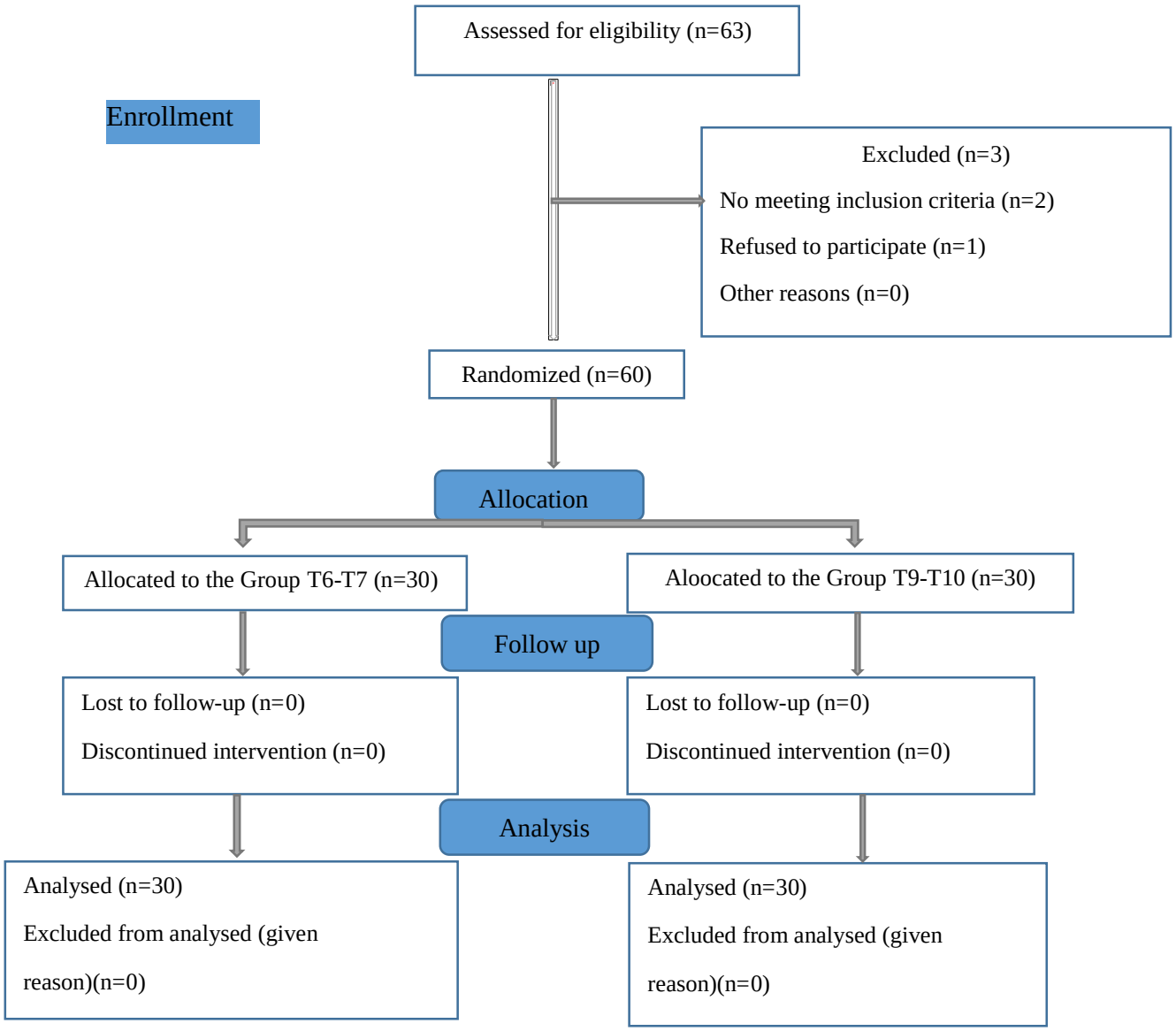

Figure 1: CONSORT flow diagram.

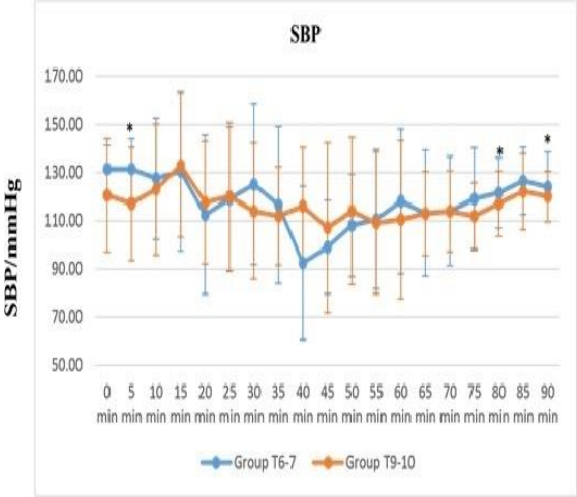

Figure 2: Change in systolic blood pressure across measurement times.
All values are presented as mean±standard deviation (SD) or numerical values. *p<0.05 between T6-7 and T9-10 group SBP: systolic blood pressure, min: minutes.

3.6. Nausea, Vomiting, and Itching

Cases with nausea, vomiting, and itching are presented in Table 6. While there was no statistically significant difference for vomiting and itching (p>0.05), there was statistically significantly difference for nausea between the two groups (p=0.02).

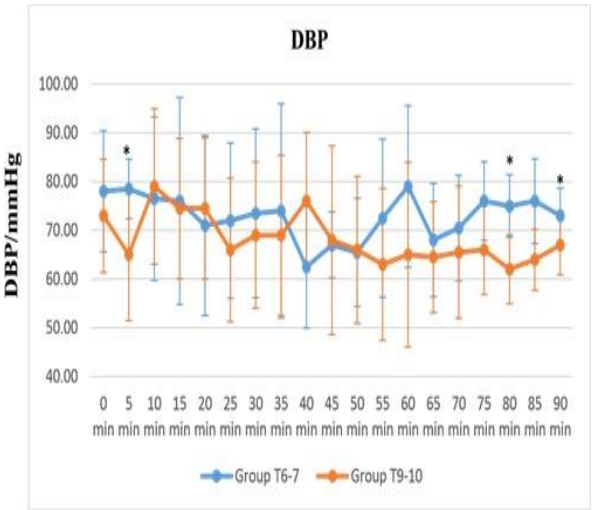

Figure 3: Change in diastolic blood pressure across measurement times.
All values are presented as mean±standard deviation (SD) or numerical values. *p<0.05 between T6-7 and T9-10 groups. DBP: diastolic blood pressure, min: minutes.

3.7. Atropine and Ephedrine Requirement

The groups did not differ in atropine or ephedrine requirement (p>0.05). 3 cases needed atropine and 7 needed ephedrine in Group T6-7 while no patients required atropine and 3 required ephedrine in Group T9-10.

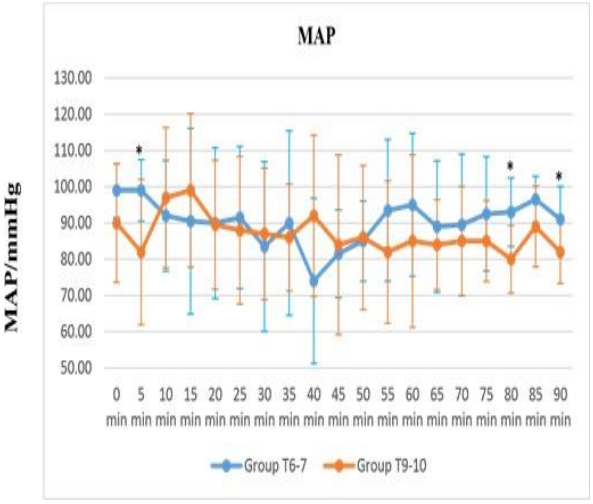

Figure 4: Change in mean arterial pressure across measurement times.
All values are presented as mean±standard deviation (SD) or numerical values**.** *p<0.05 between T6-7 and T9-10 groups, MAP; mean arterial pressure, min: minutes

Figure 5: Change in heart rate across measurement times.
All values are presented as mean ± standard deviation (SD) or numerical values. *p<0.05 between T6-7 and T9-10 groups. HR: heart rate, min: minutes.

4. Discussion

Our study demonstrated that TEA at a higher level resulted in a more stable hemodynamic response compared to lower level TEA. While higher level TEA resulted in a more profound drop in heart rate, it was associated with fewer cases of hypotension.

A study on patients aged 60 or above undergoing coronary artery bypass surgery compared a group receiving high thoracic epidural anesthesia (HTEA) at T_2-T_4 level with a group that did not receive TEA. Cardiac index, stroke volume index, central venous pressure, and central venous oxygen saturation were higher in the HTEA group. The authors also observed a lower MAP in the HTEA group with no difference in

heart rate. They concluded that HTEA positively affects cardiac performance in the elderly [6].

A study on 18 pigs compared epidural catheters at $L_{3/4}$ and $L_{4/5}$ levels. Catheters were proceeded to L_2 and T_2 under radioscopic guidance. Bupivacaine was administered for TEA and heart rate, MAP, SVR, right and left ventricular contractility were recorded. In the pigs with block at T_2, heart rate significantly dropped, with a minimal decrease in MAP and left ventricular contractility. In the pigs with block at L_2, MAP and SVR dropped significantly with a prominent rise in heart rate [7].

In our study, heart rate in the T_{6-7} group was significantly lower than in the T_{9-10} group at the 10th minute. In the first 15 minutes, heart rate was lower in the T_{6-7} group albeit insignificantly. We believe this decrease in heart rate is due to the increased block of cardiac sympathetic fibers at T_1-T_5 levels in the T_{6-7} group. The prominent decrease in SBP, DBP, and MAP in the T_{9-10} group can be explained by an increased block of sympathetic vasomotor fibers between T_5-L_1 levels. The level of sympathetic blockade is related to the area of drug distribution in the epidural space. We did not find a significant difference between groups in terms of atropine and ephedrine requirement.

No research has been conducted to compare atropine and ephedrine requirement across different levels of TEA. In a study on coronary artery bypass patients, no significant difference was reported for inotrope or vasoconstrictor requirement between patients who received HTEA and those who received no TEA [8]. Rectus abdominis, internal and external oblique, and transversus abdominis muscles contribute to respiration by maintaining abdominal support. Abdominal muscles are the primary muscles involved in forced respiration. TEA increases diaphragm activity by blocking inhibitory afferent fibers despite weakening respiratory intrathoracic respiratory muscles and intercostal musculature. The net effect is an increase in respiratory activity in patients undergoing upper abdominal surgery [9, 10]. In a study on TEA, block was performed to T_1-T_5 sensory dermatome levels and authors reported a drop of 5.6% in FVC and of 4.9% in FEV_1. These decreases in respiratory functions are explained by block of intercostal muscles [11, 12]. Another study compared two groups of TEA patients with block at C4-C7 and T_5-L_4 levels. FVC decreased by 25% in both groups, while FEV_1 decreased by 13% in the C4- C7 group and by

12% in the T5-L4 group [13]. Our results outline better respiratory functions when TEA was applied at T_{6-7} than at T_{9-10}. We believe this to be caused by an increased block of abdominal muscles in the T_{9-10} group.

Intestinal contractility is mediated by hormonal and neural factors. Parasympathetic activity increases gastrointestinal motility while sympathetic activity decreases it. In a study on patients undergoing major abdominal surgery under TEA, the number of segments with block at and above T_{12} level corresponded with faster reversal of gastrointestinal functions.[14, 15] Reversal of gastrointestinal motility was faster in the T_{6-7} group of our study which we associated with the increased extent of thoracic segments blocked in this group.

A study on patients operated for primary gastrointestinal malignancies compared a group receiving TEA with general anesthesia with another group receiving only general anesthesia. The group with TEA had a significantly shorter length of stay resulting from fewer cases of gastrointestinal system disorders.[16] The effect of different levels of TEA on length of hospital stay is not reported in prior research. Our results revealed a significantly shorter length of stay in the T_{6-7} group. We believe the faster return of gastrointestinal motility and better respiratory functions contribute to the shorter length of stay in this group.

5. Conclusion

In conclusion, TEA at a higher level resulted in a lesser drop in heart rate and blood pressure while atropine and ephedrine requirements did not differ between groups. The groups did not differ in terms of the number of segments with block but highest and lowest dermatome levels with analgesia were significantly differed between the group T6-7 and T9-10. The ambulation times of the groups were similar. Motor block did not develop in any patient. Nausea was detected in more patients in the T6-7 group. There was no difference between the groups in terms of nausea and itching. Higher TEA was beneficial as it allowed better hemodynamics, respiratory functions, gastrointestinal motility and shorter length of stay compared to lower TEA.

Limitations of the Study

We have some limitations in our study. Invasive hemodynamic measurements could provide more precise hemodynamic monitoring for cardiac index, stroke volume index, and SVR. However, invasive hemodynamic monitoring is not routinely practiced in our clinic and was not utilized in our study patients. Additionally, patients were not evaluated fluid responsiveness preoperatively. Our study was conducted in the geriatric patient group. Controlled hypertension patients were also included in our study. Studies can be planned in different patient groups. Sample size was calculated according to blood pressure change further studies can be planned with a larger sample size.

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Conflict of Interests

The authors declare that there is no potential conflict of interest for the research, authorship, and/or publication of this article. All authors read and approved the final manuscript.

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Author Contributions

Design of the study: AK, AD Sample collection: AK, SMC, Data Collection and/or Processing: AK, SMC, Writing Original Manuscript: AK, II, MA, AD. AK contributed to revising the work and final approval of the final version of the manuscript.

Ethical Approval

This study was approved by the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (05/04-24.04.2014).

Data sharing statement

The data that support the findings of this study are available on request from the corresponding author.

Consent to participate

Consent was obtained from the patients participating in the study.

Informed Statement

The patient and control group who agreed to participate in the study signed the informed consent form.

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The Effect of Surface Properties of Different Types of Post Materials on Fracture Type

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Abstract: In this article, it is aimed to examine the fracture strength of peek posts to the ferrule under provided and unprovided conditions.66 extracted human central incisors were used (n=11) from Ni-Cr alloy, fiber, and peek materials to form six groups (N, NF, F, FF, P, and PF). Crown materials, compatible with the central maxillary incisor anatomy, were produced for 66 samples. Subsequently, the samples were subjected to fracture strength testing. After the test, the samples were classified into three groups based on the type of fracture: adhesive, cohesive, and mixed. The significance of the difference between the groups was evaluated statistically. The surface roughness value of the peek post group (1.42±0.21) was significantly lower than that of the metal and fiber post groups. Although no significant difference was found in terms of the fracture type, the adhesive failure rate was higher in the peek post group (P<0.05). Adhesive type joint failure is most commonly seen in non-ferrule and ferrule peep post groups ©2024 NTMS.
Keywords: Fracture strength; polietereterketon; surface properties.

1. Introduction

The prognosis of teeth undergoing endodontic treatment is influenced by many factors[1-3]. When the coronal tissue loss is 50% or more, post-core treatment can be applied to ensure continuity of the remaining dental tissues [4, 5]. Additionally, it is known that the ferrule effect and the amount of remaining dental tissue also increase the resistance of the tooth to fracture [6, 7] Ferrule is defined as a vertical band surrounding the tooth structure in the gingival region during crown preparation [8, 9]. Previous literature studies have observed that even a 1 mm ferrule effect is a minimum width effective in stabilizing restoration. Than Whang et al [10]. Fontana et al. observed that the effect of a 0.5 mm ferrule width was low [11]. Studies have shown that ferrule height is more important in terms of durability. The minimum ferrule height required for post-core restorations has been reported to be 1.5-2 mm [7, 9]. In addition to the amount of remaining dental tissue, the type of restoration and material selection are also crucial for the prognosis of endodontically treated teeth [12]. The use of prefabricated fiber posts ensures a balanced distribution of occlusal forces on the tooth [13]. These systems have various advantages and disadvantages. The use of prefabricated fiber posts ensures a balanced distribution of occlusal forces on the tooth [14].

The elastic modulus values of the metal and ceramic posts produced according to the canal structure are higher than those of dentine [15]. Furthermore, due to many disadvantages of cast post-cores, such as

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displaying a metallic color, corrosion, disintegration, retention loss, and root fracture formation, there has been a shift toward fiber post systems [16]. Despite being able to solve many problems associated with metal posts, fiber posts cause mechanical stress at the cervical dentine and restoration border and do not reinforce the tooth structure [17]. In addition, despite having a lower elasticity modulus than metal posts, fiber posts still have a modulus almost three times that of dentine [18]. Polyetheretherketone (PEEK) is a semi-crystalline high-performance thermoplastic polymer that has become increasingly popular in dentistry [19, 20]. Mechanical properties such as elastic modulus can also be adjusted by modifying the filler content and incorporating inorganic filler materials [21]. The dentine-like elastic modulus of PEEK allows it to function as a stress reliever that reduces the forces transferred to restorations. The fact that the elastic modulus value is close to the elastic modulus of dentin is a very good feature in terms of stress homogeneity [22].

This study aims to investigate the effect of the ferrule on the fracture resistance of posts prepared with PEEK material, which is increasingly being used in prosthetic dentistry, in addition to current post materials.

This study has two hypotheses: The first hypothesis is that the PEEK post groups will show significantly higher surface roughness than the other groups. The second hypothesis is that the frequency of adhesive fractures in the PEEK post groups does not differ from that of other materials.

2. Material and Methods

The number of teeth used in this study was calculated using parameters from a study conducted by Fontana et al.[11] based on the G*power software. The sample size was calculated for situations where the fracture resistance test results of the 'cast post-core' control group, conducted with and without a 1 mm ferrule, were 339±153 and 575±2.4 respectively.

Accordingly, it was calculated that each group with 80% power and 95% confidence level should consist of 11 maxillary incisor teeth. All teeth were cleaned of soft tissue remnants and calculus and immersed in 0.1% thymol solution (*Thymol; Supelco®, Missouri, USA)*. 66 teeth were randomized into 6 subgroups. The group scheme is shown in Table 1.

2.1. Simulation of Periodontal Ligament

The modeling wax used to simulate the periodontal ligament within an acrylic model was liquefied at 65 °C. A 0.2 mm thick layer of wax was applied to each tooth root, starting 3mm coronally from the apex. The teeth were then embedded in a delrin (polyoxymethylene) cylinder after applying autopolymerizing acrylic resin (*Integra*) onto the wax layer. An elastomeric impression material was used to mimic the periodontal ligament (*Impregum F, 3M-ESPE, Seefeld, Germany).*

Table 1: Study design.

Post Type	Ferrule Thickness	Group Code
PEEK	Non-ferrule	P
PEEK	2mm height with 1mm thickness ferrule effect	PF
Metal	Non-ferrule	N
Metal	2mm height with 1mm thickness ferrule effect	NF
Fiber	Non-ferrule	F
Fiber	2mm height with 1mm thickness ferrule effect	FF

2.2. Endodontic Treatment Procedure

The crowns of the teeth were removed using a high-speed handpiece with a diamond bur, leaving a root length of 10mm behind. Teeth with single and straight root canals were used, with root lengths of at least 10 mm each. A standard endodontic protocol was applied.

2.3. Canal Preparation for Post Space

The length of the post space was designed to be 1 mm for groups without ferrules and 12 mm for groups with a ferrule height of 2 mm.

2.4. Ferrule Preparation

In their study of ferrule length, Libman and Nicholls [23] showed that 0.5 mm and 1.0 mm ferrule lengths were significantly less successful at a lower number of cycles compared with 1.5 mm and 2.0 mm ferrule lengths. Therefore, a ferrule of 2 mm height and 1 mm width was prepared. For CP-1, PP-1, and FP-1 groups, ferrule preparation was manually performed using a high-speed water-cooled micromotor with a diamond bur attached (*Extra Torque 605C; Kavo do Brasil, Joinville) (No.3216, KG Sorensen, Barueri, Brazil)* (Figure 1 A, B).

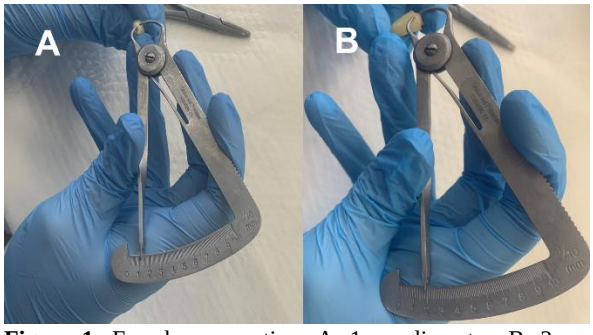

Figure 1: Ferrule preparation; A. 1mm diameter. B. 2mm height.

2.5. Post Production

For cast and PEEK posts, plastic dowels (*Pinjet Angelus, Londrina, Parana, Brazil*) were coated with chemically activated acrylic resin (*Bosworth Trim Plus Company, Skokie, IL, USA*). The production of PEEK

posts involved indirect measurement from the canal, transferring it into a digital format using a digital scanner (*Shining 3D EinScan H 3D Scanner VHF K5*) (Figure 2). All completed post types are shown in Figure 3.

Figure 2: CAD-CAM image of the designed PEEK post sample.

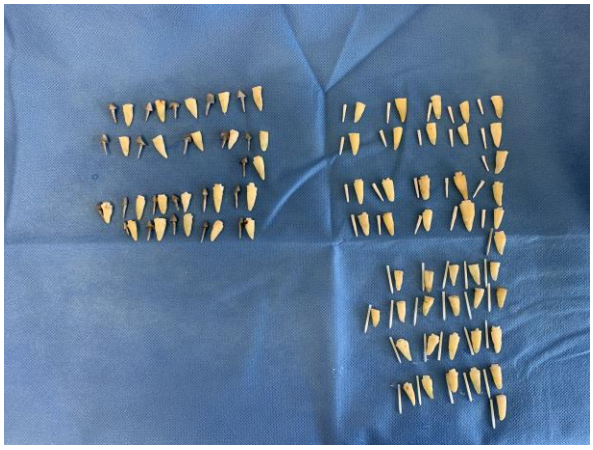

Figure 3: All post materials and corresponding tooth specimens.

2.6. Surface Treatments

All the samples were cleaned with 70% ethanol after production and dried. Subsequently, phosphoric acid (*K Etchant GEL; Kuraray, Umeda, Osaka, Japan*) was applied to the fiber post surfaces, according to the manufacturer's instructions. After 15 s of acid application, the fiber surfaces were rinsed with water. The surface treatment of the PEEK post groups was achieved by applying 98% sulfuric acid to the material surface for 60 s. Following the acid treatment, the materials were washed with distilled water for one minute and dried. Surface treatments for cast posts were conducted by spraying Al_2O_3 particles of 15-nanometer particle size onto the post surface at a pressure of 50 Mpa for 15 s.

2.7. Surface Measurements and Surface Observation

The surface roughness (*Ra*) of the surface-treated post materials was measured using a noncontact profilometer (*3D noncontact profilometer Kla Tencor Stylus Profiler P7*). Following the surface treatment, the structural surface topography of each group was observed under a scanning electron microscope.

2.8. Application and Cementation of Post Materials into the Canal

All posts were fixed in the canal with dual cure resin cement (*Allcem, FGM*).

Table 2: ANOVA results for fracture resistance test outcomes.

Group Number	Fracture Resistance (N)	Standard Deviation	Median	Minimum	Maximum	F	P
CP-0	415.0300	126.4174	412.4400	182.3600	642.7600		
CP-1	555.7564	112.1193	559.2190	359.7890	775.1420		
FP-0	310.8080	998.8239	312.4499	163.5478	458.9001		
FP-1	322.4682	109.1813	320.0600	141.5800	508.2200	7.565	P<0.05
PP-0	341.2164	129.6218	330.6500	120.5600	534.6500		
PP-1	377.6036	115.9855	364.0800	173.4500	558.1500		

2.9. Core Production

A composite resin (*Opallis, FGM*) was used for core production. To ensure standardization of the core material across all groups, a previously prepared acetate matrix post system was adapted to the coronal portion.

2.10. Aging Procedure

The samples were aged by keeping them at 5°C for 20 seconds and at 55°C for 20 seconds in a machine (Acumen III; MTS Systems Corp.) simulating the oral environment and by subjecting them to 6000 thermal cycles, with 20 seconds between cycles, to correspond

to a five-year service period in the mouth, and were then subjected to the fracture resistance test. After aging and fracture strength testing, the types of fractures (adhesive, cohesive, and mixed), fracture locations (buccal, palatal, mesial, and distal), and reparability of fractures (requiring extraction and repairable) were evaluated using an optical microscope.

Table 3: ANOVA results for roughness values.

Group Number	Surface Roughness (Ra)	Standard Deviation	Median	Minimum	Maximum	F	P
N	2.13	0.13	2.13	1.91	2.29		
NF	2.15	0.14	2,25	1.92	2.32		
F	2.86	0.09	2.95	2.78	3.16	314.321	0.000
FF	2.86	0.15	2.93	2.69	3.21		
P	1.65	0.08	1.66	1.53	1.77		
PF	1.64	0.05	1.65	1.53	1.73		

2.11. Fracture Strength Test

Fracture tests were conducted on the palatal region of the zirconia crown material at a low speed (1 mm/min) and an angle of 135 to the long axis of the tooth, using a universal testing machine (*Model 4202; Instron*). At the end of the test, each sample was examined under an optical microscope at x10 magnification to determine its fracture mode. Root fractures were classified as catastrophic, to be extracted, or repairable.

2.12. Statistical Analysis

Analyses were conducted using IBM SPSS 20 statistical analysis software. For the comparison of continuous variables among more than two independent groups, the ANOVA. Pearson chi-squared and the Fisher-Freeman-Halton test was used when it post-hoc. Statistical significance was set at $p<0.05$.

3. Results

The average maximum fracture resistance of the six different experimental groups exceeded the maximum force values (286 N) reported in the literature for the anterior region [40]. According to the fracture resistance test results, the groups with metal custom posts (N and NF) demonstrated higher fracture resistance than the other groups. According to the ANOVA test results, cast post specimens with ferrule preparation (NF) exhibited a significantly higher fracture resistance ($p<0.05$). Table 2 presents the statistical results of the fracture resistance test values according to the ANOVA.

Table 4: Freeman-Halton test results.

Group no (n=66)	N	NF	F	FF	P	PF	Total	P
Adhesive	7	2	6	7	8	8	43	
Cohesive	2	0	0	0	0	0	2	0.857
Mixed	2	4	5	4	3	3	21	

Table 4 displays the results of examining fracture types under an optical microscope and the analysis of fracture types using the Fisher-Freeman-Halton test. Based on the failure mode of the bonding mechanism of the samples subjected to fracture testing, the fracture types occurring on the posts were observed under an optical microscope (x10), and statistical analysis of the fracture types was conducted. Significant differences were found among the groups. The rate of adhesive fractures was significantly higher in the PEEK and fiber post groups than in the other groups ($p<0.05$). There was no significant difference between the fiber (F, FF) and PEEK (P, PF) post groups ($p>0.05$).

4. Discussion

This study has two hypotheses: The first hypothesis posited that the peek post groups would exhibit significantly higher surface roughness than the other groups. Since the fiber post groups showed significantly higher fracture resistance than the other post groups, the first hypothesis of the study was rejected. Many other studies in the literature concerning fiber posts have similarly reported high surface roughness values. The second hypothesis was that adhesive fractures would not differ significantly between the Peek post groups and other materials.

However, as adhesive fracture frequency was found to

be significantly higher in the Peek post groups than in the other groups, the second hypothesis of the study was also rejected.

This finding is consistent with those of many previous studies [24, 25]. Atais Bacchi et al.[26] similarly investigated the 'ferrule effect' on fracture resistance in finite element analysis studies involving metal and glass fiber posts, both with and without observed ferrule effect conditions, and found that the 'ferrule effect' increased fracture resistance independently of the materials examined ($p<0.05$). Michael Naumann et al. [27] in their systematic review, similarly concluded that the 'ferrule effect' had a much larger impact than the various material types used.

In this study, it was measured that the fracture resistance test values observed were higher than the known values for anterior teeth (190-290N) When the test results were examined, it was observed that the fracture resistance values of NF were significantly higher than those of all groups ($p<0.05$). This situation is consistent with the literatüre [28] . Similarly, a previous study examined two experimental post groups; prefabricated fiber posts with composite cores and cast post cores with 2 mm ferrule preparation. It was observed that the fracture resistance of the metal post core group was significantly higher than that of the other group [29]. In the study conducted by Fraga et al., among the experimental groups with 2mm ferrule preparation, metal post cores exhibited significantly higher statistical fracture resistance compared with those of prefabricated fiber posts with composite cores. It has been reported in previous similar studies that 2 mm ferrule preparation significantly increased the fracture resistance of cast metal posts [30]. Although not statistically significant, the fracture resistance values of the Peek post groups were higher than those of the fiber post groups. Similarly, in a study using extracted premolar teeth, the fracture resistance values of the Peek post group were higher, but no statistically significant difference was found [31].

Kul et al.[32] examined the fracture strengths of zirconia ceramic posts, fiber posts, and glass fiber-reinforced composite resin posts. Similar to this study, they observed that all samples without ferrule preparation fractured catastrophically. In conditions where the ferrule effect was not achieved, the use of Peek posts may be considered a more advantageous option than previously tested materials. However, in this study, it does not seem sufficient to prevent the formation of irreparable fractures. In vivo studies are needed to restore real teeth with Peek posts, where the periodontal feedback mechanism is present.

When the groups with ferrule preparation were examined, it was observed that the likelihood of catastrophic fracture was much higher in the metal groups with high fracture resistance (81.1%). The frequency of catastrophic fractures in NF was observed to be statistically significantly high ($p<0.05$). Previous studies have reached a consensus that regardless of the presence of the ferrule effect, metal posts lead to catastrophic fractures in the root. [33] The frequency of repairable fractures in PF was found to be statistically high ($p<0.05$). Using peek posts reduces the incidence of catastrophic fractures [31]. However, there are relatively few studies on this subject.

Surface roughness is a critical factor in adhesive procedures and requires various surface treatment methods to enhance the bonding area and micro-roughness of dental materials [34]. Peek, as confirmed by SEM images, exhibited pits and pores distributed with filler particles on the surface, as shown in previous studies [35]. The measured surface roughness values for all examined experimental groups are consistent with the Ra values found in the literature [36, 37]. When surface roughness values were examined, fiber post groups (F, FF) showed significantly higher roughness values than all other materials ($p<0.05$). This may be attributed to the difficulty of surface treatments for metal posts and the chemically inert nature and low surface energy of Peek post materials [38].

After the fracture resistance test, when the failure modes of the extracted samples were examined, predominantly adhesive failures were observed. There was no significant difference between the fiber and Peek post groups ($p > 0.05$). Adhesive failures observed in the PEEK and fiber post groups were significantly higher than those in metal post groups ($p>0.05$). This is thought to be due to the much higher fracture resistance of metal post groups, resulting in the formation of fracture lines comprising dental structures [39]. For groups F and FF, some resin residues were observed adhering to the post surface, but this group primarily fractured in the adhesive type as observed in previous studies [40].

5. Conclusion

1.The reason for the significantly higher occurrence of fracture lines comprising dental structures in the metal post groups is thought to be due to the significantly higher fracture resistance values exhibited by the metal post ($p<0.05$).

2.The incidence of adhesive type failure in peek and fiber posts is significantly higher than in other types of materials used in this study ($p<0.05$).

Limitations of the Study

This article has certain limitations:

1.This study is an in vitro study and cannot encompass many factors in the oral environment, particularly feedback mechanisms.

2.The produced zirconia crowns are designed to serve as a substructure material and are relatively smaller in size compared to the actual central tooth dimensions.

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Conflict of Interests

There is no conflict of interest.

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Author Contributions

Conception: BT, FB. Design: BT, FB. Supervision: BT, FB. Materials: BT, FB. Data Collection and/or Processing: BT, FB. Analysis and Interpretation: BT, FB. Literature: BT, FB. Review: BT, FB. Writing: BT, FB. Crital Review: BT, FB.

Ethical Approval

This study was approved by the etic committee of Atatürk University Faculty of Dentisty (No: 34).

Data sharing statement

It is mentioned in the article that all the data supporting the results are provided within the article itself and there is no need for additional source data.

Consent to participate

None.

Informed Statement

None.

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Cases of Childhood Mastocytosis: A Single Center Experience

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Abstract: Cutaneous mastocytosis, primarily affecting children, is confined to the skin and generally carries a good prognosis. In our study, we aimed to evaluate the clinical findings, laboratory values and treatment-related data of 10 patients who were followed up with a diagnosis of mastocytosis in our clinic between 2014 and 2022. Age, gender, family history, clinical findings, type of lesions, laboratory values and treatment-related data of the patients were analyzed within the scope of the study. Skin biopsy was taken from clinically suspected patients and the diagnosis was made with histopathologic confirmation. Histopathologic diagnosis was made by demonstration of mast cells showing metachromasia with toluidine blue in full-thickness skin biopsy. The median age at presentation was 10.0 months (min-max: 1.0-117.0). While rash and pruritus were the most common complaints seen in all patients; erythema was seen in 9 (90%) patients. The most common rash type was maculopapular. One (10.0%) patient had nodules and mastocytoma. When the laboratory findings of the patients were evaluated, no patient had thrombocytopenia or leukopenia. One patient had anemia. The median value of total IgE values was 65.0 IU/ml (8.0-1719.0). In our study, all patients had symptoms of rash and pruritus. The most common lesion type in our study was maculopapular rash (UP type) seen in 4 patients (40%). Nodules and mastocytoma (NM type) were seen in 1 patient (10%). In our study covering an eight-year period, all of our patients had cutaneous mastocytosis and none of them had systemic involvement. ©2024 NTMS.

Keywords: Mastocytosis; Rash; Urticaria Pigmentosa.

1. Introduction

Mastocytosis is an uncommon and diverse disorder marked by the abnormal proliferation and activation of morphologically and immunophenotypically atypical mast cells (MCs) in different tissues, such as bone marrow, lymph nodes, liver and spleen. This condition is notably observed in the skin (cutaneous mastocytosis-CM) and internal organs (systemic mastocytosis-SM) [1-3]. The classification by WHO categorizes cutaneous mastocytosis (CM) into three primary groups: maculopapular cutaneous

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mastocytosis (MPCM), diffuse cutaneous mastocytosis (DCM), and cutaneous mastocytoma only. Cutaneous mastocytosis, primarily affecting children, is confined to the skin and generally carries a good prognosis. If cutaneous mastocytosis (CM) comprises three or fewer lesions, they are identified as mastocytomas, whereas maculopapular cutaneous mastocytosis (MPCM) is defined by the presence of 4 to 100 lesions. The diffuse cutaneous mastocytosis (DCM) classification encompasses widespread skin involvement [4-6].

Mast cells arise from the bone marrow and travel in a precursor state to connective tissue, where they fulfill diverse functions. Although pediatric mastocytosis is typically viewed as a sporadic condition, a few uncommon familial cases have been documented [7-9]. Despite some progress, the precise pathogenesis remains inadequately comprehended. Clinical manifestations and course of mastocytosis are examined under two main categories as 'childhood (pediatric)' and 'adult-onset' depending on the age of onset. Generally, childhood mastocytosis is diagnosed before the age of two years and the most common type of childhood mastocytosis is characterized by a skin disease called urticaria pigmentosa (UP) [10]. Lesions develop in the first year of life in 60-80% of patients. Mastocytoma and UP lesions can be seen even at birth [11-12].

Cases of cutaneous mastocytosis (CM) can lead to symptoms related to mast cell (MC) mediators, either locally and/or systemically. Flushing is a commonly observed symptom, while cyanosis, respiratory arrest, arterial hypotension and anaphylactic reactions are less frequent in maculopapular cutaneous mastocytosis (MPCM). Additionally, CM cases may manifest with gastrointestinal symptoms, such as abdominal pain, diarrhea, hyperacidity or peptic ulcers [4]. In instances of (solitary) mastocytomas or polymorphic MPCM with nodular dermal lesions or plaque, blistering may seldom develop in early childhood period, especially in response to mechanical irritation, but typically recovers without leaving a scar [6].

In cases of mastocytosis in adults, the causes of anaphylaxis vary compared to pediatric cutaneous mastocytosis (CM). In two-thirds of pediatric cases, a specific trigger cannot be identified, leading to idiopathic anaphylaxis. Food allergies have been reported in 10-20% of cases, drugs in less than 10% and toxic animals do not seem to be the primary triggers of anaphylactic reactions in children as much as in adults [6].

In our study, we aimed to evaluate the clinical findings, laboratory values and treatment-related data of 10 patients who were followed up with a diagnosis of mastocytosis in our clinic between 2014 and 2022.

2. Material and Methods

2.1. Study Type and Design

Our descriptive study was carried out by retrospective examination of the database of Istanbul Umraniye Training and Research Hospital. The files of 10 patients diagnosed with mastocytosis between 2014 and 2022 were retrospectively evaluated. This study was conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all participants.

2.2. Evaluation

Patients with diagnosis code Q82.2 were identified. Age, gender, family history, clinical findings, type of lesions, laboratory values and treatment-related data were analyzed in the study. Mastocytosis was classified according to WHO. The WHO classification distinguishes three main manifestations: maculopapular cutaneous mastocytosis (MPCM), diffuse cutaneous mastocytosis (DCM) and cutaneous mastocytoma. MPCM is defined as urticaria pigmentosa [13]. Skin biopsy was obtained from clinically suspected patients and the diagnosis was made with histopathologic confirmation. Histopathologic diagnosis was made by observation of mast cells showing metachromasia with toluidine blue on full-thickness skin biopsy [14]. Patients were evaluated with complete blood count, liver and renal function tests and abdominal ultrasonography for systemic mastocytosis involvement and referred to pediatric hematology and oncology.

2.3. Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows 25.0 was used for data recording. Normal distrubition was evaluated with *Kolmogorov Smirnov test and* the *Shapiro-Wilk tests.* Descriptive results were presented with median, minimum, maximum values, numbers (n), and percentages (%).

2.4. Ethics

Ethics committee approval was obtained from the Ethics Committee of Umraniye Training and Research Hospital with decision number 26 on February 23, 2023 for the conduct of the study.

3. Results

The data of 10 pediatric cases with mastocytosis were evaluated in the study. All ten patients had cutaneous mastocytosis. None of the patients had systemic findings. Six (60.0%) of the patients were male and 4 (40.0%) were female. Family history was positive in one (10.0%) patient. The median age at presentation was 10.0 months (min-max: 1.0-117.0). While rash and pruritus were the most common complaints in all patients, erythema was observed in 9 (90%) patients. Abdominal pain, reflux, diarrhea, myalgia and bone pain were other symptoms. The most common rash type was maculopapular. One (10.0%) patient had nodules and mastocytoma (Table 1).

Four (40%) patients had additional allergic diseases. The diagnoses of the four patients with comorbidities were allergic rhinitis, allergic rhinitis and atopic dermatitis, asthma and atopic dermatitis, allergic rhinitis and food allergy, respectively.

When the laboratory findings of the patients were evaluated, there were no patients with thrombocytopenia or leukopenia. One patient had anemia. The median value of total IgE values was 65.0 IU/ml (8.0-1719.0). The median AST and ALT values were 27.0 (18.0-52.0) and 19.0 (11.0-50.0), respectively. Immunoglobulin values and other laboratory data are given in Table 2.

Table 1: Clinical characteristics and demographic data of the patients.

		Median (min-max)
Age at onset of symptoms (months)		10.0 (1-117.0)
Age at diagnosis (months)		33.0 (8-120.0)
		N (%)
Positive family history		1 (10.0)
Gender	Male	6 (60.0)
	Female	4 (40.0)
Complaints	Rash	10 (100.0)
	Itching	10 (100.0)
	Redness	9 (90.0)
	Reflux	5 (50.0)
	Diarrhea	1 (10.0)
	Abdominal pain	1 (10.0)
	Vomiting	1 (10.0)
	Muscle pain	1 (10.0)
	Bone pain	1 (10.0)
Lesion size	≤1 cm	7 (70.0)
	>1 cm	3 (30.0)
Lesion type	Maculopapular rash	4 (40.0)
	Macular rash	3 (30.0)
	Nodule and mastocytoma	1 (10.0)
	Papular rash	1 (10.0)
	Macular rash and plaque	1 (10.0)
Treatment	Antihistamines and humidifiers	10 (100)
	Montelukast	1 (10.0)

Antihistamines and humidifiers were used in the treatment of all patients, while montelukast was additionally used in one patient. Prophylactic medication was used in 7 patients (70.0%). Antihistamines and montelukast were used in prophylaxis in one patient.

Table 2: Laboratory values of the patients.

	Median	**Minimum**	**Maximum**
Total IgE(IU/ml)	65.0	8.0	1719.0
AST (U/L)	27.0	18.0	52.0
ALT (U/L)	19.0	11.0	50.0
IgG (mg/dl)	906.5	391.0	1234.0
IgA (mg/dl)	10.4	1.6	15.0
IgM (mg/dl)	12.1	1.5	15.7

4. Discussion

Mastocytosis is a rare clonal disease of hematopoietic stem cells that develops with the accumulation of mast cells in the skin (cutaneous form) or in multiple organs including bone marrow, spleen, liver and lymph nodes (systemic type) [15]. The identification of hepatosplenomegaly, lymphadenopathy or abnormal blood tests may indicate systemic mastocytosis (SM) and might necessitate additional examinations such as abdominal ultrasound or computed tomography scans and a bone marrow biopsy. In such instances, a thorough set of laboratory tests, including a complete blood count, renal and liver function tests, and serum tryptase levels, should be contemplated [4, 5]. Since our patients did not have systemic involvement, bone marrow biopsy was not performed.

In our study, the male-female ratio of pediatric mastocytosis cases was found to be 1.5. In the literature, the male-female ratio in pediatric mastocytosis is estimated to be 1.4 and this ratio is similar to the results found in our study [16]. Tüysüz et al. also found a male-female ratio of 1.6 in mastocytosis cases in their study [17]. The mean age at the onset of the patients' complaints was 10 months. In the literature, it has been shown that approximately 90% of children develop their first skin lesions in the first two years of their lives [16, 18]. In the study by Tüysüz et al. the median age at presentation in mastocytosis cases was found to be 12.1 months [17].

While the majority of pediatric patients don't exhibit a family history of cutaneous mastocytosis (CM), occasional instances of familial cases have been observed. Reports indicate that familial cases involving a first-degree family member occur in 2% to 4% of cases, and the majority of these cases are linked to c-kit genetic mutations [8]. In our study, family history was found to be positive in 1 (10%) of our patients.

In cases of mastocytosis, inquire about systemic symptoms such as itching, facial flushing, dizziness,

palpitations, fainting, abdominal pain and diarrhea [19]. According to a study conducted by the National Institutes of Health, itching was reported in 83% of patients, rash in 65%, abdominal pain in 41%, vesicles in 53%, bone pain in 18% and headache in 12% [20]. In our study, it was found that all patients had symptoms of rash and pruritus. In the study by Tüysüz et al. Rash was the most common symptom and pruritus was found in the second frequency [17].

In a study of 173 patients investigating childhood mastocytosis in the literature, systemic involvement was reported in only two patients [21]. In our study covering an eight-year period, all of our patients had cutaneous mastocytosis and systemic involvement was not observed in any of them. Our patients are being followed up and no systemic involvement has developed.

In our study, the most common lesion type was maculopapular rash (UP type) seen in 4 patients (40%) and macular rashes were found in 3 patients (30%). Nodules and mastocytoma (NM type) were seen in 1 patient (10%). Hannaford et al. Evaluated 173 patients and reported NM in 51%, UP in 47% and DCM in 2% [21]. Alvarez-Twose et al. Evaluated 111 pediatric patients with cutaneous mastocytosis and reported UP in 68%, NM in 20% and DCM in 8% of the patients [22]. In our study, we found additional allergic diseases in 4 (40%) of the patients. Hannaford et al. Found no increase in asthma, atopic dermatitis and dermographism in their study in patients with mastocytosis [21]. Müller et al. Found no significant difference in the prevalence of atopic disease between urticaria pigmentosa patients and healthy control group in their study. Atopic disease was found in 21% of the patients [23].

5. Conclusion

In conclusion, although the number of cases in our single-center study was small, it can be emphasized that childhood mastocytosis cases are frequently cutaneous type and patients should be evaluated in detail in terms of differential diagnoses before making a diagnosis.

Limitations of the Study

The limitations of the study are small sample size and retrospective design.

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Conflict of Interests

The authors declare that there is no conflict of interest in the preparation and publication of this article.

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Author Contributions

Conceived and designed the experiments; FÇ, AÇ, MYÖ, SÇ. Analyzed and interpreted the data; UA, ZMA, SÇ, MYÖ. Contributed reagents, materials, analysis tools or data; ZMA, SÇ, AÇ, FÇ. Wrote the paper; SÇ, UA. Study of biostatistics; ZMA, UA.

Ethical Approval

Ethics committee approval was obtained from the Ethics Committee of Umraniye Training and Research Hospital with decision number 26 on February 23, 2023 for the conduct of the study.

Data sharing statement

All data relevant to the study are included in the article.

Consent to participate

Consent was obtained from all patients for the use of data under ethical conditions.

Informed Statement

Informed consent forms were obtained from all patients the patient data could be used in the our study.

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Epidemiological Investigation of COVID-19 Effects in Pregnant Women and Their Infants

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Abstract: This study was conducted to investigate in pregnant women after being infected with Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and whether any possible complications develop for the pregnant woman and the baby. This study was conducted on 301 pregnant women who were registered and being followed up at the COVID-19 Home Follow-up and Monitoring Coordination Centre. A questionnaire consisting of a Personal Information Form questioning sociodemographic characteristics and questions about the COVID-19 history of the pregnant women during their pregnancies and information about the baby after birth was administered to them by telephone. The mean age of the pregnant women was 30.21±5.34 years and 79 (26.2%) had received COVID-19 vaccine. Preeclampsia was observed in 1.0%, miscarriage in 5.8% and stillbirth in 0.3% of the pregnant women. Two (0.7%) of the babies died after birth. 21.6% of the babies had to be hospitalised due to a health problem. 2.3% of the babies had COVID-19. 12.1% of the babies had respiratory distress and 55.0% had jaundice (32.3% in the first 24 hours). Of the jaundiced babies, 64 (41.3%) received treatment for jaundice. 13.9% of the babies had breastfeeding problems after birth. Developmental delay was found in 3.6% of the babies. There was no increase in the risk of congenital anomalies and miscarriage rates due to COVID-19 in pregnant women, but the incidence of cardiac anomalies increased compared to other anomalies. Abortion rates were higher in vaccinated pregnant women compared to unvaccinated pregnant women. ©2024 NTMS.

Keywords: Pregnancy; COVID-19 Effect; Congenital Anomaly.

1. Introduction

The COVID-19 pandemic, one of the largest pandemics affecting the whole world and spreading rapidly, started in China in 2019. The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has affected special groups such as the elderly, pregnant women and individuals with chronic diseases more. It has also increased mortality rates in these groups [1]. COVID-19 has been held responsible for seven million human deaths [2]. Pregnant women are one of the important risk groups. A number of adverse effects including preterm labour, pre-eclampsia (PE) and infant loss have been observed in pregnant women. In addition, vertical transmission is observed between 1.1-3.2% in pregnant women [3]. Although effects such as low birth weight and postnatal respiratory stress have been observed in newborns, it has been reported that the risk of teratogenicity and malformation has not increased [4]. Some studies have reported that prenatal

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exposure to SARS-CoV-2, especially in the third trimester, causes significant neurodevelopmental abnormalities in neonates related with motor function, speech and language [5]. Other studies suggest that SARS-CoV-2 infection during pregnancy may have detrimental effects on fetal brain development [6,7].

It is known that both cardiovascular complications and new-onset hypertension develop more frequently in those with severe COVID-19 disease [7]. It has been reported that a picture similar to preeclampsia due to COVID-19 may occur in pregnant women [8]. In a study, it was found that the rate of PE was around 10% in women who had COVID-19 infection while pregnant, and women with COVID-19 who had a history of chronic hypertension or obesity were more likely to have pre-eclampsia [9]. This study was conducted to investigate which symptoms developed most frequently after being infected with SARS-CoV2 infection in pregnant women who were registered and followed up at the COVID-19 Home Follow-up and Monitoring Coordination Centre, and whether a possible complication developed for the pregnant woman and the baby.

2. Material and Methods

2.1. Research Design and Sample Selection

In the cross-sectional study, the population of the study was 3200 pregnant women registered in the COVID-19 Home Follow-up and Monitoring Coordination Centre in Kütahya. Power analysis using the G*Power 3.1.9 programme showed that a total sample of n:297 individuals would be needed to detect medium effects (d:0.3) with an alpha value of 0.05 and 99% power using the Chi-square test [10]. In order to reach the minimum sample size of 297 without bias in sample selection, the number 330 was reached when the dropout rate formula (N1=n/1-d) was calculated by accepting 10%. Three hundred thirty pregnant women to be sampled were determined by simple random sampling method from the pregnancy lists. Pregnant women under the age of 18 years and over the age of 45 years, and pregnant women with anomalies in their family and themselves were not included in the study because they might affect the risk of anomaly.

The research was conducted on a voluntary basis by telephone between January-December 2022. When the pregnant women who did not accept to participate in the study were excluded, the study was completed with 301 pregnant women. A two-part data collection tool was used in the study prepared in accordance with STROBE criteria. The first part of the data collection tool consisted of a Personal Information Form questioning sociodemographic characteristics and the second part consisted of questions questioning the COVID-19 history of the pregnant women during pregnancy and the information of the baby after birth.

2.2. Statistical Analysis

The study data were analysed using SPSS 24 package programme. Numerical variables were presented as mean±standard deviation, median and quartiles, and categorical variables were presented as number and percentage. Chi-square test was used for categorical variables in the analyses. In all analyses, results were considered significant when $p<0.05$.

2.3. Ethical Issues

The research was conducted with the permission of KSBU Faculty of Medicine Non-Interventional Research Ethics Committee dated 09.02.2022 and decision number 2022/02-24.

3. Results

This study was conducted with the participation of 301 pregnant women. The mean age of the participants was 30.21±5.34 years (min:19 and max:44 years). Of the pregnant women 128 (42.5%) had their first pregnancy, 115 (38.2%) were undergraduate graduates, and 219 (72.8%) were housewives. Of the pregnant women, 33 (11.0%) were smokers and 25 (8.3%) had a chronic disease, the most common of which was hypothyroidism.

Of the pregnant women, 76 (25.2%) were diagnosed with COVID-19 in the 1st trimester, 107 (35.5%) in the 2nd trimester, 118 (39.2%) in the 3rd trimester and 32 (8.1%) had lung involvement. While the variant was uncertain in 121 (40.2%) of the pregnant women, it was Delta in 144 (47.8%), mutant-suspected in 37 (7.6%), English in 11 (3.7%) and SGPH V1 in 2 (0.7%).

When the initial signs and symptoms of COVID-19 were questioned, influenza (n:57; 18.9%), nasal congestion (n:28; 9.3%), fatigue (n:64; 21.3%), myalgia (n:1; 0.3%), loss of smell (n:127; 42.2%), taste disturbance (n:106; 35.2%), cough (n:107; 35.5%), fever (n:65; 21.6%), arthralgia (n:116; 38.5%), chills (n:3; 1.0%), sore throat (n:13; 4.3%), headache (n:24; 8.0%), nausea-vomiting (n:3; 1.0%), shortness of breath (n:18; 6.0%), and other complaints (n:12; 3.8%) were observed (Figure 1). The recovery period was between 1-90 days (mean 13.14±13.09 days). Loss of odour (n:81; 26.9), cough (n:49; 16.3%) and joint pain (n:32; 10.6%) were the most prolonged symptoms. Forty seven (15.6%) of the pregnant women received treatment in the hospital for a mean of 7.64±33.35 days (min:1-max:15 days) during pregnancy. It was observed that 242 (80.4%) of the pregnant women used a drug to prevent coagulation. Heparin 299 (99.6%) and aspirin 1 (0.4%) were the most commonly used drugs to prevent coagulation. In addition, 43 (14.3%) of the pregnant women received antibiotics and 142 (47.2%) received alternative treatment (such as linden tea, vitamin C) for healing or relaxation.

The number of pregnant women vaccinated with the COVID-19 vaccine was 79 (26.2%) [1 dose Sinovac: (8.9%), 2 doses Sinovac: (15.2%), 3 doses Sinovac: (1.3%), 1 dose Biontec: (24.1%), 2 doses Biontec: (46.8%), 3 doses Biontec: (2.5%) 2 Sinovac and Biontec: (1.0%)].

Table 1: Some descriptive characteristics of mothers of babies with congenital problems.

Anomaly	Number of pregnancies	Trimester	Smoking	Chronic Disease	COVID-19 vaccine	COVID-19 Variant
Aortic stenosis (n:1)	2nd pregnancy	2nd trimester (16th week)	None	None	None	Uncertain
Arrhythmia (n:1)	4 or more pregnancies	3rd trimester (38th week)	Yes	Yes	None	Delta
ASD (n:1)	3rd pregnancy	3rd trimester (31th week)	None	None	None	Delta
Hypothyroidism (n:1)	3rd pregnancy	1st trimester (8th week)	None	None	Yes (1 dose of sinovac)	Undetermined
PDA (n:2)	2rd pregnancy (n:1) 3rd pregnancy (n:1)	2nd trimester (24th week) (n:1) and 3rd (36th week) (n:1)	None (n:2)	Yes (n:1) None (n:1)	Yes (2 doz biontec) (n:1) None (n:1)	Delta (n:2)
Polycystic kidney disease (n:1)	1st pregnancy	1st trimester (12th week)	None	None	None	Undetermined
Transposition+VSD (n:1)	2nd pregnancy	3rd trimester (35th week)	None	None	None	Delta
Vitiligo (n:1)	2nd pregnancy	2. trimester (20. Hafta)	Yes	None	None	Delta
VSD (n:2)	1st (n:1) and 2nd pregnancy (n:1)	2nd trimester (20th week) (n:1) and 2nd trimester (23rd week) (n:1)	None (n:2)	None (n:2)	Yes (2 doz sinovac) (n:1) Yes (1 doz biontec) (n:1)	Undetermined (n:2)
Miscarriage (n:18)	1st pregnancy (n:4) 2nd pregnancy (n:3) 3rd pregnancy (n:5) 4 or more pregnancies (n:6)	1. trimester (n:13) 2. trimester (n:5)	Yes (n:1) None (n:17)	Yes (n:4) None(n:14)	Yes (n:9) 2 doz sinovac (n:1) 1 doz biontec (n:2) 2 doz biontec (n:6) None (n:9)	Undetermined (n:6) English(n:1) Delta(n:10) Mutant suspect (n:1)
Dead birth (n:1)	1st pregnancy	3rd pregnancy	None	None	None	Delta
Infant mortality (n:2)	1st pregnancy 4th pregnancy	2nd trimester (n:1) 3rd trimester (n:1)	Yes (n:1) None	None (n:2)	None (n:2)	Indeterminate (n:1) Mutant suspect (n:1)

Of the unvaccinated pregnant women, 148 (66.7%) were not vaccinated due to "concern that it might harm the baby". The reasons for not being vaccinated included the unavailability of the vaccine in health facilities (8.0%), having COVID-19 at the time of considering vaccination (5.4%), being negatively affected by the people around them (5.4%), thinking that COVID-19 was a simple disease (8.6%) and other reasons (5.5%).

The number of pregnant women who stated that they had preeclampsia was 3 (1.0%) and 18 (5.8%) pregnant women had miscarriage and 1 (0.3%) had stillbirth. Of the pregnant women who gave birth (n:282), 205 (72.7%) pregnant women had caesarean section. Two (0.7%) of the babies died after birth. Sixty one (21.6%) of the babies had to be hospitalised due to a health problem. Seven (2.3%) of the babies had COVID-19. In these babies, 34 (12.1%) were found to have respiratory distress. In addition, it was observed that 155 (55.0%) developed jaundice (n:50; 32.3% in the first 24 hours). Of the jaundiced infants, 64 (41.3%) received treatment for jaundice (n:6, 9.4% drug-phenobarbital; n:57, 89.1% radiotherapy; n:1, 1.6% exchange transfusion therapy). Of the babies (n:280), 39 (13.9%) had breastfeeding problems after birth. Developmental delay was found in 10 (3.6%) of the babies. A congenital problem was detected in 11 (3.9%) of the babies born (n:282). In these babies, VSD (n:2); arrhythmia (n:1); ASD (n:1); hypothyroidism (n:1); PDA (n:2); vitiligo (n:1); transposition+VSD (n:1); polycystic kidney disease (n:1) were detected. Table 1 shows the characteristics of the babies with congenital problems and their mothers. Table 1. Some descriptive characteristics of mothers of babies with congenital problems.

Table 2: Distribution of some problems experienced by pregnant women and infants according to the trimester in which pregnant women had COVID-19.

Some characteristics of pregnant women and babies		1st trimester n (%)	2nd trimester n (%)	3rd trimester n (%)	Total n (%)	x^2; p
Miscarriage (n:18)	Yes	13 (17.1)	5 (4.7)		18 (9.8)	7.745; 0.005387
	None	63 (82.9)	102 (95.3)		165 (90.2)	
Eclampsia/preeclampsia	Yes	2 (2.6)	1 (0.9)	0 (0.0)	3 (1.0)	0.187
	None	74 (97.4)	106 (99.1)	118 (100.0)	298 (99.0)	
Infant respiratory distress	Yes	10 (15.9)	9 (8.8)	15 (12.8)	34 (87.9)	0.380
	None	53 (84.1)	93 (91.2)	102 (87.2)	248 (12.1)	
Baby hospitalisation# p:0.004 (a, b); p:0.079 (a, c); p:0.203 (b, c)	Yes	21 (33.3)	15 (14.7)	25 (21.4)		0.019
	None	42 (66.7)	87 (85.3)	92 (78.6)		
Baby problem	Yes	5 (7.9)	9 (8.8)	8 (6.8)	22 (7.9)	0.3033; 0.859
	None	58 (92.1)	92 (90.2)	108 (92.3)	258 (92.1)	
Anomaly	Yes	2 (3.2)	5 (4.9)	4 (3.4)	11 (3.9)	0.795*
	None	61 (96.8)	97 (95.1)	113 (96.6)	271 (96.1)	
Infant jaundice	Yes	38 (60.3)	59 (57.8)	58 (49.6)	155 (55.0)	0.295
	None	25 (39.7)	43 (42.2)	59 (50.4)	127 (45.0)	
Breastfeeding problems	Yes	10 (15.9)	16 (15.8)	13 (11.2)	39 (13.9)	0.542
	None	53 (84.1)	85 (84.2)	103 (88.8)	241 (86.1)	
Weight and development problems	Delay	4 (6.3)	2 (2.0)	4 (3.4)	10 (3.6)	0.347*
	Normal	59 (93.7)	99 (98.0)	112 (96.6)	270 (96.4)	

#a: 1.Trimester; b: 2.Trimester; c: 3.Trimester. *: Exact test.

Of the pregnant women (n:18) in whom miscarriage was observed, 13 (17.1%) had COVID-19 disease in the 1st trimester and 5 (4.7%) in the 2nd trimester. Table 2 shows the distribution of some problems experienced by pregnant women and infants according to the trimester in which the pregnant women had COVID-19.

Of the pregnant women with miscarriage (n:18), 9 had been vaccinated for COVID-19 and the rate of miscarriage among all vaccinated pregnant women was 11.4%. The remaining n:9 pregnant women with miscarriage had not been vaccinated for COVID-19 and the rate of miscarriage among all unvaccinated pregnant women was 4.1%. Of the jaundiced babies (n:155, 100%), 50 (32.3%) had jaundice in the first 24 hours and 105 (67.7%) had jaundice after the first 24 hours. Table 3 shows the distribution of some health problems experienced by pregnant women and infants according to the COVID-19 vaccination status of pregnant women.

Table 3: Distribution of some problems experienced by pregnant women and infants according to COVID-19 vaccination status.

		COVID-19 vaccine (+) n (%)	COVID-19 vaccine (-) n (%)	Total n (%)	x^2; p
Anomaly	Yes	4 (5.7)	7 (3.3)	11 (3.9)	*0.474*
	None	66 (94.3)	205 (96.7)	271 (96.1)	
Miscarriage	Yes	9 (11.4)	9 (4.1)	18 (6.0)	0.026
	None	70 (88.6)	213 (95.9)	283 (94.0)	
Eclampsia/preeclampsia	Yes	2 (2.5)	1 (0.5)	3 (1.0)	0.170
	None	77 (97.5)	221 (99.5)	298 (99.0)	
Infant respiratory distress	Yes	8 (11.4)	26 (12.3)	34 (12.1)	0.852
	None	62 (88.6)	186 (87.7)	248 (87.9)	
Baby hospitalisation	Yes	20 (32.8)	41 (19.3)	61 (21.6)	0.104
	None	50 (71.4)	171 (80.7)	221 (78.4)	
Infant jaundice	Yes	44 (62.9)	111 (52.4)	155 (55.0)	0.126
	None	26 (37.1)	101 (47.6)	127 (45.0)	
Breastfeeding	Yes	12 (17.1)	27 (12.9)	39 (13.9)	0.370
	None	58 (82.9)	183 (87.1)	241 (86.1)	
Weight and development	Delay	3 (4.3)	7 (3.3)	10 (3.6)	0.710
	Normal	67 (95.7)	203 (96.7)	270 (96.4)	

4. Discussion

Patients may experience different symptoms of COVID-19. In COVID-19, especially upper respiratory tract infection symptoms are at the forefront [2]. According to WHO, the most common symptoms in the general population are fever, chills and sore throat. Joint pain, loss of smell and taste are less common symptoms [11]. In a systematic review including pregnant women with COVID-19, the most common symptoms were reported to be fever, cough and muscle pain. Sore throat, runny nose, nasal congestion, loss of appetite, nausea, vomiting, smell and taste disorders are less common [12]. The most common symptoms of COVID-19 in pregnant women who participated in our study were loss of odour, joint pain and cough. The fact that loss of smell and joint pain were observed frequently in our study, which is different from the literature, may be due to the fact that pregnant women did not pay attention to the upper respiratory tract symptoms that developed at the beginning and applied to healthcare institutions late for diagnosis. In this way, the initial symptoms may have been missed.

In a study conducted in the Turkish population and in non-COVID-19 pregnant women, hospitalisation rate was found to be 4% [13]. In our study conducted in pregnant women, it was observed that 15.6% of pregnant women required hospitalisation. In addition, in our study, 14.3% of pregnant women needed to use various antibiotics due to secondary infections developing after COVID-19. Jamieson et al. found that pregnant women with COVID-19 had higher rates of admission to the intensive care unit, more need for invasive ventilation and extracorpuscular oxygenation, and higher mortality rates compared to non-pregnant women [14]. In the COVI-PREG study conducted by Favre et al., it was found that drug utilisation rates increased in pregnant women due to COVID-19 [15]. In the CANCOVID-PREG study conducted in Canada, the risk of hospitalisation of SARS-CoV-2 patients during pregnancy was found to increase significantly when compared with women aged 20 to 49 years diagnosed with SARS-CoV-2 [16]. In our study, similarly, the hospitalisation rates of pregnant women and thus the use of antibiotics and other agents increased. The finding that the hospitalisation rates and treatment needs of pregnant women with COVID-19 were higher than those without COVID-19 is consistent with the literature.

In a study conducted in France, it was found that there was an increase in infant loss rates during the pandemic. It was stated that this may be related to COVID-19 [17]. In a study conducted in England, it was found that miscarriage rates were observed more frequently in women with COVID-19 compared to those without [18]. In Türkiye, miscarriage rates were reported to be 10.4% in the general population and in all gestational months [19]. In the pregnant women who participated in our study, the abortion rate was found to be 5.9% according to all months. According to this result, it can be said that COVID-19 did not increase the miscarriage rates in the pregnant women who participated in our study compared to the general population, and even the miscarriage rates decreased in a part of the Turkish population in this study. According to studies, miscarriages are more common in the first trimester. In the world, the rate of miscarriage after the twelfth gestational week in the general population is around 1 per cent [20]. However, this rate is between 9-20% in the first trimester [21, 22]. In our study, while miscarriage rates were high in the first trimester (17.1%), these rates decreased in the following trimester (2nd trimester) (4.7%). The first trimester miscarriage rates in non-COVID-19 pregnant women are similar to the findings of this study with pregnant women. However, in the second trimester, despite the decreased abortion rates compared to the

first trimester, abortion rates were approximately five times higher than the abortion rates in the general population. The reason for the increased abortion rates in the second trimester compared to the general population should be confirmed by studies to be conducted in different populations.

In its latest update in 2023, the American College of Obstetricians and Gynaecologists Association recommends that pregnant women can be vaccinated in all trimesters, but especially after six months, COVID-19 vaccine should be administered [23]. Rahmati et al. also reported that COVID-19 vaccination during pregnancy is safe and highly effective in preventing maternal SARS-CoV-2 infection during pregnancy without increasing the risk of adverse maternal and neonatal outcomes and reduces stillbirth, preterm births and neonatal intensive care unit admission. In addition, there was no finding that adverse outcome effects such as miscarriage, gestational diabetes, gestational hypertension, heart problems, oligohydramnios, polyhydramnios, unassisted vaginal delivery, caesarean section, postpartum haemorrhage, gestational age at delivery, placental abruption, Apgar score at the fifth minute were high due to vaccination [24]. However, in our study, miscarriage rate was found to be higher in vaccinated pregnant women. In our study, pregnant women were vaccinated for COVID-19 especially in the first trimester. The fact that miscarriages are already high in the first trimester may explain this situation.

The rate of congenital anomaly is found to be around 3-4% in newborns in the community [25]. Whether COVID-19 has an effect on congenital anomaly has been the subject of some studies. For example, in the PAN-COVID study conducted by Mullins et al. it was observed that it had no effect on congenital malformations in newborns born to women affected by SARS-CoV-2 infection during pregnancy [26]. In our study, the rate of congenital anomaly was found to be 3.9% when all trimesters were evaluated together. This finding suggested that infection with SARS-CoV2 did not significantly increase the risk of foetal anomalies. However, it may cause a difference in congenital anomaly rates in pregnant women with COVID-19 infection. In a study conducted by Balcı et al. on babies born to mothers without COVID-19 and in whom fetal malformations were detected, it was found that the most frequently observed fetal anomaly was cardiovascular system anomalies (23.07%) [27]. In our study, cardiovascular system anomalies were observed in 36.36% of the eleven babies with anomalies. It is seen that cardiovascular anomaly continues to be the most common anomaly. However, cardiovascular anomalies increased in babies born to mothers with COVID-19. The increase in this rate may be due to high fever due to COVID-19. The increase in cardiovascular anomalies in babies born to pregnant women with COVID-19 may not be a real increase. The reason for the increase may also be due to the fact that the two studies were conducted at different times and samples.

Preeclampsia is the most common hypertensive disorder in pregnancy and its incidence in pregnancy is 3-8% [28]. In our study, preeclampsia was observed in 3 pregnant women (1.0%). The rate of stillbirth in the world is reported to be approximately 5 per thousand. This rate and its causes may vary according to countries and even regions of countries. Stillbirth rates have been shown to be 0.2% in developed countries, 0.7% in developing countries and 2% in South Africa and some countries in Asia [29]. In our study, stillbirth was observed in 1 (0.3%) of the pregnant women. In our study, 205 (72.7%) of the live births (n:282) had caesarean section. In Türkiye, 60.1 percent of live births and 67.6 percent of live births in the Aegean region including Kütahya are performed by caesarean section [30]. Among the pregnant women who participated in our study, 2 (‰7) of the infants died after birth. The infant mortality rate (per 1,000 live births) in Türkiye was 9.1 ‰ in 2022 [30]. Neonatal jaundice is still an unpreventable condition in 60-80% of newborn babies worldwide [31]. It has been reported that neonatal jaundice is still an important problem in Türkiye. However, there are no clear data on the frequency of neonatal jaundice in Türkiye. One of the criteria for pathological jaundice is clinical jaundice that appears in the first 24 hours of life [32]. In our study, a total of 155 (55.0%) babies were found to have jaundice. Jaundice occurred in the first 24 hours in 50 (32.3%) of these babies. Hospitalisation rates of newborn babies in the first year of life are generally between 4.4-9.5% [33]. The first two reasons for hospitalisation of infants include high fever and fluid dehydration [34]. In our study, 61 (21.6%) of the infants required hospitalisation because of a health problem. Respiratory distress was experienced by 34 (12.1%) of the babies. According to studies, the risk of developmental retardation may occur in babies whose mothers do not have a healthy pregnancy [35]. In our study, developmental delay was found in 10 (3.6%) of the babies. In the CANCOVID-Preg study, it was found that the rates of pre-eclampsia, caesarean delivery and stillbirth increased in SARS-CoV2-infected pregnant women and their babies. It has even been reported that preterm birth and mild disease cases that do not require hospitalisation occur at a high rate [16]. In the PAN-COVID study by Mullins et al. it was observed that SARS-CoV2 infection in pregnant women was associated with preterm delivery. Mullins et al. reported that there was no effect on the birth weight of the newborn in women affected by SARS-CoV-2 infection during pregnancy (26). Worldwide, 15-20% of newborns are born with low birth weight [36]. In some meta-analyses, COVID-19 has been found to be associated with preeclampsia, preterm birth, stillbirth, and hospitalisation in the neonatal intensive care unit [37,38]. In our study, the frequency of preeclampsia, stillbirth, infant death, and neonatal jaundice was found less frequently compared to the data in the world and Türkiye. However, an increase in the frequency of caesarean section and hospitalisation was found.

5. Conclusion

Based on the findings of the study, it was observed that there was no increase in the risk of congenital anomalies due to COVID-19 in pregnant women, but the incidence of cardiac anomalies increased compared to other anomalies. There was no increase in miscarriage rates, but miscarriage rates were higher in vaccinated pregnant women compared to non-vaccinated pregnant women. Infants of pregnant women infected with SARS-CoV2 in the first trimester required hospitalisation at a higher rate than those infected in the second trimester. The most common reason for hospitalisation was respiratory distress.

Limitations of the Study

The limitations of the study is cross-sectional design. Since the study is based on voluntary participation, it may lead to sampling bias. Since the data is collected through a survey, it may cause memory bias. The results of the study cannot be generalized to all of Türkiye, represents only patients in Kütahya.

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Conflict of Interests

The authors declare no conflict of interest.

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Author Contributions

Design: AD, MY, HG; Literature review: AD, MY, HG; Creating a survey: AD, MY; Data collection: AD, HG; Analysis and interpretation: AD, MY; Writing article: AD, MY; Critical evaluation: AD, MY, HG.

Ethical Approval

The research was conducted with the permission of KSBU Faculty of Medicine Non-Interventional Research Ethics Committee dated 09.02.2022 and decision number 2022/02-24.

Data sharing statement

All data relevant to the study are included in the article.

Consent to participate

Consent for the study was obtained from all participants for the study.

Informed Statement

The patient and control group who agreed to participate in the study signed the informed consent form.

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Psychological Impact of COVID-19 Pandemic in Patients with Cancer and the Relation with Traumatic Events, Difficulty in Emotion Regulation and Social Support

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Abstract: We aimed to investigate the psychological effect of the COVID-19 pandemic in cancer patients and its relationship with traumatic events, difficulty in emotion regulation and social support during the COVID-19 Pandemic. This cross sectional study was conducted with 149 patients diagnosed with cancer. Patients between the ages of 18 and 75 who were diagnosed with any type of cancer and received active chemotherapy treatment during the Covid-19 pandemic period in the oncology outpatient clinic were evaluated with various psychological assessment tools and scales. Patients were assessed with Post-Traumatic Stress Disorder Checklist (PTSDCL), Depression, Anxiety and Stress Scale for DSM-5 (DASS-21), Adverse Childhood Experiences Scale (ACE), Stressful Life Events List do to Pandemic, Difficulty in Emotion Regulation Scale-Short Form (DERS), Multidimensional Scale of Perceived Social Supports(MSPSS). 92 (61.7%) of the 149 participants were female and 118 (79.2%) were married. The median age was 51 years. 66 (%44.3) experienced moderate-to-severe distress on any or more of the DASS-21 scales. High DERS-Goals levels and SELP scores were the major components determining high PTSD severity ($p<0.001$ and $p=0.004$ respectively). Moreover, higher DERS-Strategies, DERS-Goals and ACE scores showed significant parallelism with higher depression severity ($p=0.008$, $p=0.007$ and $p=0.009$ respectively). Higher anxiety level was found to be significantly correlated with higher DERS-Goals scores and lower MSPSS-Family scores ($p<0.001$ and $p=0.038$ respectively). Stress severity level was statistically significantly correlated to DERS-Goals and DERS-Clarity scores ($p<0.001$ and $p=0.033$). A considerable proportion of patients presenting with PTSD, depression, anxiety and stress disorder was mainly impressed regarding difficulty engaging in goal-directed behavior (DERS-Goals). These findings emphasize the importance of targeted psychosocial interventions to address the unique needs of cancer patients. Childhood adversities, emotion regulation difficulties, and social support especially from the families should be considered for the patients with cancer during the pandemic to prevent them from negative outcomes. ©2024 NTMS.

Keywords: Pandemic; Cancer; Traumatic Events; Difficulty in Emotion Regulation; Social Support.

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1. Introduction

Corona Virus Disease 2019 (COVID-19) was first detected in December 2019 as a new pneumonia causing respiratory infection in Wuhan, China [1, 2]**.** This COVID-19 pandemic has created an unprecedented change in the social and ordinary lives of people around the world. The psychological status of some special groups has been more affected by the pandemic [3-5]. Particularly those with chronic diseases were the more affected populations [5, 6]. Patients with cancer may be particularly vulnerable to more severe disease due to immune-suppressed states resulting from the underlying malignancy itself, as well as reduced immunity from treatments for cancer, additional medical comorbidities, and malnutrition [6]. While the psychological status of cancer patients was affected by the pandemic, it was started to be investigated which patients were more at risk and what the protective factors were. Some of the risk factors were reported as having a history of mental disorder, excessive alcohol consumption, more frequent concern about cancer treatment due to COVID-19, and having high levels of fatigue, pain and stressfull life events [5]. The better quality of life and good relationships with family members were reported as protective factors.

One of the negative psychological consequences of the pandemic is post-traumatic stress disorder (PTSD). In the current pandemic, the rate of probable PTSD was reported as 31.6% in a study conducted on 187 oncology patients [7]. It can be expected that the increasing distress, associated to anxiety, stress and depression, with the pandemic will negatively affect the already difficult life of cancer patients. Previous studies have shown that increased levels of distress can lead to decreased satisfaction with care and non-adherence to treatment, lower survival rates, a desire to accelerate death, and poor quality of life for both patients and their relatives [8, 9].

Emotion regulation, which is predicted as an important factor affecting the social interactions especially during difficult modifications in life-style conditions, it is the ability to manage the emotions experienced and the way these emotions are expressed [10]. It is known that individuals who experience negative emotions and show psychopathological effects basically have ineffective coping strategies [11]. Emotion regulation was found to be a critical mediator of resilience in cancer and to significantly predict the quality of life change during the pandemic [12, 13].

In line with the above, it is important to define the psychological symptoms of cancer patients during the COVID-19 pandemic. In addition, it will be guiding to investigate the relationship between psychological status of the patients during pandemic and intertwined factors such as trauma, emotion regulation, and social support, which are related to both the pandemic and resilience. Actually we planned a study to not only filling a gap in the literature but also addressing a crucial aspect of epidemic management, its psychosocial component. The potential to provide effective social and psychological support in future epidemics can contribute significantly to the well-being of affected communities and enhance our overall resilience in the face of health crises. Therefore, in this study, the psychological effect of the COVID-19 pandemic in cancer patients and its relationship with traumatic events, difficulty in emotion regulation and social support will be investigated.

2. Material and Methods

The study was conducted with patients diagnosed with cancer who applied to the Health Sciences University Bağcılar Training and Research Hospital, Medical Oncology Clinic and Chemotherapy Unit between July 01 and September 01, 2020, during the period when the pandemic was most intense, hospitalizations and deaths were at the highest, and COVID-19 vaccines were not yet available and met the criteria for inclusion in the study. Inclusion criteria for the study were; being diagnosed with any type of cancer, being between the ages of 18 and 75, and being voluntarily agree to participate in the study. Exclusion criteria in the study were; pregnancy, illiteracy, having a serious psychiatric or neurological disease that may affect decision-making, not having the mental capacity to understand the questions asked, having a major additional psychiatric disorder (Schizophrenia, Bipolar Disorder, Mental Retardation, Alcohol-Substance Addiction). The purpose of the study was explained to the patients, and they were asked whether they would participate in the study voluntarily, and informed consent forms were obtained from those who agreed to participate before the study. This study was approved by the ethics committee of Istanbul Bağcılar Training and Research Hospital with reference number 2020.07.1.02.095 and was conducted in accordance with the Declaration of Helsinki.

Patients were assessed with 1. 'Post-Traumatic Stress Disorder Checklist' and 'Depression, Anxiety and Stress Scale-2 for DSM-5' to evaluate psychological symptoms, 2.To assess traumatic experiences a) ACE Childhood Trauma Score for traumatic experiences up to 18 years of age, b) Life Events Checklist-5 for the period between 18 years age and the onset of pandemic c) Stressful Life Events Inquiry List for the Pandemic Process, 3. Difficulty in Emotion Regulation Scale-Short Form, 4. Multidimensional Scale of Perceived Social Supportş, and 5. Sociodemographic and clinical characteristics form have been applied. 160 patients were included in the study 11 patients were excluded

because they filled in the forms incompletely. The analyzes of the study were performed based on 149 patients.

2.1. Socio-demographic and Clinical Characteristics Form

There are 9 items in the form prepared by the authors in line with the research purpose. With these items, the participants' age, gender, marital status, education level, age when they were diagnosed with cancer, duration of disease, type of cancer and whether they received treatment for cancer were obtained.

2.2. Adverse Childhood Experiences Scale (ACE)

This scale developed in order to question the adverse experiences in childhood during the first 18 years of life by Permanente, such as domestic emotional violence, physical violence, sexual violence, abuse, emotional and physical neglect, and questioning of divorce. These self report scale is a 10-item scale. Each item specified as ''Yes'' is considered 1 score, and is summed to obtain the total score. Turkish validity and reliability study was performed by Gündüz et al. in 2018 [14].

2.3. Stressful Events List due to Pandemic

The scale was prepared by authors, using the Stressful Life Events Screening Questionnaire [15] and review of the literature, and used to measure the stressful life event burden during the pandemic. The scale consists of 18 questions answered as yes or no (no:0 point, yes:1 point), and total score ranges from 0 to 18. Higher scores on the scale are associated with stressful event burden (see Supplementary Table 1). Cronbach's alpha internal consistency coefficient was determined as 0.76.

2.4. Life events checklist for DSM-5 (LEC-5)

The LEC-5 is a self-report measure designed to screen for lifetime traumatic events. The LEC-5 assesses exposure to 16 events known to potentially result in PTSD or distress and includes one additional item assessing any other extraordinarily stressful event not captured in the first 16 items [16]. The LEC-5 was validated with the Turkish sample [17]. In this study, the Cronbach Alpha internal consistency reliability coefficient of the scale was determined as 0.96.

2.5. Post Traumatic Stress Disorder Checklist (PTSDCL) for DSM-5

It is a self-reported scale consisting of 20 questions, each item scored between 0 and 4, to assess the severity of PTSD symptoms. High score indicates increased PTSD symptom severity [18]. The Turkish validity and reliability study was conducted by Boysan et al. [17]. In this study, the Cronbach Alpha internal consistency reliability coefficient of the scale was determined as 0.96.

2.6. Depression, Anxiety and Stress Scale-Short Form-21 (DASS-21)

The scale was developed to measure the symptoms of depression, anxiety and stress in both clinical samples and normal samples. There are 7 items in total for each factor. The scale has a 5-point Likert-type response format and the lowest score that can be obtained from each dimension is 7 and the highest score is 35. Increasing scores on the scale indicate an increase in symptoms [19]. The Turkish adaptation of the scale was made by Sarıçam (2018) [6]. In the DASS-21 guideline, scores of DASS-D≥7, DASS-A≥5, or DASS-S>9 are interpreted as at least moderate distress [21]. In this study, the Cronbach Alpha internal consistency reliability coefficient of the scale was determined as 0.88 for depression, 0.82 for anxiety and 0.85 for stress.

2.7. Difficulties in Emotion Regulation Scale-Short Form (DERS-16)

The scale was developed by Bjureberg et al. in 2016 [22]. It measures the difficulty levels of individuals in emotion regulation. The scale consists of 16 items in a 5-point Likert type (0=almost never, 4=almost always). The five-factor scale has sub-dimensions of openness, goals, drive, strategies, and rejection. The Turkish adaptation of the scale was carried out by Yiğit and Yiğit [23]. While the internal consistency coefficient was found to be 0.92 in the original study, this value was found to be 0.92 in the adaptation study. In this study, an internal consistency coefficient was found to be 0.89 for the overall scale.

2.8. The Multidimensional Scale of Perceived Social Support (MSPSS)

The scale evaluates the adequacy of social support from three different sources: family, friends and a private other, and consists of 12 items of 7 Likert type. The lowest score that can be obtained from the subscales is 4, and the highest score is 28. The lowest score is 12 and the highest score is 84 obtained from the total scale A high score indicates that perceived social support is high [24]. Reliability and validity study of the scale was made by Eker and Arkar in Turkey [25]. In the current study, the Cronbach Alpha internal consistency coefficient for the whole scale was found to be 0.94. The Cronbach Alpha internal consistency coefficient obtained for the 'a special person' sub-factor was 0.95, 0.94 for the 'family' sub-factor and 0.96 for the 'friend' sub-factor.

2.9. Statistical Analyses

Descriptive statistics were presented in median values and interquartile ranges (IQR) (25% to 75%) for the quantitative variables, and frequencies and percentages for the categorical variables. Normality tests were carried out by using one-sample Kolmogorov–Smirnov

and Shapiro-Wilk tests and through histogram graphs. To assess the relationship between variables Spearman's (rs) correlation analysis was used. Multiple linear regression models were used with stepwise method to investigate potentially predictive factors for the PTSS, depression, anxiety and stress symptoms severity in the patients with cancer. The variables evaluated were determined as significant variables derived from our results and literature review, in accordance with clinical experience. The tests for assumptions-linearity, homoscedasticity and multicollinearity were carried out by the authors (assumptions met). All the analyses were 2-sided with alpha of 0.05, and performed with SPSS statistical software (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.).

3. Results

The demographic-clinical characteristics of participants are summarized in Table 1. 92 (61.7%) of the 149 participants were female and 118 (79.2%) were married. The median age was 51 years (IQR=44.25 to 61 years), age of diagnosis 49 years (IQR=41 to 58 years), and time since current diagnosis was 13 months (IQR=6 to 36 months).

Cancer type of 57 patients were (38.3%) breast, 39 (26.2%) esophageal/gastrointestinal, 9 (6.0%) lung, and 44 (29.5%) others.

Psychometric properties for self-rating scales and subscales of participants are summarized in Table 2. The medians of PCL-5 total score, intrusions, avoidance, NACM and hyperarousal were 23 (IQR=8 to 41.5), 6 (IQR=2 to 10), 2 (IQR=0 to 4), 8 (IQR=2 to 14.5) and 6 (IQR=2 to 13), respectively. The medians of depression, anxiety, and stress were 3 (IQR=1 to 6), 3 (IQR=1 to 6), and 5 (IQR=2 to 8), respectively. The medians of DERS total score, clarity, goals, impulsiveness, and strategies non-acceptance were 29 (IQR=22 to 39), 4 (IQR=3 to 6), 7 (IQR=4 to 10), 5 (IQR=3 to 7), 8 (IQR=5 to 12) and 5 (IQR=3 to 7), respectively. The medians of MSPSS total score family, friends, and special person were 66 (IQR=47.5 to 82.5), 28 (IQR=24 to 28), 22 (IQR=14 to 28), and 20 (IQR=10 to 28), respectively. The medians of SELP, LEC-5, and ACE scores were 3 (IQR=2 to 5), 2 (IQR=1 to 4), and 0 (IQR=0 to 2), respectively.

According to DASS-21 scale 33 participants (%22.1) had depressive symptoms, 54 participants (%36.2) had anxiety symptoms, and 29 participants (% 19.5) had stress symptoms at least moderate level. 66 (%44.3) experienced moderate-to-severe distress on any or more of the DASS-21 scales.

A positive correlation was found between PCL-5 and SELP (rs=.388, p<0.001), LEC-5 (rs=.210, p<0.05) and ACE (rs=.166, p<0.05). A positive correlation was found between DERS total score and PCL-5 (rs=.361, p<0.001), clarity (rs=.221, p<0.001), goals (rs=.358, p<0.001), impulsiveness (rs=.340, p<0.001), strategies (rs=.348, p<0.001), and non-acceptance (rs=.379, p<0.001). While there was a negative significant correlation between PCL-5 and the family subscale of MSPSS (rs=-.230, p<0.001), No significant correlation was found between MSPSS total score (rs=-.092, p>0.05), friends (rs=-.045, (p>0.05) and special person (rs=-.028, p>0.05) (Table 3).

Table 1: Demographic and clinical characteristics.

Variables	n (%)/ Median (IQR)
Age, years	51 (44.25-61)
Gender	
Female	92 (61.7)
Male	57 (38.3)
Marital status	
Married	118 (79.2)
Single	15 (10.1)
Widowed/Divorced	16 (10.7)
Education	
Literate	29 (19.5)
Primary education	83 (55.7)
High school and above	37 (24.8)
Age of diagnosis, years	49 (41-58)
Time since diagnosis, months	13 (6-36)
Cancer type	
Breast	57 (38.3)
Esophageal/gastrointestinal	39 (26.2)
Lung	9 (6.0)
Others	44 (29.5)
Present treatment	
Any treatment[a]	102 (68.5)
Follow-up	47 (31.5)

[a]: Chemotherapy, Surgery, Radiation, Hormone therapy or combined.

A positive correlation was found between depression and SELP (rs=.274, p<0.001) and LEC-5 (r_S=.189, p<0.05). Depression was found to be positively correlated with DERS total score (r_s=.473, p<0.001), clarity (r_s=.425, p<0.001), goals (r_s=.473, p<0.001), impulsiveness (r_s=.331, p<0.001), strategies (r_s=.414, p<0.001) and non-acceptance (r_s=.377, p<0.001). A negative relationship was found between depression and MSPSS total score (rs=-.238, p<0.001), family (rs=-.257, p<0.001), friends (rs=-.209, p<0.05) and special person (rs=-.170, p<0.05) (Table 3).

Multiple linear regression analysis was carried out for predicting PTSD, Depression, Anxiety and Stress severity in patients with cancer (Table 4). High DERS-Goals levels (p<0.001) and SELP scores (p=0.004) predicted high PTSD severity (N=149, R2=0.222, F(2, 146)=20.85, p<0.001). High DERS-Strategies (p=0.008), DERS-Goals (p=0.007) and ACE (p=0.009) scores predicted high depression severity (N=149, R2=0.358, F(3,145)=26.94, p<0.001). High COURSE-Goals scores (p<0.001) and low MSPSS-Family scores (p=0.038) predicted high anxiety severity (N=149, R2=0.260, F(2,146)=25.61, p<0.001) -Goals (p<0.001) and DERS-Clarity (p=0.033) scores predicted high stress severity (N=149, R2=0.243, F(2,146)=23.42, p<0.001).

Table 2: Psychometric Properties for Self-Rating Scales and Subscales.

Scales	*Median (IQR)*	*[95% CI; Lower-Upper]*
PCL-5 total score	23 (8-41.5)	[20-29]
Intrusions	6 (2-10)	[5-7]
Avoidance	2 (0-4)	[2-3]
NACM	8 (2-14.5)	[6-10]
Hyperarousal	6 (2-13)	[5-9]
DASS-Depression	3 (1-6)	[2-4]
DASS-Anxiety	3 (1-6)	[2-4]
DASS-Stress	5 (2-8)	[4-6]
DERS-total	29 (22-39)	[27-31]
Clarity	4 (3-6)	[4-4]
Goals	7 (4-10)	[6-8]
Impulsiveness	5 (3-7)	[4-5]
Strategies	8 (5-12)	[7-9]
Non-acceptance	5 (3-7)	[4-6]
MSPSS-total	66 (47.5-82.5)	[60-70]
Family	28 (24-28)	[27-28]
Friends	22 (14-28)	[19-25]
Special Person	20 (10-28)	[16-23]
SELP	3 (2-5)	[3-4]
LEC-5	2 (1-4)	[2-3]
ACE	0 (0-2)	[0-1]

PCL-5: Posttraumatic stress disorder checklist for DSM-5; SELP: Stressful Events List due to Pandemic; LEC-5: Life Events Checklist for DSM-5; DERS: Difficulties in Emotion Regulation Scale; ACE: Adverse childhood experiences; MSPSS: Multidimensional Scale of Perceived Social Support.

Table 3: Correlation analysis results.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. PCL-5	-															
2. Depression	.502†	-														
3. Anxiety	.526†	.715†	-													
4. Stress	.560†	.714†	.639†	-												
5. SELP	.388†	.274†	.266†	.324†	-											
6. LEC-5	.210*	.189*	.214†	.089	.122	-										
7. ACE	.166*	.128	.136	.082	.043	.222†	-									
8. Clarity	.221†	.425†	.272†	.383†	.290†	.119	.165*	-								
9. Goals	.358†	.473†	.435†	.409†	.395†	.270†	.043	.562†	-							
10. Impulsiveness	.340†	.331†	.319†	.353†	.263†	.310†	.123	.432†	.628†	-						
11. Strategies	.348†	.414†	.356†	.336†	.367†	.302†	.051	.454†	.725†	.663†	-					
12. Nonacceptance	.279†	.377†	.343†	.261†	.266†	.283†	.109	.457†	.604†	.587†	.773†	-				
13. DERS-total	.361†	.473†	.416†	.401†	.405†	.315†	.112	.650†	.874†	.794†	.900†	.818†	-			
14. Family	-.230†	-.257†	-.260†	-.174*	-.214†	-.225†	-.110	-.164*	-.246†	-.061	-.177*	-.283†	-.219†	-		
15. Friends	-.045	-.209*	-.151	-.129	-.032	-.155	-.164*	-.240†	-.225†	-.150	-.182*	-.254†	-.233†	.498†	-	
16. Special Person	-.028	-.170*	-.162*	-.125	-.078	-.172*	-.248†	-.238†	-.208*	-.130	-.160	-.130	-.213†	.426†	.693†	-
17. MSPSS-total	-.092	-.238†	-.204*	-.168*	-.109	-.208*	-.231†	-.271†	-.261†	-.163*	-.208*	-.247†	-.268†	.625†	.888†	.908†

Spearman's r_s correlations; *p <0.05; †p <0.001. PCL-5: Posttraumatic stress disorder checklist for DSM-5; SELP: Stressful Events List due to Pandemic; LEC-5: Life Events Checklist for DSM-5; DERS: Difficulties in Emotion Regulation Scale; ACE: Adverse childhood experiences; MSPSS: Multidimensional Scale of Perceived Social Support.
Note: Clarity, Goals, Impulsiveness, Strategies and Nonacceptance are subscales of DERS. Family, Friends and Special Person are subscales of MSPS.

Table 4: Multiple linear regression analyses for psychological symptoms severity.

	Unstandardized Coefficients					95% CI		
	B	SE	ß	t	p	Lower Bound	Upper Bound	VIF
PTSS[1]								
DERS-Goals	1.960	0.466	0.333	4.209	<0.001	1.040	2.880	1.174
SELP	1.683	0.581	0.229	2.899	0.004	0.536	2.831	1.174
Depression[2]								
DERS-Strategies	0.224	0.083	0.288	2.698	0.008	0.060	0.387	2.577
DERS-Goals	0.329	0.120	0.291	2.731	0.007	0.091	0.567	2.567
ACE	0.374	0.140	0.179	2.661	0.009	0.096	0.651	1.020
Anxiety[3]								
DERS-Goals	0.421	0.069	0.450	6.121	<0.001	0.285	0.557	1.064
MSPSS-Family	-0.096	0.046	-0.154	-2.091	0.038	-0.188	-0.005	1.064
Stress[4]								
DERS-Goals	0.449	0.105	0.367	4.272	<0.001	0.241	0.657	1.424
DERS-Clarity	0.416	0.193	0.185	2.151	0.033	0.034	0.798	1.424

B: Unstandardized Coefficients; SE: Standard Error of the Estimate; β: Adjusted Coefficients; CI: Confidence Interval; VIF: Variance inflation factor.
BRS: Brief resilience scale. DERS: Difficulties in Emotion Regulation Scale; SELP: Stressful Events List due to Pandemic; ACE: Adverse childhood experiences; MSPSS: Multidimensional Scale of Perceived Social Support.
[1]:N = 149, R^2 = 0.222, F(2, 146) = 20.85, p <0.001. [2]:N = 149, R^2 = 0.358, F(3, 145) = 26.94, p <0.001. [3]:N = 149, R^2 = 0.260, F(2, 146) = 25.61, p <0.001. [4]:N = 149, R^2 = 0.243, F(2, 146) = 23.42, p <0.001.

4. Discussion

In this study, developed psychological symptoms were detected in patients diagnosed with cancer during the pandemic, and their relationship with traumatic experiences, difficulty in emotion regulation and social support was determined. The main findings of the study are discussed in the following topics.

First, 44.3% of the participants experienced moderate-to-severe distress on any or more of the DASS-21 scales. It has been previously reported that the psychological impact was high and that the pandemic could reveal stress and anxiety in cancer patients [5].e.g. overwhelming psychological pressure from COVID-19 was found to be the predominant risk factor for mental issue problems in patients with cancer [5]. Similarly, the stressful life events associated with the pandemic was positively correlated with anxiety, stress and depression, and difficulties in emotion regulation. Moreover, stressful life events associated with the pandemic and the goals sub-dimension of DERS was predicted high PTSD severity. In other words, the increased distress of the patients with the pandemic and the increased difficulty in engaging in goal directed cognition and behavior when the patient distressed seem to increase the risk of possible PTSD in cancer patients during the pandemic.

In the regression analysis of this study, adverse childhood experiences were found to be predictive only for the severity of depressive symptoms. It has been determined that negative childhood experiences can change the way traumatic events in adulthood are experienced [26]. Exposure of children's developing brains to stress can result in permanent impairment of multiple neurological structures and functions and psychological vulnerability [27]. This biological change may have resulted in an increased vulnerability to subsequent pandemic stress as well as the development of depression.

It was determined that social support received from the family predicted low anxiety while the goals sub-dimension of DERS was predicted high anxiety. Social relations at every stage of life maintain its importance[28]. Especially in this pandemic period, individuals who can provide social support have been limited due to quarantines, and the family has come to the fore. And the expected result showed that family support can be protective against anxiety during the pandemic.

It was found that goals and clarity sub-dimension of DERS was predicted high stress severity in patients with cancer during the pandemic. These subscales can be interpreted as: increased difficulty in engaging in goal directed cognition and behavior when the patient distressed and lack of emotional clarity seem to increase stress. Considering the relationship between difficulty in emotion regulation and the risk of PTSD and stress, emotion regulation should be an issue that must be addressed during therapies.

In a study conducted with breast cancer patients by Massicotte et.al., it was revealed that cancer patients experience a significant number of stressors related to the COVID-19 pandemic, mostly associated with increased psychological symptoms including higher levels of anxiety, depressive symptoms, insomnia, and fear of cancer recurrence [29]. They also emphasized that their study data had relevancy with the vulnerability of cancer patients toward experiencing a significantly higher level of psychological distress during pandemic periods and with the need to increase access to relevant professional psychosocial support opportunities [29].On the other hand, this study did not delve into the origins of the factors that cause this incerased stress and lack a comparison with the underlying factors. In another study, in July 2020 Wang and his colleagues made a significant contribution to the literature regarding the epidemiology of mental health problems among patients with cancer during COVID-19 pandemic. This article was distinct in its approach due to two significant developmental dimensions, and the first one highlights the central role of pandemic-related data. This approach is likely to contribute to a comprehensive understanding of the situation by integrating various epidemiological factors complicating both the cancer disease itsel and the preferred treatment modalities [30]. Both this study and the later one conducted by Tsamakis et.al. appeared to uncover a notable prevalence of mental health problems among cancer patients and mentioned that the ongoing pandemic has contributed to increased challenges and mental health concerns for cancer patients [30, 31]. These findings underscore the importance of addressing mental health issues in the context of cancer care, particularly considering the additional stressors posed by the COVID-19 pandemic.

One of the most important outcomes of our study is the difference in terms of previously described significant effect of adverse childhood experiences on psychosocial problems in cancer patients during the covid 19 pandemic. In a recently published article, Montague et al. reported that a noteworthy connection between cancer patients and Adverse Childhood Experiences (ACEs). The statement emphasizes the importance of adopting a trauma-informed care approach during the treatment of cancer patients who have a history of ACEs [32]. Likewise, in several studies conducted on various types of cancer patients, including lung, colorectal and cervical cancer, ACEs were reported as one of the main stressors in mental health problems encountered during especiallt chemotherapy period and posed also an important negative impact on healing period both physically and mentally [30-34]. On the other hand, our study revealed that in a stressfull life time period like COVID-19 pandemic, stressor factors conducting the mental health course may show manifest modifications. We found that within all four parameters that we had evaluated, PTSD, anxiety, depression and stress, effective in determining mental health and psychosocial status of cancer patients, difficulties engaging in goal-directed behaviour and limitation access to emotion regulation strategies are the main factors predicting the overall

scene. Childhood adversities were an important factor in depressive disorders of cancer patients but emotion regulation difficulties and lack of support refers to problems that make psychosocial recovery difficult or impossible to occur during the difficult time periods like pandemics. Psychosocial recovery especially in oncological patient population, involves addressing not only the physical aspects of well-being but also the psychological and social dimensions. Recognizing and managing emotions, especially in the face of difficulties, is integral to this process. Adequate support, whether from friends, family, or mental health professionals, plays a crucial role in helping individuals navigate and overcome these challenges.

Another interesting outcome of the present study is the emphasis on the relationship between childhood traumas and depression during the pandemic, but while there is a significant positive correlation between childhood traumas and depression, these traumas are ranked at the bottom of the list of risk factors during the pandemic period. This finding implies that, despite the correlation between childhood traumas and depression, other factors may have a more pronounced impact on mental health during the pandemic. Identifying and understanding the various risk factors can contribute to a more nuanced comprehension of the complex interplay between past traumas and current mental health outcomes, especially in the context of challenging situations like a pandemic.

5. Conclusion

This study put forth the importance of the childhood adversities, emotion regulation difficulties, and social support especially from the families for the patients with cancer during the pandemic to prevent them from negative outcomes. Emotion regulation strategies should be used in therapies for patients with cancer to protect them from PTSD. Considering the mental health of cancer patients under pandemic conditions, negative childhood experiences of cancer patients should also be taken into account during psychiatric interviews. It is recommended to provide psychological support to increase the communication within the family and the social support received from the family.

Limitations of the Study

The first limitation of this study is the absence of a control group. Due to the cross-sectional nature of the study, we analyzed psychosocial effects of COVID-19 pandemic on a specialized group of patients treated for any type of cancer at a time period when the pandemic was at its highest level and in one of the regions where it was most active. The second limitation is that the questionnaires are self-assessment and the psychopathologies could not be directly detected through a structured interview. Finally, this study's data had not been strengthened by a COVID-19 stressor questionnaire, since there was no Turkish validation of such questionnaires at the time period when the study was conducted.

ACE (Adverse Childhood Experiences) and LEC-5 (Life Events Checklist for DSM-5) are tools used to assess different life events and childhood traumas. Although they examine interrelated psychological dimensions, they cover different constructs and focus areas. Therefore, their simultaneous use in the analysis of the same group in a study does not inherently lead to multicollinearity issues. However, interpreting these tests together during the COVID-19 period may indeed pose challenges due to the unique circumstances of the pandemic. The unprecedented stressors and traumatic experiences associated with the COVID-19 period may complicate the interpretation of results from the ACE and LEC-5 assessments. This is one of the limiting factors of our study.

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None.

Conflict of Interests

The authors declare that they have no competing interest.

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Author Contributions

Conceived and designed the experiments; EK. Analyzed and interpreted the data; ES. Contributed reagents, materials, analysis tools or data; EK, OS, MS, ACK. Wrote the paper; EK. Study of biostatistics; ES. Review and editing: ACK.

Ethical Approval

This study was approved by the ethics committee of Istanbul Bağcılar Training and Research Hospital with reference number 2020.07.1.02.095 and was conducted in accordance with the Declaration of Helsinki

Data sharing statement

All data relevant to the study are included in the article.

Consent to participate

Consent for the study was obtained from all participants for the study.

Informed Statement

The patient who agreed to participate in the study signed the informed consent form.

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The Toxic Effects of Flutamide vs. Bicalutamide vs. Cyproterone Acetate on the Testis: An Experimental Rat Study

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Abstract: The aim of this study was to investigate the toxic effects on the rat testis of flutamide, bicalutamide, and cyproterone acetate using histopathological methods. Twenty-four male Sprague-Dawley rats were randomly divided into four groups, control (Group 1), flutamide (Group 2), bicalutamide (Group 3), and cyproterone acetate (Group 4). Physiological saline solution or anti-androgens were administered via oral gavage for 14 days. At the end of the study, the testes were harvested for histological toxic effect scoring. The mean histopathology scores were 0 in Group 1, 0.33±0.81 in Group 2, 1.66±1.36 in Group 3, and 2.93±0.98 in Group 4. The histopathology score in Group 4 was significantly higher than that in Group 1 (p=0.002), but was not significantly different to those in groups 2 and 3 (p=0.317 and p=0.028, respectively). No significant difference was also observed between the other groups. Cyproterone acetate, a steroidal antiandrogen, resulted in significant impairment of testis histology relative to the non-steroidal antiandrogens flutamide and bicalutamide. A non-steroidal agent such as flutamide or bicalutamide should therefore be selected if antiandrogen therapy is to be initiated for reasons such as acne, hirsutism, and paraphilias, particularly in young males. ©2024 NTMS.

Keywords: Flutamide; Bicalutamide; Cyproterone Acetate; Testis; Histopathology.

1. Introduction

Antiandrogens are agents that bind to intracellular androgen receptors. They compete with both dihydrotestosterone and testosterone at the receptor level in the cell nucleus, thus obviating the effects of endogenous androgens on target tissues including the testes, hair follicles, hypothalamus, pituitary and prostate glands, and ovaries. They are employed to treat a range of hyperandrogenic states, such as acne,

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hirsutism, and paraphilias, although their principal use is in the treatment of prostate cancer [1]. Anti-androgens are classified as steroidal (such as cyproterone acetate, medroxyprogesterone acetate, and megestrol acetate) and non-steroidal (including nilutamide, bicalutamide, and flutamide). Members of both classes compete with androgens at the receptor level, and non-steroidal anti-androgens are limited to this. However, steroidal anti-androgens also exhibit progestational characteristics by crossing the blood-brain barrier, resulting in central inhibition of the pituitary gland. Non-steroidal anti-androgens therefore do not reduce testosterone levels, which remain either normal or else mildly elevated [2].

The onset and progression of prostate cancers seem to be linked to the aberrant activation of androgen signaling. The activation of such signaling has been shown to exhibit a positive effect on prostate cancer cell growth both in vitro and in vivo [3]. Because of androgens on prostate cancer, anti-androgens have long been used in treatment. Cyproterone acetate, flutamide, and bicalutamide were approved for use in the treatment of prostate cancer by the Food and Drug Administration in 1989, 1989, and 1996, respectively [4]. The European Association of Urology guideline currently recommends the use of anti-androgens in the treatment of prostate cancer to prevent the 'flare-up' phenomenon or for maximum androgen deviation therapy [2]. However, anti-androgens have a number of toxic effects on the body. The principal pharmacological effects of steroidal anti-androgens occur secondary to castration (gynecomastia is unusual), while their non-pharmacological side-effects involve cardiovascular toxicity (4–40% for cyproterone acetate). The principal reported pharmacological side-effects of non-steroidal anti-androgens are gynecomastia (70%) and breast pain (68%) [2].

Androgen signaling is also of crucial importance to the development and preservation of the male reproductive organs and to pathological events concerning these [3,5,6]. Moderate androgen signaling is also essential for normal testis development and function [5]. Anti-androgen drugs exhibit adverse effects on spermatogenesis and toxic effects on testis tissue [1,7]. No direct comparisons have been performed between the anti-androgens in terms of toxic effects on the testes. The present study was intended to determine the toxic effect of anti-androgens on the testis tissue using histopathological methods.

2. Material and Methods

2.1. Animals

The experimental protocol employed in this study was approved by the Karadeniz Technical University Animal Care and Ethics Committee (no. 2009/15-2). Twenty-four Sprague-Dawley male rats aged 9-12 weeks were obtained from the Karadeniz Experimental Animals Laboratory (Trabzon, Türkiye). These were housed in individual cages in a specific-pathogen-free environment at 22±1˚C, at a relative humidity of 40-70%, and in a 12 h/12 h light/dark cycle. Ad libitum access was permitted to food and water.

2.2. Experimental Design

Following a seven-day adaptation period, the 24 male rats were randomly and equally assigned into control, and three experimental groups (n = 6) as follows:

Group 1 (Control): Physiological saline solution was administered via oral gavage for 14 days.

Group 2 (Flutamide): Flutamide dissolved in physiological saline solution was administered via oral gavage at a dose of 50 mg kg^{-1} day^{-1} for 14 days as recommended by Wang et al. [8].

Group 3 (Bicalutamide): Bicalutamide dissolved in physiological saline solution was administered via oral gavage at a dose of 25 mg kg^{-1} day^{-1} for 14 days as recommended by Singh et al. [9].

Group 4 (Cyproterone acetate): Cyproterone acetate dissolved in physiological saline solution was administered via oral gavage at a dose of 25 mg kg^{-1} day^{-1} for 14 days as recommended by Gual et al. [10].

Fifteen days after the commencement of the experiment, all rats were fasted for six hours before being anesthetized via intramuscular injection of 60 mg kg^{-1} ketamine hydrochloride. The abdominal region was first shaved and sterilized using povidone iodine solution. A 3-cm midline incision was then made (Figure 1), and the abdominal viscera were extended upward to reveal the bladder. This was then pulled upward, and the prostate and bilateral seminal vesicles were located and excised. The testes were delivered through the inguinal canal, and bilateral orchiectomy was performed. The rats were finally euthanized with a lethal intraperitoneal dose of ketamine.

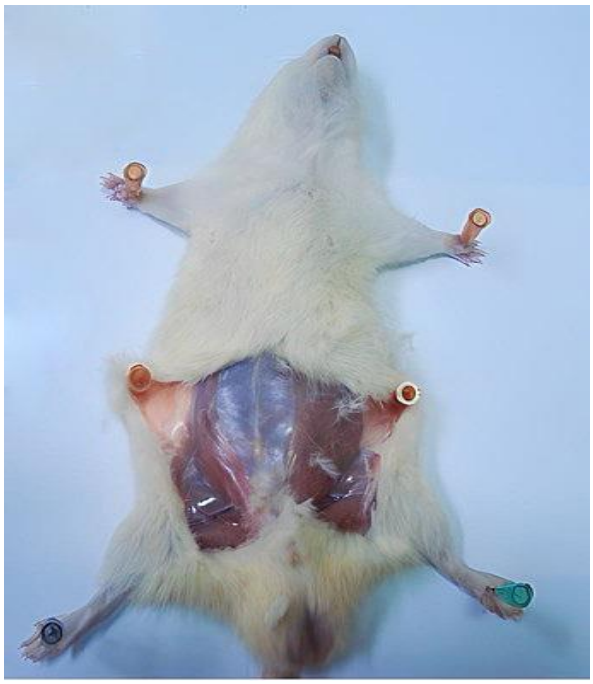

Figure 1: Surgical incision of the rat under general anesthesia for the removal of male reproductive organs.

2.3. Macroscopic evaluation

The isolated organs were weighed using sensitive scales before being placed into the solutions.

2.4. Histopathological examination

The extracted testes were fixed in formalin, and sections from the upper, middle and lower parts were embedded in paraffin. Multiple three-micrometer sections were cut and stained with hematoxylin/eosin (H&E). Evaluation of the effects on the testes of the three distinct anti-androgen drugs was based on the criteria specified by Dianne M. Creasy, and pathologies observed in testis tissues were scored accordingly [11].

This scoring system is employed to show the toxic effect on the testis of a drug, chemical, or herbal agent:

Score 0: Normal.

Score 1: Spermatid retention emerging with chemicals or hormonal disturbance.

Score 2: Missing germ cell layers in seminiferous tubules.

Score 3: The presence of multinucleate giant cells formed from cell cytoskeletal disintegration and cytoplasm fusion due to a slow degenerative process

Score 4: Impairment of the spermatogenic cycle due to the slow degenerative process and sloughing of spermatogenic cells into the lumen.

Score 5: Increased interstitial space volume associated with seminiferous tubule cell loss [11].

A minimum of 10 high-power fields (magnification, x200) were examined per section for each sample.

2.5. Statistical analysis

All statistical analyses were performed on computerized software (IBM SPSS version 25, Chicago, IL, USA). Data are presented as mean±standard deviation at a significance level of 0.05. Differences were analyzed using the Kruskal Wallis-H test. The Bonferroni-corrected Mann-Whitney U test was employed to identify the source of significance in variables identified as significant.

3. Results

The mean weight of the 24 rats was 293±19.17 g. The mean weight of the right testis was 1.37±0.32 g, the mean weight of the left testis was 1.36±0.34 g, the mean weight of the prostate was 0.73±0.26 g, and the mean weight of the bilateral seminal vesicles was 0.68±0.25 g. The mean weights of the rats were 299.33±25.1 g in Group 1, 293.66±22.5 g in Group 2, 291.83±20.1 g in Group 3, and 294.16±12.1 g in Group 4 (p=0.980). No differences were found in terms of right testis, left testis, prostate, or seminal vesicle weights. The groups' weight data are shown in Table 1.

No pathological findings were observed in Group 1 (control). Figure 2 shows the histological image of normal testicular tissue in the control group. The most severe pathological change in Group 2 (flutamide) was missing germ cell layers in the seminiferous tubules. The worst pathological change in Group 3 (bicalutamide) was the presence of multinucleate giant cells, while that in Group 4 (cyproterone acetate) was sloughing of spermatogenic cells into the lumen (Figure 3). An increased interstitial space volume, the worst pathological finding of the scoring system used, was not encountered in any rat.

Mean score values were 0 in Group 1 (control), 0.33±0.81 in Group 2 (flutamide), 1.66±1.36 in Group 3 (bicalutamide), and 2.93±0.98 in Group 4 (cyproterone acetate). The elevation in Group 4 was significant compared to Group 1 (p=0.002), but not compared to groups 2 (flutamide) or 3 (bicalutamide) (p=0.317 and p=0.028, respectively). No significant difference was observed between groups 2 and 3 (p=0.071). The groups' histological scores are shown in Table 2.

Table 1: Rat and organ weights.

Weight (gram)	Group 1 (Control)	Group 2 (Flutamide)	Group 3 (Bicalutamide)	Group 4 (Cyproterone)	p*
Rat	299.33 ± 25.1	293.66 ± 22.5	291.83 ± 20.1	294.16 ± 12.1	0.980
Right testis	1.35 ± 0.42	1.49 ± 0.35	1.23 ± 0.37	1.43 ± 0.42	0.436
Left testis	1.37 ± 0.45	1.5 ± 0.3	1.13 ± 0.39	1.44 ± 0.53	0.288
Prostate	0.88 ± 0.3	0.81 ± 0.19	0.5 ± 0.16	0.73 ± 0.23	0.085
Seminal vesicle	0.75 ± 0.25	0.67 ± 0.16	0.51 ± 0.15	0.78 ± 0.35	0.196

*Kruskal Wallis-H Test.

Table 2: Mean histopathological scores in groups.

Histology	Group 1 (Control)	Group 2 (Flutamide)	Group 3 (Bicalutamide)	Group 4 (Cyproterone)	p*
Mean score	0	0.33 ± 0.81	1.66 ± 1.36	2.93 ± 0.98[#]	0.002

*Kruskal Wallis-H Test, [#]significantly different from the Control group (p=0.002).

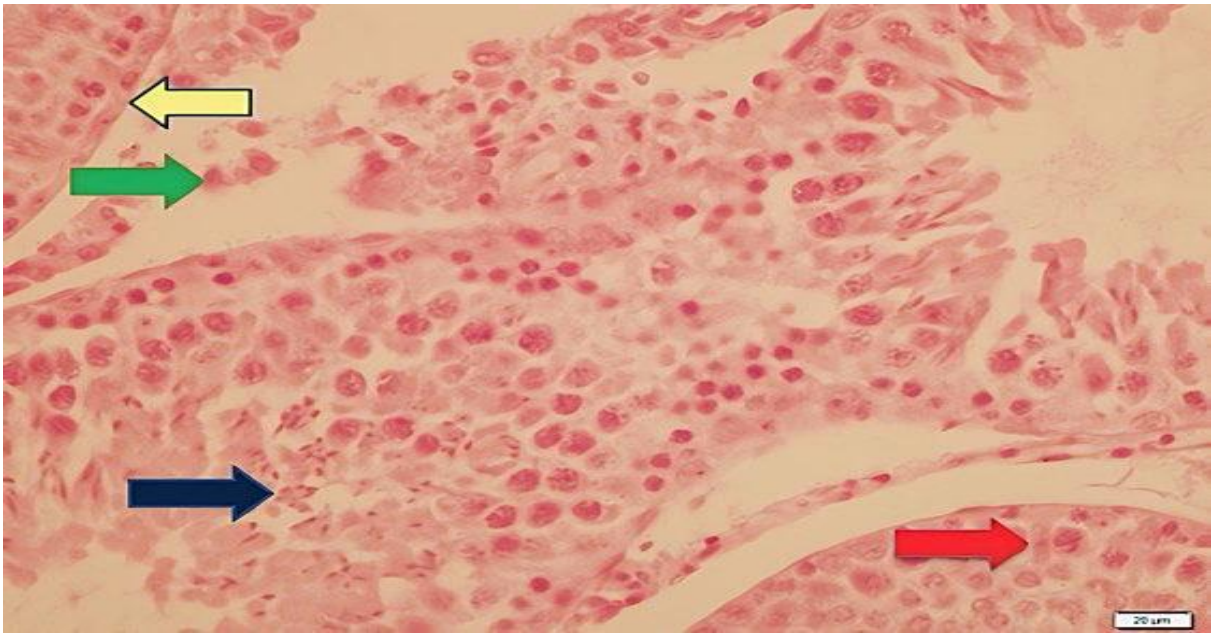

Figure 2: Normal histological findings of rat testis (yellow arrow, basement membrane; green arrow, Leydig cell; blue arrow, spermatocyte; red arrow, Sertoli cell) (x40).

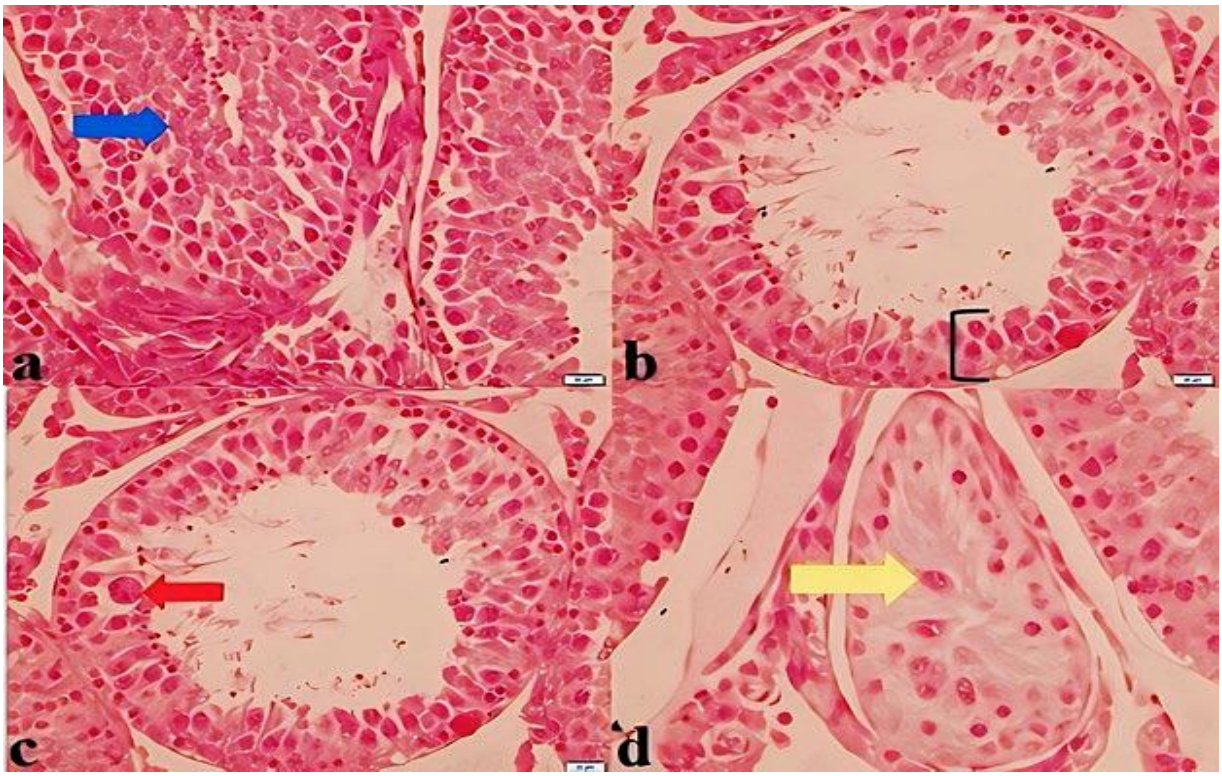

Figure 3: Different morphological changes scored by the pathologist with Hematoxylin-Eosin stain (a: blue arrow, retained spermatid; b: **(**, missing germ cell layers; c: red arrow, multinucleate giant cells; d: yellow arrow, sloughing of spermatogenic cells into the lumen)(x40).

4. Discussion

This study involved a histopathological investigation of the effects of steroid (cyproterone acetate) and non-steroid (flutamide and bicalutamide) anti-androgens on normal testis tissue. The non-steroidal antiandrogens flutamide and bicalutamide had no toxic effect on testis tissue compared with the control group, while cyproterone acetate exhibited a significant toxic effect. Although anti-androgen agents are mainly employed in the treatment of prostate cancer, they are also used in acne, hirsutism, paraphilias and coronavirus-related respiratory diseases [1, 2, 12]. Chemically, antiandrogens are classified as either steroidal (such as cyproterone acetate, medroxyprogesterone acetate, and megestrol acetate) or non-steroidal (including nilutamide, bicalutamide, and flutamide). In addition, anti-androgens are also currently classified as older generation androgen receptor antagonists (non-steroidal and steroidal) and second generation androgen receptor antagonists (enzalutamide, darolutamide, and apalutamide) [2, 13]. Second generation androgen receptor antagonists are currently used in the treatment of prostate cancer, while the European Association of Urology recommends the use of older generation androgen receptor antagonists to prevent the 'flare-up' phenomenon and for maximum androgen deviation therapy [2].

Histopathological examination of testis tissues in the present study revealed no damage in the control group, while the most severe injury was in Group 4 (cyproterone acetate). The seminiferous tubules from the control group rats exhibited a normal histological structure with well-developed spermatozoa in the lumens. The administration of cyproterone acetate resulted in an alteration of the histological testis structure, such as the appearance of retained spermatids in seminiferous tubules and missing germ cell layers of seminiferous tubules into their lumens, which in turn led to a decreased germinal epithelium thickness. In the seminiferous tubules, multinucleate giant cells formed as a result of cell cytoskeletal disintegration and cytoplasm fusion, and spermatogenic cells resulting from the separation of spermatids and disruption of the spermatogenic cycle in their lumen were observed to slough into the lumen and accumulate. Group 2 (flutamide) and Group 3 (bicalutamide) exhibited no significant histopathological difference relative to the control group. The most severe injury caused by flutamide was the observation of missing germ cell layers in the seminiferous tubules. The damage caused by bicalutamide involved the presence of multinucleate giant cells in seminiferous tubules. An experimental rat study involving cyproterone acetate reported that this agent resulted in degeneration of germ cell layers and decreased seminiferous tubular diameters and significant testis damage [14]. An experimental rat study involving bicalutamide reported the appearance of vacuoles and sloughing of germ cells from the germinal layer of seminiferous tubules into their lumens, resulting in a decreased germinal epithelium thickness. Spermatid detachment and accumulation of desquamated spermatocytes together with spermatids and cellular debris were observed in the seminiferous tubule lumens following administration of bicalutamide [15]. Anahara et al. summarized the effects of flutamide on the mouse testis in their mini-review, and concluded that it resulted in structural changes in the spermatid acrosome and nuclei, and increased the numbers of abnormal spermatids, but caused no significant injury to Sertoli cells, Leydig cells, germ cells, or ectoplasmic specialization [7]. In the present study, the agent with the least toxic effect on testis tissue was flutamide, with a mean score of 0.33±0.81. From that perspective, the current research was consistent with Anahara et al.

A general examination of the literature shows that flutamide, bicalutamide, and cyproterone acetate all exhibit histopathological toxic effects on the rat testis [7, 14-17]. These three agents also exhibited toxic effects on the testis in the present study, the most severe injury being observed with cyproterone acetate and the mildest with flutamide. However, a comparison of the three agents revealed no significant difference between them in terms of toxic damage. Our search of the literature revealed no previous studies comparing the toxic effects of flutamide, bicalutamide, and cyproterone acetate on normal testis tissue using histopathological methods. The fact that our research is one of the first studies to investigate the toxic effects of these three anti-androgens on the rat testis in terms of histopathology therefore represents one of its particular strengths.

No difference was determined among the groups in terms of bilateral testis weights. The greatest toxic effect in this study was exhibited by cyproterone acetate. A decrease in testis weight might therefore have been anticipated in the cyproterone acetate group. In terms of testis weights, however, there was no difference between the cyproterone acetate and either the control group or the other study groups. Similarly, to the present study, Aleem et al. also found that cyproterone acetate had no effect on testis weights [16]. A previous study examining the effect of daily treatment with flutamide on testicular function in adult male rats observed no effect on testicular weights [17]. Macleod et al. reported no effect on testis weights calculated in early puberty in male rats exposed to flutamide in utero [18]. In contrast, other studies involving bicalutamide and flutamide have reported that both agents significantly reduced testis weights [15, 19, 20]. However, it should be remembered that the treatment period in the present study was 14 days, compared to 28 days in the majority of these studies.

In this study, the prostate gland and bilateral seminal vesicles were excised, weighed using sensitive scales, and compared between the groups. Unfortunately, due to technical deficiencies, prostate and seminal vesicle tissues could not be subjected to advanced histopathological examination. Only prostate and bilateral seminal vesicle weights were compared

between the groups, and no significant differences were observed (p=0.085 and p=0.196, respectively). No similar previous studies have compared prostate and seminal vesicle weights. However, in a study performed at the histopathological level, Elzoghby at al. showed that flutamide significantly reduced hyperplasic and dysplastic lesions in prostate tissue [21]. Sarrabay et al. investigated the effects of different doses of flutamide on prostate and seminal vesicle tissues, and reported that flutamide causes atrophy in the prostate and also the seminal vesicle beginning from a dosage of 1 mg kg^{-1} day^{-1} [22]. A study of bicalutamide in the rat prostate reported that this agent increased apoptosis in prostate cell lines [23]. A study performed with cyproterone acetate showed that this resulted in glandular atrophy in prostate tissue [24]. An experimental rat study showed that all three anti-androgens caused atrophy and apoptosis in prostate tissue. A decreased weight in these organs may therefore be expected under these conditions. However, no differences were observed between the groups in terms of organ weights in the present study. This may be attributable to our relatively short treatment period (14 days). Similarly, to our hypothesis, Anahara et al. also stated that they believed that flutamide reduced prostate weight in mini-review, but were unable to demonstrate this in an objective manner [7].

5. Conclusion

The primary aim of this study was to investigate the effects of different anti-androgens on testis tissue. The results showed that the steroidal anti-androgen cyproterone acetate exhibited toxic effects on testis tissue relative to the control group. However, the non-steroidal anti-androgens flutamide and bicalutamide had no toxic effects on testis tissue. We therefore think a non-steroidal agent such as flutamide and bicalutamide will represent an appropriate option, especially in young men, if anti-androgen therapy is to be initiated for reasons such as acne, hirsutism, and paraphilias.

Limitations of the Study

This study has a number of limitations due to technical factors. Hormones such as luteinizing hormone, follicle-stimulating hormone, and testosterone could not be investigated in rat sera. In addition, stereological investigation aimed at a more detailed examination of toxic effects on testis tissue could not be performed. Semen analysis was also not carried out with the collection of semen samples from the cauda epididymis of sacrificed rats. Moreover, the tumoral effects of the anti-androgens on testis tissue could not be investigated. However, despite all these limitations and the fact that we were only able to perform histopathological examinations, we think that this study is valuable as experimental research into the effects of steroidal and non-steroidal anti-androgens on testis tissue.

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Conflict of Interests

The authors declare that there is no potential conflict of interest for the research, authorship, and/or publication of this article.

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Author Contributions

Conceived and designed the experiments; MG, ED, NIK, RO. Supervision; UC, RO. Data Collection and/or Processing; MG, ED, UC. Analyzed and interpreted the data; ED, EA, UC, NIK, MT. Literature Review; EA, NIK, MT. Writing; MG, EA, UC, RO. Critical Review; UC, MT, RO. Study of biostatistics; MT. All authors read and approved the final manuscript.

Ethical Approval

Karadeniz Technical University Animal Care and Ethics Committee approved by the study (no. 2009/15-2).

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None.

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Can Maximum, Mean or Minimum ADC Values of the Cervix-Parametrium Boundary Estimate Parametrial Invasion for Cervical Carcinoma?

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Abstract: Diffusion weighted imaging (DWI), which is quantified by apparent diffusion coefficient (ADC), can predict tissue microstructure. It has become an essential part of the gynecological magnetic resonance imaging (MRI) protocol. In our study it was aimed to evaluate the value of the maximum, mean, and minimum ADC values of the cervix-parametrium boundary to estimate parametrial invasion for cervix carcinoma. Totally 50 patients with cervical carcinoma, 18 of which had no parametrial invasion (48±11-year-old) and 32 had parametrial invasion (58±12-year-old) according to conventional T2 weighted imaging were enrolled. Maximum, mean, and minimum ADC values of cervix-parametrium boundary of primary tumors were statistically compared between the groups without and with parametrial invasion. The diagnostic performances of the maximum, mean and minimum ADC values were evaluated by ROC analysis in terms of estimating parametrial invasion. The mean maximum, mean and minimum ADC values were lower for the patients with parametrial invasion. However, only the minimum ADC values had statistically significant differences between the groups. ROC analysis showed an AUC value of 0.726 for minimum ADC in estimating parametrial invasion. A minimum ADC cut-off value of $0.553x10^{-3}$ mm^2/s had a sensitivity of 63%, specificity of 73%, negative predictive value of 52% and positive predictive value of 80% and accuracy of 66%. ADC values can be applied for the determination of parametrial invasion of cervical carcinoma. Lower minimum ADC values obtained from cervix-parametrium boundary of primary cervical carcinoma may help parametrial invasion. Especially positive predictive value of the cervix-parametrium boundary ADC is remarkable. ©2024 NTMS.

Keywords: Apparent Diffusion Coefficient; Cervix Carcinoma; Diffusion-Weighted Imaging; Magnetic Resonance Imaging; Parametrial Invasion.

1. Introduction

The staging of cervical carcinoma is determined by the revised International Federation of Gynecology and Obstetrics system (FIGO) [1]. This system incorporates multiple parameters, such as tumor size, degree of local invasion, and the existence of metastasis, in order to determine the stage of the disease [1, 2]. The involvement of the parametrium is a significant factor in determining the extent of the local spread, staging, prognosis, and treatment strategies of cervical carcinoma [3]. Parametrial invasion (PMI) is a term used

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to describe the infiltration of malignant cells into the parametrial tissues. The presence of a significant amount of lymphatic and vascular structures in the parametrium may explain the frequent association of PMI with carcinoma metastasis, recurrence, and decreased survival rate [4, 5].

Treatment options of cervical carcinoma include radical hysterectomy, primary or adjuvant chemotherapy, and radiotherapy. Cervical carcinoma patients with PMI were advised to be treated with primary chemoradiotherapy or undergo radical surgery involving the excision of the parametrium and adjuvant treatment [6]. Performing parametrectomy is not recommended in patients diagnosed with early-stage cervical carcinoma due to the increased risk of morbidity and mortality associated with complications [7]. Therefore, an accurate assessment of PMI is crucial to determine appropriate treatment. This emphasizes the significance of utilizing non-invasive techniques such as magnetic resonance imaging (MRI) to assess PMI.

T2-weighted imaging (T2-WI) has played a pivotal role in assessing cervical carcinoma stages due to its exceptional soft-tissue contrast, providing detailed anatomical information [8]. A preserved hypointense stromal rim on T2-WI is a specific finding indicating the absence of parametrial invasion, whereas focal or diffuse full-thickness disruption of the low T2 signal intensity of the cervical stromal ring is highly sensitive to parametrial invasion [9]. However, challenges emerge when dealing with larger tumors that disturb the stromal ring, or the hypointense ring is interrupted by non-tumorous tissue, such as edema. In such circumstances, it becomes hard to accurately identify parametrial invasion based solely on T2-WI, as it may be susceptible to creating false-positive findings [10]. Diffusion-weighted magnetic resonance imaging (DWI) has become a significant companion to conventional imaging techniques, providing functional information about tumor characteristics. DWI shows higher signal intensity and lower apparent diffusion coefficient (ADC) values in tumors compared to nearby normal tissue. This provides important insights on cellular density and the microstructure of the tissue [11, 12].

This study aims to investigate potential applications of DWI in evaluating PMI in cervical carcinoma. While previous studies have explored DWI in tumor detection, prognosis, and therapeutic response prediction, our research focuses on evaluating ADC values (minimum, mean, or maximum) at the cervix-parametrium boundary to determine the presence of PMI. We propose that integrating DWI into the diagnostic framework could significantly improve MRI accuracy in predicting PMI, offering valuable insights for clinical decision-making, particularly in avoiding unnecessary parametrectomy for low-risk patients in early-stage cervical carcinoma.

2. Material and Methods

The institutional review board obtained approval for this retrospective study and waived the need for informed consent.

2.1. Patient Cohort

We retrospectively reviewed our medical records and MRI scans between January 2017 and December 2021. A total of 102 patients diagnosed with cervical carcinoma were reviewed.

Exclusion criteria were as follows: (a) patients who received any chemoradiotherapy before MRI; (b) DWI sequence was not included in the MRI; (c) the presence of inadequate imaging, due to artifacts or distortion. Of the 102 patients, 6 were excluded due to insufficient MRI scans, and 46 were excluded due to a previous history of chemotherapy or radiotherapy for cervical carcinoma. Consequently, the study cohort consisted of 50 patients who had not received prior chemotherapy or radiotherapy and who had pelvic MRI scans including T2-WI and DWI. According to the T2-WI, 18 patients without parametrial invasion and 32 patients with parametrial invasion were included in the retrospective study (Fig 1).

2.2. Pelvic MRI Protocol

MR examinations were performed using a 3.0-Tesla MR scanner, equipped with a phased-array coil. In order to decrease the movement of the bowel, a dose of 20 mg of butyl scopolamine was administered before the examination. The vagina is filled with ultrasound gel if the patient can tolerate. The MRI protocol included T2-WI and DWI. Axial, sagittal, and coronal planes were obtained with a T2-weighted turbo spin-echo sequence. The axial and coronal images were oriented perpendicularly and parallel to the cervical axis, respectively. The imaging settings of T2-WI were TR/TE, 4,560–5,300/100 ms; intersection gap, 0.4 mm; matrix, 800 x 690. The DWI gradients were applied in axial and sagittal directions. The parameters for diffusion sequence were as follows: repetition time ms/echo time ms, 6800/98; FOV, 250x250 mm^2; matrix, 192x130; section thickness, 3.0 mm. Diffusion was measured with b values of 0 and 800 s/mm^2, and ADC maps were automatically created by the software.

2.3. Image Analysis and Measurement

All images were evaluated by one radiologist (ADK) with 21 years of experience in pelvic MRI. To reduce bias, the radiologist was blind to the clinical findings and histological results for each patient. The DWI and T2-WI were evaluated together on a Picture Archiving and Communication System (PACS) workstation, using the anatomical features of T2-WI. The automatic cursor placement function of the PACS workstation was utilized to facilitate the synchronization of corresponding locations on T2-WI and DWI.

The diagnostic criterion for cervical carcinoma on T2-

WI alone was a focal cervical lesion of high signal intensity compared with normal uterine myometrium. PMI on T2-WI was considered present if the cervical stromal ring was disrupted with nodular or irregular tumor signal intensity extending to the parametrium.

To determine the ADC values of the cervical tumor with or without PMI, a circular or ellipsoid region of interest (ROI) was manually placed on the ADC map (Fig 2). ROI was delineated on the ADC map to cover the largest possible extent of the primary tumor closest to the parametrial border. This was done on the slice that displayed the greatest visible size of the tumor, as determined by the anatomical features observed on T2-WI. ROIs were chosen to specifically exclude any cystic or necrotic changes within the tumors. In cases showing parametrial invasion on T2-WI, measurement was made from the point closest to the parametrium at the invasive border. The ADC values were measured twice, and the average of the two measurements was calculated to minimize error. Maximum (ADC-max), mean (ADC-mean) and minimum (ADC-min) values were recorded.

2.4. Statistical Analysis

The statistical calculations were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY). The patients were classified into two groups based on the presence of PMI, as evaluated by T2-WI. Distribution was determined by the Kolmogorov-Smirnov test. Maximum, mean, and minimum ADC values of the tumors were compared by independent samples t-test between the patients without and with PMI. Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic performance, cut-off points for the prediction of PMI, and their sensitivity and specificity values. The significance level was set as 0.05.

3. Results

Of the 102 patients reviewed, 52 were excluded due to insufficient MRI scans and previous history of chemotherapy or radiotherapy for cervical carcinoma. Ultimately, a cohort of 50 cases diagnosed with cervical carcinoma, who had not received any previous chemotherapy or radiotherapy treatments and had completed pelvic MRI scans that contained T2WI and DWI, were included in the study. The retrospective study included 18 patients (48±11-year-old) without parametrial invasion and 32 patients (58±12-year-old) with parametrial invasion, as determined by the T2-WI. The patients with PMI had ADC-max of 1.16±0.22, ADC-mean of 0.72±0.19, and ADC-min of 0.48±0.13. Whereas the patients without PMI had ADC-max of 1.24±0.21, ADC-mean of 0.83±0.18, and ADC-min of 0.62±0.11. The patients with parametrial invasion showed lower maximum, mean, and minimum ADC values, with corresponding p-values of 0.709, 0.059, and 0.019, respectively (Table 1, Fig 3). Only the minimum ADC values were significantly different between the groups (p=0.019).

Table 1: Comparison of ADC values between the patients with and without parametrial invasion.

Variables *(10^{-3} mm²/s)*	**Parametrial invasion (+) (n=32)**	**Parametrial invasion (-) (n=18)**	***p* value**
ADC-max	1.16 ± 0.22	1.24 ± 0.21	0.709
ADC-mean	0.72 ± 0.19	0.83 ± 0.18	0.059
ADC-min	0.48 ± 0.13	0.62 ± 0.11	0.019

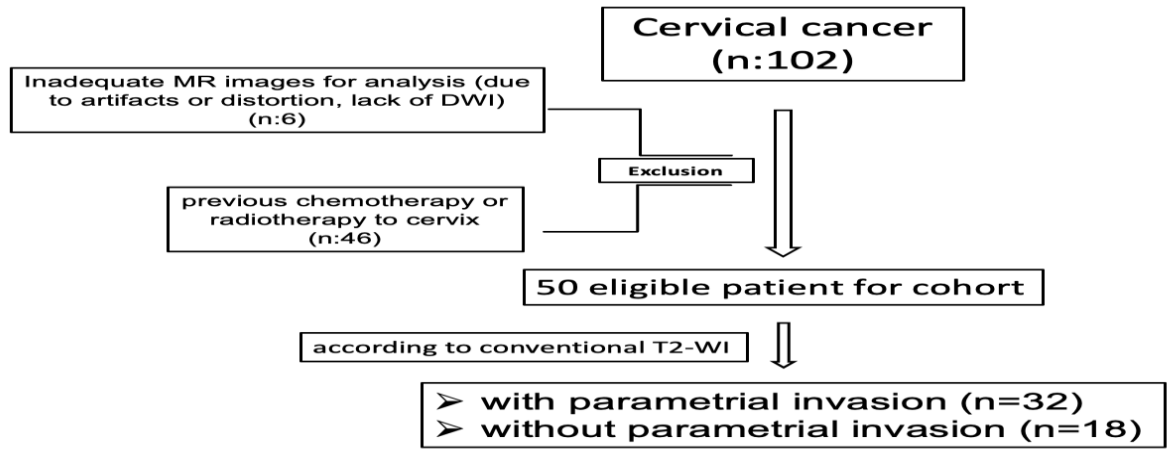

Figure 1: Flowchart of the study.

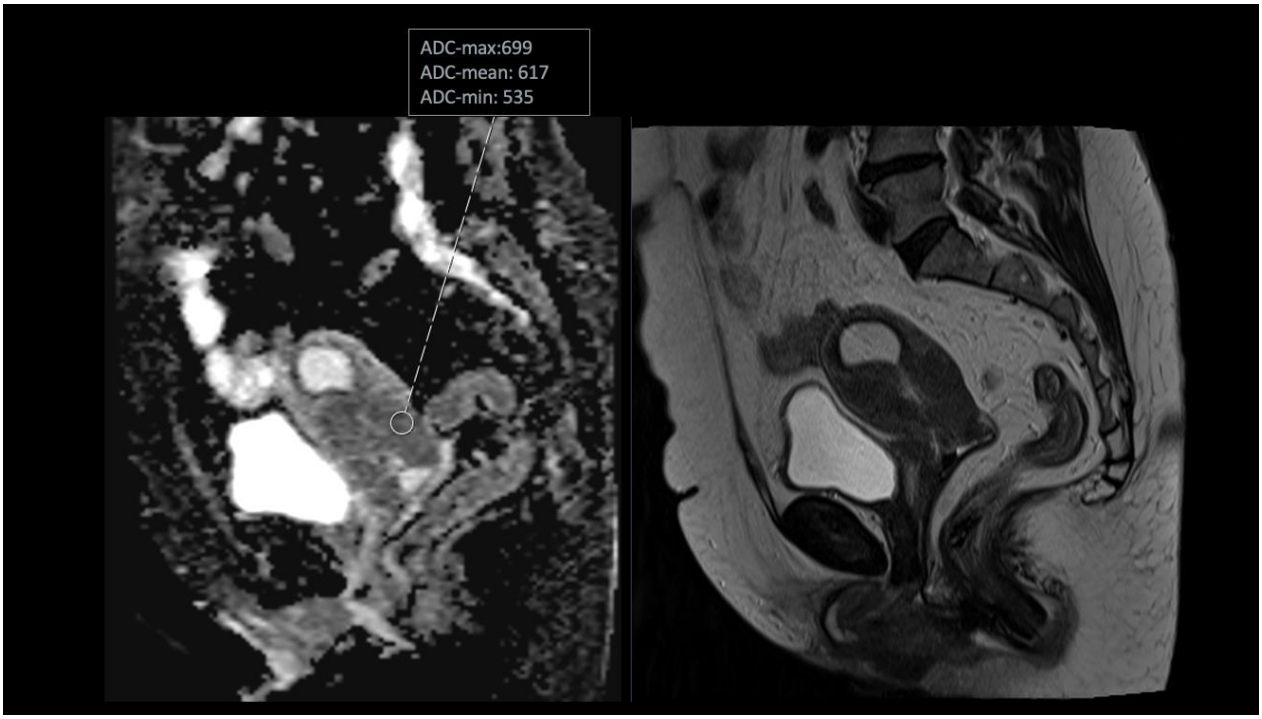

Figure 2: Placing ROI on ADC map and corresponding images on T2-WI.

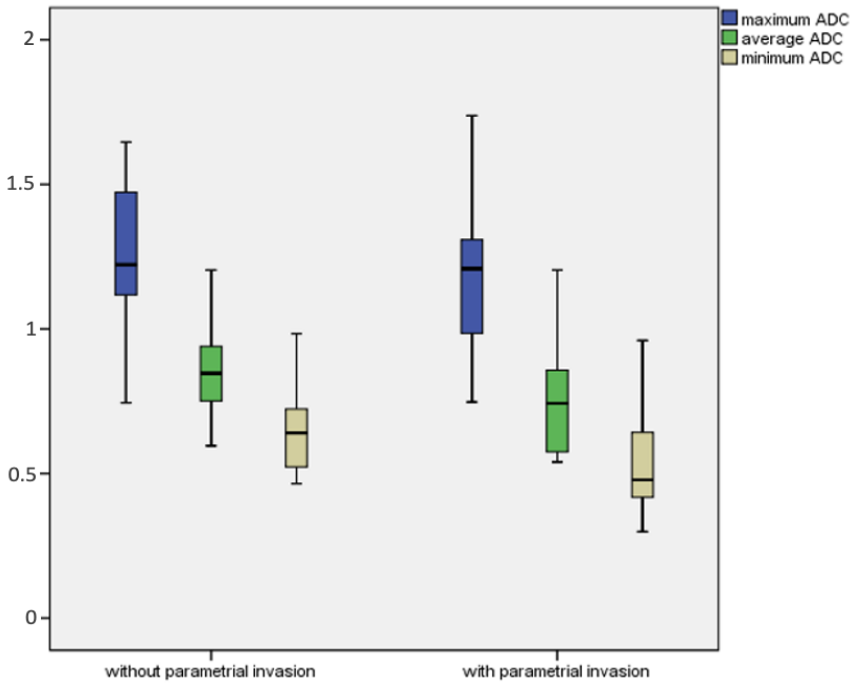

Figure 3: Comparison of the maximum, mean, and minimum ADC values between the patients with and without parametrial invasion.

The ROC analysis was applied to determine the optimal threshold of ADC-min values for determining PMI. Based on the ADC-min cut-off value of $0.553x10^{-3}$ mm^2/s, the sensitivity, specificity, negative predictive value, positive predictive value, and accuracy were calculated as follows: 63%, 73%, 52%, 80%, and 66% respectively. With this cut-off level, the area under the curve (AUC) value for estimating PMI with ADC-min was 0.726 (Fig 4).

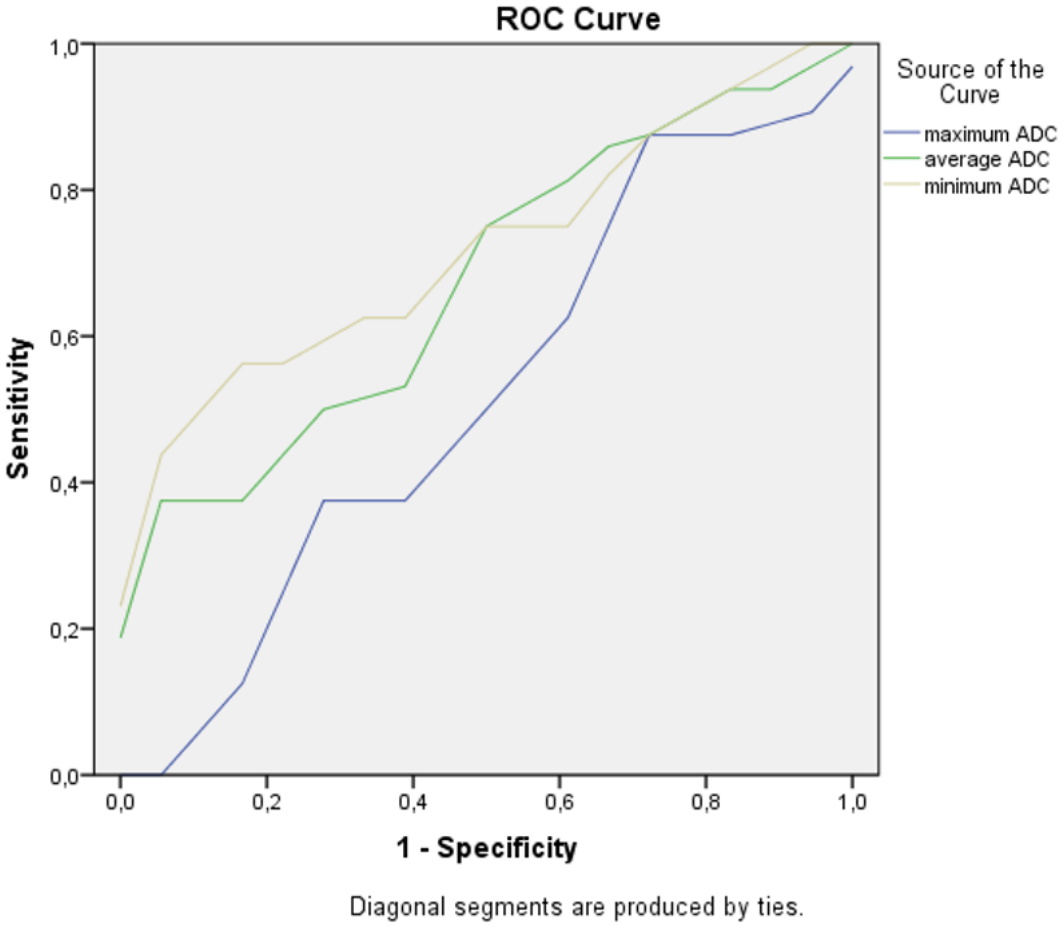

Figure 4: ROC analysis of maximum, mean, and minimum ADC values for the parametrial invasion.

4. Discussion

In our study, we aimed to compare the maximum, mean, and minimum ADC values obtained from the tumor-parametrium border in patients with cervical carcinoma to differentiate between patients with and without PMI. The present study demonstrated minimum ADC values obtained from the parametrium boundary of primary cervical carcinoma can potentially serve as an indicator of PMI. The especially positive predictive value of the ADC level obtained from the cervix-parametrium boundary is remarkable. The results indicate that the minimum ADC value could offer valuable additional information for evaluating the PMI, which may assist in determining appropriate treatment for patients diagnosed with early-stage cervical carcinoma.

It is crucial to make an accurate evaluation of parametrial invasion in order to determine which patients require chemoradiation therapy. If parametrial invasion is detected following surgery, it is recommended to have further chemoradiation to improve local control and survival [6]. However, this treatment approach is linked to increased morbidity and higher costs. The current study found an improvement in both negative and positive predictive values in assessing PMI with the utilization of minimal ADC values in imaging.

T2-WI is an MRI sequence that is utilized to rule out parametrial invasion in cervical carcinoma. The presence of a preserved cervical stromal rim with low signal intensity on T2-WI is a consistent MRI finding suggesting an intact parametrium [8, 9]. T2-WI has been shown to have a 97% accuracy rate for parametrial invasion [13]. Nevertheless, when a tumor extends through the entire thickness of the cervical stroma, it becomes challenging to assess whether parametrial invasion is present or not. In this case, the accuracy of T2-WI is restricted to 80% [14]. Also the presence of peritumoral edema or inflammation, which exhibits comparable high signal intensity to cervical carcinoma, frequently limits the accurate identification of the tumor boundary.

DWI is a technique used to observe to the three-dimensional microscopic movement of water molecules in both intra- and extracellular compartments. DWI visualizes the variability in water mobility due to changes in tissue cellularity, membrane integrity, and viscosity [15]. The presence of restricted diffusion can differentiate inflammation from malignancy. Several studies have documented the

efficacy of ADC in assessing the severity of cervical carcinoma or the prognosis of patients following treatment. Kuang et al. showed a significant statistical difference in the apparent diffusion coefficient (ADC) between well-/moderately differentiated tumors and poorly differentiated tumors [16]. Downey et al also found that the median ADC of cervical carcinoma was decreased in poorly differentiated tumors [17]. These results indicate that the ADC values of cervical malignancies may be associated with their aggressiveness, including PMI. Qu et al. reported a higher sensitivity specificity PPV accuracy and AUC values of the combination of T2-WI and ADC values in detecting parametrial invasion than T2-WI alone [18]. In this study, the minimum ADC values of cervical carcinoma in patients with PMI were significantly lower compared to those in patients without PMI. Our findings support prior studies.

In this study, the importance of ADC value in determining the PMI which has not been studied in the literature has been investigated. In our study, in patients with parametrial invasion, the ADC values obtained from the tumor-parametrium border were lower than those without invasion. In the field of invasion, tumoral infiltration leads to an increase in cellularity, resulting in a high ratio of nucleus to cytoplasm, the presence of intracellular organelles and macromolecules, and restricted diffusion of extracellular matrix. Patients with parametrial invasion demonstrated lower maximum, mean, and minimum ADC values obtained from the cervix-parametrium border. However, only the minimum ADC values exhibited a significant difference among the groups ($p<0.05$). This may indicate that the minimum ADC value is more strongly associated with the tumor stage.

5. Conclusion

In conclusion, cervical carcinoma patients with parametrial invasion have lower ADC values than patients without parametrial invasion. Especially minimum ADC values at the boundary of the parametrium in primary cervical carcinoma might potentially serve as a significant predictor of parametrial invasion in addition to T2-WI. The positive predictive value of the ADC levels derived from the cervix-parametrium boundary is particularly remarkable. These results suggest that minimum ADC values can provide valuable additional information for the assessment of PMI, which could be helpful in determining the most appropriate treatment strategies for patients diagnosed with early-stage cervical carcinoma.

Limitations of the Study

The most important limitations of this study were retrospective methodology and relatively small sample size. The sample size was limited due to the exclusion of patients with confirmed PMI who had undergone previous or concurrent therapies. These treatments are known to affect the MRI characteristics and histopathologic outcomes by causing tumor cell death. There is a need for further research on more patients with prospective design and pathological confirmation.

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Conflict of Interests

The authors declare that they have no conflict of interest.

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Author Contributions

Conception: MS, HÖA, ADK. Design: MS, HÖA, ADK. Supervision: ADK. Materials: MS. Data Collection and/or Processing: MS, HÖA. Analysis and Interpretation: HÖA, ADK. Literature Review: HÖA. Writing: MS, ADK. Critical Review: ADK.

Ethical Approval

The ethical guidelines were strictly adhered to and laid out in the Declaration of Helsinki by the World Medical Association. The study was sanctioned by the Koç University's ethics committee.

Data sharing statement

All data relevant to the study are included in the article.

Consent to participate

Consent for the study was obtained from all participants for the study.

Informed Statement

All the patients who agreed to participate in the study signed the informed consent form.

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Potential Beneficial Effects of Apelin-13 on Testicular Ischemia-Reperfusion Injury

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Abstract: Testicular ischemia-reperfusion (T I/R) injury leads to oxidative stress with excessive accumulation of reactive oxygen species in the tissue. This phenomenon has an essential place in the pathophysiology of testicular torsion injury. The presented study aimed to reveal the prophylactic beneficial effects of apelin 13 (APE-13) on T I/R damage. Twenty-four male Sprague Dawley rats were randomly divided into sham, I/R, 10µg/kg APE-13, and 100µg/kg APE-13 groups. I/R protocol and APE-13 application doses were applied in previous studies. At the end of the experiment, all rats were sacrificed, and their testicular tissues were quickly removed. It was stored under appropriate conditions until biochemical analysis was performed. In the biochemical analysis of the tissues, oxidative parameters and inflammatory cytokine levels increased, and antioxidant levels decreased in the testicular tissue due to I/R. On the other hand, these results changed significantly in the 10µg/kg and 100µg/kg APE-13 groups. Considering the presented data, the severity of T I/R-induced tissue damage was reduced when APE-13 was administered at doses of 10µg/kg and 100µg/kg. ©2024 NTMS.
Keywords: Apelin-13; Testis; Ischemia-Reperfusion.

1. Introduction

The clinical phenomenon defined as testicular torsion is the obstruction of blood flow to the testicles due to the twisting of the spermatic cord around its axis, insufficiency of metabolism, and deterioration of

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testicular function. Testicular torsion is a risk factor that can occur in all age groups but is more critical for newborns and young adults. Medical diagnosis should be made quickly, and surgical intervention should be performed as soon as possible to treat it [1, 2].

Testicular torsion and detorsion directly results in ischemia-reperfusion (I/R). In addition to causing infertility and testicular atrophy, I/R injuries can lead to fatal clinical events such as acute heart failure, acute myocardial infarction, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome and require urgent intervention [3-5]. Experimental and clinical studies have revealed that there is a significant relationship between male infertility and oxidative stress. This relationship is explained by the fact that free radicals produced intensively in the molecular processes of testicular torsion and I/R cause oxidative stress, causing damage to seminiferous tissues and resulting in sterility in men [4, 6]. Free radicals attack polyunsaturated fatty acids, cellular molecules, and DNA, causing intense lipid peroxidation. In this regard, the fact that spermatozoa have abundant polyunsaturated fatty acids causes them to be exposed to radical attacks and disrupt spermatogenesis [1, 7, 8]. Many researchers have experimentally tested drugs or agents with various pharmacological activities to alleviate or eliminate testicular I/R injury [1, 5, 8, 9]. Apelin, a peptide compound, is a pro-hormone with 77 amino acids and was first isolated from bovine stomach extract [10]. Various apelin isoforms, such as apelin-12, apelin-13, apelin-17, and apelin-36, are formed from preproapelin, a precursor protein containing 77 amino acids. [11]. Pyroglutamyl-apelin13 ([Pyr1] apelin-13), which is more resistant to enzymatic destruction, is formed from apelin-13 (APE-13) by posttranslational modification. Additionally, apelin and G-protein coupled apelin receptor APJ is expressed in various tissues containing the pancreas, brain, stomach, skeletal muscle, and heart and exerts various protective biological effects by inhibiting inflammation and attenuating apoptosis [12]. As a result of our extensive literature research, we could not find any study showing that APE-13 prophylactic application was tested in the T I/R model. Therefore, the presented study aimed to determine the possible beneficial effects of APE-13 application in alleviating T I/R damage.

2. Material and Methods

2.1. Experimental Procedure and Rats

The animals were obtained from Atatürk University Animal Experiments Research Center, and animal experiments were carried out at the same center. Additionally, ethical permissions for the study were obtained from Atatürk University Animal Experiments Local Ethics Committee (Date and number 30.03.2018/54). All experimental animals were kept under standard laboratory conditions (55% humidity, 25 degrees' temperature, 12/12 hours' dark/light cycle) and fed with standard pellet feed and tap water. The 24 Sprague Dawley male rats used in the study were weighed and randomly divided into four groups: sham, I/R, 10µg/kg APE-13, and 100µg/kg APE-13 groups. Since the sham group was the control group of this study, the I/R model or APE-13 doses weren't applied. Just to standardize the stress levels of animals in all groups, a median laparotomy incision of 1-2 cm in size was made and closed under anesthesia (ketamine/xylazine 60/10 mg/kg bw, intraperitoneally). in the sham group. Animals in the I/R group were anesthetized and fixed in a supine position, the incision area was cleaned with povidone-iodine solution, and a 1-2 cm incision was made. The spermatic cord was clamped by twisting at 720 degrees, thus initiating 2 hours of ischemia. At the end of the period, reperfusion was created by opening the clamp and re-blooding the testicles for 2 hours. The incision area was closed again. In the 10µg/kg APE-13 and 100µg/kg APE-13 groups, the experimental I/R model defined in the I/R group was created, and APE-13 was administered intraperitoneally to these groups at doses of 10 and 100 µg/kg 30 minutes before reperfusion. At the end of the experiments, the testicles were removed and stored under appropriate conditions until biochemical analysis. Notably, the experimental I/R model used in this study and the anesthesia, and the APE-13 doses used were chosen based on previous studies [2, 13, 14].

2.2. Biochemical Analysis

For biochemical analysis, myeloperoxidase (MPO) activity, malondialdehyde (MDA) level, and superoxide dismutase activity (SOD) in homogenized testicular tissues were studied according to the methods specified by Bradley et al., Sun et al., Ohkawa et al. [15-17]. These results were expressed as U/mg protein, nmol/g, and U/mg protein. Total antioxidant status (TAS), total oxidant status (TOS) values, Interleukin- 1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α) levels were measured using appropriate kits (Rel Assay Diagnosis and Elabscience, Wuhan, China). The oxidative stress index (OSI) calculation was expressed as the TOS/TAS ratio.

2.3. Statistical *Analysis*

SPSS 20 (SPSS Corporation, Chicago, IL, USA) statistical program was used for data analysis. The results were expressed as Mean±Standard Deviation (SD), and $p<0.05$ was considered statistically significant. One-way analysis of variance was used for statistical analysis, and the Tukey post hoc test was applied to determine the difference between groups.

3. Results

When the biochemical results announced in the presented study were evaluated for oxidative parameters, the OSI and TOS value, MDA level, and MPO activity increased dramatically in the I/R group compared to the sham group. It triggered an intense free radical production in the testicular tissue. In contrast, two doses of APE-13 were documented to reduce oxidative markers in the 10µg/kg APE-13 and

100µg/kg APE-13 groups compared to the I/R group. The results of the study's basic indicators of antioxidant defense showed that SOD activity and TAS levels were significantly reduced in the I/R group compared to the sham group. Also APE-13. It was observed that antioxidant defense in testicular tissue was supported depending on the application at doses of 10 and 100 µg/kg, and these parameters were increased in the 10 and 100 µg/kg APE-13 groups compared to the I/R group. In the evaluation of the levels of pro-inflammatory cytokines in this study, it was revealed that TNF-α and IL-1β levels increased critically in the I/R group compared to the sham group. Still, the cytokine levels decreased in the 10 and 100 µg/kg APE-13 groups (see Figure 1 and 2; Table 1).

Table 1: Comparison of TNF-α (pg/mg protein), and IL-1β (pg/mg protein) results of all groups.

	Mean	Standart Deviaton	Minimum	Maximum
TNF-α (pg/mg protein)				
Sham	23847.05	3744.80	18637.60	29834.20
T I/R	37750.80[a]	4572.82	28435.20	42156.60
10 µg/kg APE-13	2742802[b]	2824.40	22265.50	31178.60
100 µg/kg APE-13	24238.35[b]	3890.30	20367.60	30453.00
IL-1β (pg/mg protein)				
Sham	2652548	2356.75	23365.10	29895.80
T I/R	7280017[a]	4713.91	64356.10	78945.90
10 µg/kg APE-13	3770013[b]	6381.10	27785.50	47546.50
100 µg/kg APE-13	29473.01[b*]	2589.10	25567.40	32785.90

[a]p<0.001 comperative to Sham group, [b]p<0.001 comperative to T I/R. *p<0.001 comperative to 10 µg/kg APE-13 groups. Data are presented as Mean±SD.

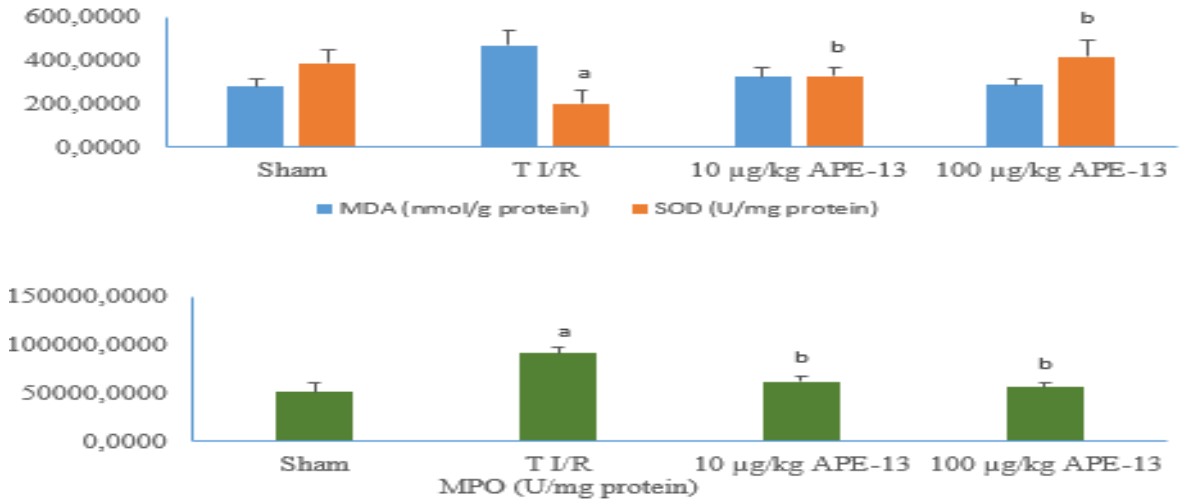

Figure 1: Comparison of MDA (nmol/g protein), SOD (U/mg protein) and MPO (U/mg protein) results of all groups. [a]p<0.001 comperative to Sham group, [b]p<0.001 comperative to T I/R. Data are presented as Mean ±SD.

4. Discussion

Current research reports that free radicals produced intensively during the I/R process directly cause testicular damage, apoptosis, and infertility [18]. The occurrence of consequences such as apoptosis, oxidative stress, and infertility varies in proportion to how long the blood flow of the testicular tissue is blocked and how fast the detorsion is made. The phenomenon of oxidative stress arises from the change in the balance between the amount of cellular oxidants and the cellular antioxidant defense system in favor of oxidants [19]. In this respect, it is critical to immediately restore the twisted testicles and apply drugs or agents that support antioxidant defense [2, 8, 9].

The primary marker of I/R-induced tissue damage is the MDA level. This marker describes lipid peroxidation, in which excessive amounts of free radicals produced in the tissue cause the peroxidation of cellular molecules [19]. As a result, oxidative stress and I/R damage are indicated by high MDA levels in the tissue. Antioxidants are defined as molecules that can prevent the oxidation of cellular molecules. Antioxidant compounds can scavenge free radicals, delay the lipid

peroxidation process, and protect the organism from radical damage. Moreover, they delay lipid peroxidation and the progression of many chronic diseases [19, 20]. Due to ischemia, various pro-inflammatory genes and transcription factors are upregulated in cells. In addition, the hypoxia-related decrease in ATP and glycogen content and the increase in testicular calcium ions (Ca^{2+}) are the critical points of testicular damage [21]. The increased cytokine production and adhesion molecule expression in the ischemic process by cells exposed to hypoxia/ischemia represents the main problem for direct reperfusion injury.

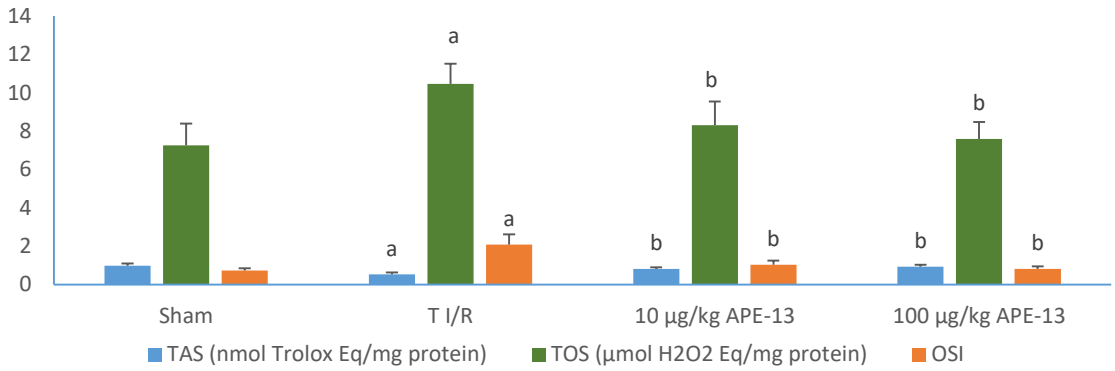

Figure 2: Comparison of TAS (nmol/Trolox Eq/mg protein), TOS (µmol H_2O_2 Eq/mg protein) and OSI levels of all groups. [a]p<0.001 comperative to Sham group, [b]p<0.001 comperative to T I/R goup. Data are presented as Mean±SD.

Moreover, the accumulation of neutrophils triggers an increase in MPO activities. Also, the accumulated neutrophils aggravate testicular damage by producing free radicals, TNF-α, and local inflammatory cytokines [22, 23]. Many studies on this subject have examined the effectiveness of different agents in alleviating T I/R-induced testicular tissue damage [7, 24]. In a few examples of studies on apelin-13, the experimental results of apelin-13 treatment provide valuable information. In one of the studies on I/R injury mitigation, Ape-13 inhibited excessive autophagy and apoptosis in cerebral ischemia/reperfusion injury [25]. Another study documented that Apelin-13 alleviates cerebral ischemia/reperfusion injury by regulating inflammation and the JAK2/STAT3 signaling pathway [14].

These studies also showed that apelin-13, TNFα, IL-1β, IL 6, and MDA levels were reduced, and the total antioxidant capacity level was increased in experimental cerebral ischemia models [14, 26]. In a study conducted on a different subject, it was reported that APE-13 suppresses the apoptotic pathway in cochlear damage caused by experimental noise exposure, reduces oxidative stress by increasing SOD activity, and thus improves cochlear damage [27]. In addition to these studies, APE-13 increased catalase activity in embryonic cardiomyocytes and decreased plasma lipid hydroperoxide levels, an essential oxidative stress finding [28]. These summarized studies showed that the severity of oxidative stress, inflammation, and apoptosis in the tissue decreased due to APE-13treatments. The findings presented in this study are compatible with the findings of various studies in the literature, and it has been proven in this study that APE-13 treatment managed to protect testicular tissue against T I/R damage significantly.

5. Conclusion

According to our literature research, this presented study is the first to reveal the protective effect of APE-13 against oxidative and inflammatory damage to testicular tissue in the T I/R rat model. The present study showed that APE-13 promoted antioxidant and anti-inflammatory status in testicular tissue in experimental animals exposed to T I/R and attenuated oxidative stress by limiting free radical production. In conclusion, APE-13 may be an effective therapeutic agent in preventing cell damage in T I/R-induced damaged testicular tissue, which may lead to improvement of the function of testicular tissue in rats. In this respect, APE-13 may serve as a therapeutic agent in the damage of testicular tissue in the future.

Limitations of the Study

Among the limitations of the study, financial inadequacies in advanced analyzes and measurement of a larger number of parameters can be mentioned.

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Conflict of Interests

The authors declare no conflict of interest.

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Author Contributions

Conceived and designed the experiments; TA, MCG, EE, SÖŞ, BB and EŞ. Analyzed and interpreted the data; EE. Contributed reagents, materials, analysis tools or data; TA, MCG, SÖŞ, BB and EŞ. Wrote the paper; FNEA Study of biostatistics; FNEA and EE.

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The Connection Between Mental Performance and Sleep

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Abstract: Although our understanding of sleep physiology is increasing, and many of the mechanisms of sleep have been explained, studies have mainly focused on the effect of sleep on learning and memory processes due to the increase in sleep after learning. However, it remains unclear what kind of information processing occurs in the brain during sleep and what effects information processing-related events have on sleep that are transferred from wakefulness. Research suggests that sleep has a positive impact on memory function. However, it is unclear whether specific sleep stages, such as NREM and REM, are exclusively dedicated to certain types of memory, such as semantic or event memory. It can be concluded that information processing occurs during sleep. However, it is important to note the limitations of studying information processing during sleep due to the challenges of conducting research in this state. Despite spending a third of our lives asleep, our understanding of the benefits of sleep remains limited. It is a fact that information processing occurs during sleep. However, studies investigating this phenomenon are limited. Research on sleep, memory, and information processing can aid in the comprehension of learning, consciousness, and memory processes during sleep, as well as the function of sleep neurophysiology. ©2024 NTMS.

Keywords: Sleep; Learning; Information Processing; Memory.

1. Introduction

On average, we spend eight hours a day sleeping, which amounts to 2920 hours a year. Therefore, it is important to get enough sleep to ensure optimal cognitive function. This means we sleep for 121.7 days a year, or roughly a third of our lives. During this time, our eyes close, our muscles relax, and we become unresponsive to sound, light, or touch of any intensity. From an external perspective, it may seem like we are doing nothing for a third of our lives. However, despite the significant amount of time we spend sleeping, our understanding of the benefits of sleep is limited [1,2]. Recent studies [3-5] have shown that sleep has both physical and psychological benefits. It was previously believed that the brain slows down or stops working during sleep, allowing it to rest. However, after the 1950s, it became clear that this was not the case [6]. After the discovery of REM sleep, it was observed that the brain continues to function during sleep and can even be more active than during the day. Sleep consists of various stages during which the brain alternates between slowing down and speeding up. These phases occur in a complex control system throughout the night and are accompanied by instant changes in hormone levels and fluctuations in body temperature. During REM sleep, which occurs every 90 minutes and makes up almost 20% of all sleep, the brain is highly active. Although cerebral blood flow decreases by up to 20% during sleep, brain cells compensate by increasing the number of signals. Furthermore, brain cells continue to function during deep sleep, also known as NREM, despite the complete loss of consciousness [7-9].

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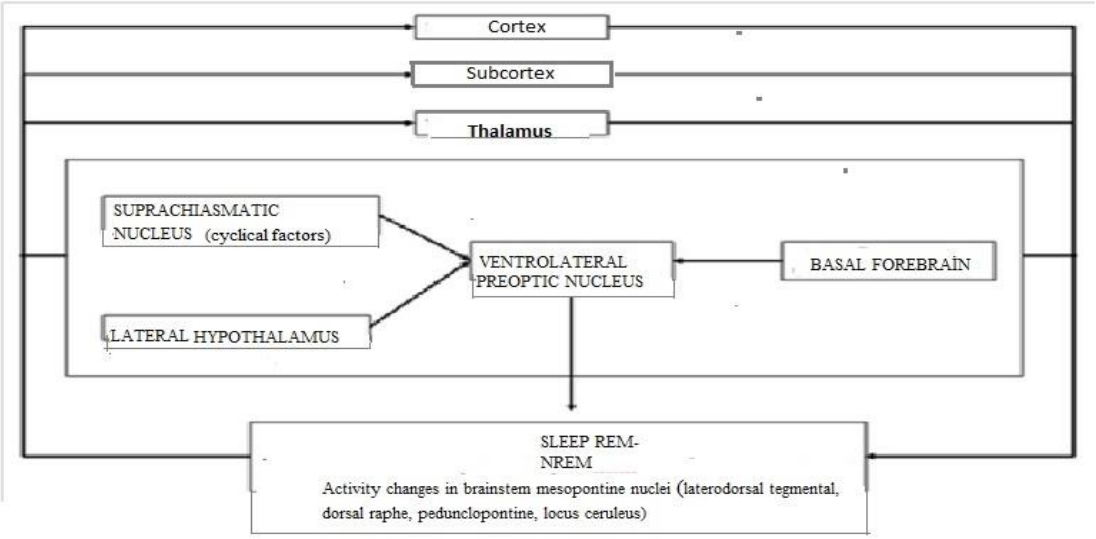

Figure 1: Brain activity during sleep.

Studies have shown that sleep is a cycle consisting of both REM and N-REM stages. This discovery highlights the functional aspect of sleep, which is shared by many species [10, 11]. The brain undergoes different speeds during different stages of sleep, which are sequential and part of a highly complex control system (see Figure 1 and Table 1).

Table 1: Characteristics of NREM and REM Periods.

Characteristics of Nonrem and Rem Periods		
	NREM Period	**REM Period**
Neurotransmıtter levels in the Brain	Decrease in norepinephrine, serotonin, cholinergic and histaminergic agents	Increase in cholinergic agents and decrease in noradrenergic, serotonergic and histaminergic agents.
Changes in brain metabolism and local blood flow	Widespread decline	Decrease in dorsolateral prefrontal cortex and increase in paralimbic and limbic regions
Characteristics of the EEG	Delta and sigma waves, sleep spindles, K complex and slow oscillations	Low wavelength fast activity, theta waves

Fluctuating hormone levels and body temperature accompany these phases. In the first few hours of sleep, brain waves slow down, and during slow-wave sleep, muscles relax, and eye movements cease. This period is characterized by a decrease in heart rate, blood pressure, and body temperature. Individuals who awaken during this phase typically report seeing images but not experiencing a dream. After the stage of slow brain waves, brain activity begins to increase between [12-14]. During REM sleep, brain waves speed up to a level similar to that of wakefulness. Eye movements increase, the body fully relaxes, and most muscles, except for the respiratory muscles, become almost paralyzed. This is the stage when dreams are most common, and blood pressure, body temperature, and heart rate fluctuate. This stage lasts approximately 15 minutes, followed by the slow-wave phase. Sleep stages alternate throughout the night and are repeated every 100 minutes. The slow-wave phase gradually becomes shallower, and the REM phase becomes longer until waking up. The timing of sleep stages varies throughout a person's life. For example, babies typically sleep for 18 hours a day, while adults usually sleep for 6-7 hours a day, with most of this time spent in deep, slow-wave sleep. Although only a small portion of this time is spent in slow-wave sleep [15-17], research suggests that sleep has a positive impact on the learning process [18-20]. Studies in various mammals have shown that sleep improves learning and task performance. The thalamus sends impulses to the cortex during sleep, which is responsible for consciousness. These impulses cause changes in brain waves, resulting in the formation of wakefulness waves. The system responsible for maintaining wakefulness is referred to as the 'red pathway', while the 'blue pathway' is another system that also contributes to wakefulness. In this system, messenger molecules such as norepinephrine and serotonin stimulate the cerebral cortex. Additionally, other messenger molecules, including histamine, dopamine, serotonin, and MCH, which are secreted from various centres in the lower parts of the thalamus and

brainstem, help to maintain our consciousness [21-23]. When we are awake, certain molecules are continuously secreted, sending alerts to the brain. During the slow-wave phase of sleep, both systems slow down and the neurons that secrete messenger molecules stop firing. In contrast, during REM sleep, acetylcholine stimulation continues, but norepinephrine and serotonin firing ceases completely. The hypothalamus is another centre that controls sleep. Two groups of neurons in this region secrete messenger molecules that control our ability to fall asleep. The secretion of the messenger substance GABA in this region induces sleep by suppressing the centres responsible for keeping us awake [24,25]. Conversely, the second group of neurons located on the side of the hypothalamus secrete stimulatory molecules, hypocretin (orexin) and dynorphin, which activate the centres responsible for keeping us awake. The mechanisms that trigger the onset of sleep are not yet fully understood. According to some theories, the sleep process is initiated by a molecule called 'adenosine', which accumulates in the brain over time. It is suggested that coffee, containing caffeine, may suppress this molecule, which could explain why it delays sleep. Additionally, a mechanism known as the 'on-off' system, based on a molecule called 'orexin', has been discovered to facilitate the transition between sleep and wakefulness. During wakefulness, the 'VLPO nucleus' is suppressed, which prevents its suppressive effect on the orexin molecule. Orexin stimulates the cerebral cortex to maintain wakefulness. When the suppression of the VLPO nucleus is lifted, this centre is activated, suppressing orexin and inducing sleep [26-29].
The regulation of sleep is controlled by the SCN nucleus, a specific biological clock located in the brain. This centre is activated every 24 hours and is sensitive to both daylight, which is perceived in the retina at the bottom of the eye, and the hormone melatonin, which is secreted by the pineal gland at night. The SCN nucleus influences the VLPO nucleus through several centres, controlling the daily transition between sleep and wakefulness. The VLPO nucleus is activated through GABAm molecules by stimuli from the Department of Mental Health (DMH) region, allowing the transition to sleep. Meanwhile, the SCN nucleus remains active as long as there is light. In some animals, such as bats, this cycle is reversed, allowing the VLPO nucleus to become active during the day. This mechanism that rhythmically controls sleep can be reversed in experimental animals [30, 31].

The Purpose of rem sleep

Sleep duration is determined by signals sent by nerve cells in the lower centres of the brain. It is interesting to note that the size of these centres does not correlate with sleep duration; in fact, it is almost inversely proportional. For instance, elephants with very large brains have very short sleep periods, while mice with very small sleep centres have longer sleep periods. Although the relationship between sleep duration and function is not fully understood, it is believed that REM sleep plays a crucial role in this process. Models used to study the purpose of sleep are typically based on the principle of depriving animals of sleep for extended periods. Long-term sleep deprivation in mice results in skin lesions, fluctuations in body temperature, increased food consumption, and ultimately death [32]. Similar outcomes are observed when the thalamus and hypothalamus regions of the brain are damaged. These experiments demonstrate the critical role of sleep in maintaining bodily functions. Sleep serves the important purpose of conserving energy, similar to hibernation in some animals. Humans conserve energy by sleeping every night [33, 34]. Recent studies have shown that NREM sleep, characterized by slow waves, promotes protein synthesis and the formation of new nerve cells in certain parts of the nervous system. Specifically, new nerve cells are formed in the olfactory cells, inner cavities of the brain, and hippocampus within 3-4 weeks. Regular exercise has been found to increase nerve cell production, while stress has been found to decrease it. Additionally, sleep deprivation has been found to reduce the formation of new neurons. In summary, sleep has a positive impact on brain cell regeneration [35, 36]. Babies have a high metabolic rate and spend most of their day sleeping to support their growth. Research indicates that there is a correlation between metabolic rate and sleep duration, with smaller animals requiring more sleep due to their higher metabolic rates. Conversely, larger animals with lower metabolic rates require less sleep. These observations indicate that sleep has a role in regulating metabolism. Cells produce significant amounts of free oxygen radicals as a by-product of metabolism when the metabolic rate is high [37, 38].

The importance of rem sleep

Sleep is considered a vital survival mechanism for early humans. It provides necessary rest and serves as an energy-saving system during times of food scarcity when early humans needed to conserve energy to survive. Additionally, sleep functions as a defence mechanism to prevent people from wandering and falling prey to their enemies during dangerous and dark nights, a trait that has survived to this day. In addition, REM sleep is vital for physical and mental health as it strengthens and forms new connections between nerves while eliminating unnecessary ones. To summarise, REM sleep plays a crucial role in restructuring the brain's connections and facilitating memory and learning. Inadequate REM sleep can result in poor memory and learning abilities. Furthermore, REM sleep is closely linked to dreaming, with approximately 95% of individuals reporting dreams upon waking from this stage of sleep. Dreaming is considered significant due to its strong association with REM sleep, which is crucial for optimal brain function. REM sleep is the stage where dreams occur, and the brain remains metabolically active despite the person being asleep. During this stage, heart and breathing rates fluctuate,

and there are rapid eye movements and small movements of limb muscles. While REM sleep uses less energy than wakefulness, it saves less energy than NREM sleep. The reason why not all sleep is non-rapid eye movement (NREM) is currently unknown [33] The duration of rapid eye movement (REM) sleep primarily depends on the development of the nervous system at birth. Animals with a well-developed nervous system at birth experience shorter REM sleep as adults. For instance, certain rodents with a well-developed nervous system at birth, even those born with teeth, experience no more than one hour of REM sleep in total as adults. For instance, some rodents have a well-developed nervous system and teeth at birth, but as adults, they experience no more than one hour of REM sleep in total [34]. In humans, the duration of REM sleep varies depending on age and other factors. It is important to note that the text already adheres to the desired characteristics and is free from errors. In contrast to humans, who experience longer periods of REM sleep as they age due to their less developed nervous system, the duration of REM sleep decreases with age. However, it is important to note that this stage of sleep is present from birth, and infants actually spend more time in REM sleep than adults. These observations demonstrate the significant role that REM sleep plays in brain development. Specifically, during REM sleep, the brain eliminates faulty nerve connections and creates new connections between nerve cells. During infancy and childhood, the programmed development of the nervous system is a crucial process [37].

The benefits of this stage of sleep in adulthood remain uncertain. It is believed that REM sleep readies the individual for wakefulness, preventing a sudden transition from NREM sleep, which is characterized by deep sleep, to a state of wakefulness. Being alert, even while asleep, is crucial for protecting animals from external threats. Animals that wake up from deep NREM sleep are more vulnerable to predation than those that wake up from REM sleep or wakefulness. Furthermore, animals awakened from NREM sleep experience negative effects on their daily bodily functions. It is worth noting that the longest period of REM sleep occurs just before waking up [38]. The initial REM phase lasts for 10-15 minutes. The phase of REM sleep that occurs just before waking up lasts for approximately 25 minutes. During this phase, changes in eye movement, breathing, and heart rate become more pronounced. These findings suggest that REM sleep prepares the body for the transition from sleep to wakefulness. Additionally, REM sleep is believed to maintain activity in the brain stem, which regulates vital internal organs and experiences continuous stimulation during this stage. REM sleep is thought to have existed before the development of the cerebral cortex, which is responsible for the brain's intellectual and fine-tuning abilities. This system affects the brain stem. Additionally, REM sleep plays a vital role in the re-synthesis of messenger molecules, whose levels decrease throughout the day [39].

1.3. Sleep, memory and information processing
learning and memory

The environment primarily affects behaviour through learning and memory. Learning is the process of acquiring information, while memory is the internal system used to retain, encode, store and retrieve acquired information for later access [40, 41].

Informatıon processing

After an organism perceives a stimulus, it undergoes cognitive evaluations known as information processing. These evaluations involve the sensory, attentional, and memory systems. During sleep, the relationships between previously perceived experiences or events are evaluated, meaning is assigned to objects or events, and cognitive-motor preparation of responses takes place. Meanwhile, individuals discover details in their experiences and encounter new and seemingly impossible events [43].

N-REM and REM periods

During the NREM period, the body undergoes physical rest and renewal while biological functions mediate the somatic and autonomic systems. During the NREM period, the body undergoes physical rest and renewal while biological functions mediate the somatic and autonomic systems. This period involves organizing the events of the past day and preparing for the new day. In contrast, REM regulates cognitive functions and is when most information processing occurs. The brain is highly active during this stage, and operations are performed without external stimulation, unlike during wakefulness. However, these cannot be translated into motor expressions, except in some sleep disorders [44].

2. Discussion

The sympathetic nervous system does not receive feedback due to the inability to execute the actions. As a result, spatiotemporal control disappears [46]. Some researchers have argued that REM is a new and unknown state, similar to waking perception and thought. During REM sleep, the brain experiences arousal that stimulates the occipital region, which is associated with vision, and activates visual events or recordings. The volunteers' increased activity in areas that also showed increased activity during the waking task demonstrates the importance of sleep in memory consolidation [45].

Recent studies support the notion that REM and REM deprivation can hinder learning, corroborating early research findings. Additionally, these studies suggest that sleep and wakefulness processes are continuous, with wakefulness processes being reflected during sleep [46]. Experiments [46, 47] have shown that there is little difference in the performance of learning tasks presented before and after REM periods following wakefulness in humans and mammals. The first striking result of such experiments is the similarity between wakefulness and REM in terms of information processing. One of the first links established between

REM and learning is the increase in protein synthesis at the cellular level in both states. Inhibition of protein synthesis during wakefulness (e.g. problem solving) and REM sleep disrupts the learning of a task. The language used is clear, objective, and value-neutral, with a formal register and precise word choice. The sentence structure is simple and logical, with causal connections between statements. The text is free from grammatical errors, spelling mistakes, and punctuation errors. This means that sleep is disturbed, while learning is slowed down or prevented. No changes in content have been made [48].

Table 2: Studies on Information Processing Processes in Sleep.

The Researches	Purpose of the Study	Methodology of the Study	The Result of the Study
Miraglia, F., Tomino, C., Vecchio, F., Gorgoni, M., De Gennaro, L., & Rossini, P. M. (2021). The brain network organization during sleep onset after deprivation. *Clinical Neurophysiology*, *132*(1), 36-44. (51)	The objective of this study is to investigate the differences in brain networks during pre- and post-sleep onset conditions following 40 hours of sleep deprivation (SD) and normal sleep onset in 39 healthy participants.	Cortical sources of electroencephalographic (EEG) current density were used to perform functional connectivity analysis. The small world (SW) index was evaluated in all EEG frequency bands, including delta, theta, alpha, sigma, and beta.	Sleep deprivation (SD) can affect the architecture of the brain's functional network. Further research is necessary to identify changes associated with SD during wake resting states and to mitigate potential harm to behavior and brain function during wakefulness.
Menicucci, D., Piarulli, A., Laurino, M., Zaccaro, A., Agrimi, J., & Gemignani, A. (2020). Sleep slow oscillations favour local cortical plasticity underlying the consolidation of reinforced procedural learning in human sleep. *Journal of Sleep Research*, *29*(5), e13117. (52)	This study examines the impact of procedural learning supported by reinforcement learning on slow wave activity at night and slow oscillations during sleep, as well as the relationship between these changes and behavioural outcomes.	During the experimental phase, participants were instructed to adjust their cursor movements to align with a visual target. In contrast, the control phase did not involve any angular bias. The task was repeated at 13:00, 17:00, and 23:00 before going to bed, as well as at 08:00 after waking up. The deflection angle was initially set at 15° during the first two sessions and was then increased to 45° during the last two sessions. High-density electroencephalogram sleep recordings were taken from 23:30 to 19:30 on both experimental and control nights.	The study found that slow oscillations during sleep significantly aid the consolidation of procedural memories. These oscillations consist of several parts that represent network activations linked to procedural visual-motor reinforcement learning. The areas where there was a relationship between the percentage of slow oscillations during sleep and the ensuing improvement in task performance were significantly affected by the treatment. To maintain objectivity, any subjective assessments have been excluded. The language used is clear, concise, and value-neutral, with a formal register and precise word choice. The text adheres to standard citation and footnote styles, as well as standard formatting and organization. The punctuation, grammar, and spelling have all been corrected. No new content has been added.
Borragán, G., Urbain, C., Schmitz, R., Mary, A., & Peigneux, P. (2015). Sleep and memory consolidation: motor performance and proactive interference effects in sequence learning. *Brain and cognition*, *95*, 54-61. (53)	Using a proactive interference paradigm, the study examined how well visual-motor sequence learning is consolidated in memory while you sleep.	On Day 1, thirty-three young adults received training on sequence A. The following night, they were either allowed regular sleep (RS) or were sleep deprived (SD). After two nights of rest, the participants were required to learn a new, potentially competitive sequence B before taking another test using sequence	The study results indicate that sleep enhances the consolidation of motor skills, specifically for sequence A, resulting in faster reaction times for RS participants overnight. No changes have been made to the content. The language is objective, concise, and clear, avoiding biased or ornamental language and

		A. The study hypothesized that proactive interference effects on sequence B would be stronger in the RS condition due to prior learning of sequence A. Proactive interference is an indirect indicator of the resilience of sequence A. It should be more consolidated during post-training sleep.	adhering to a formal register. The information is presented logically with a good sentence structure. There are no typographical, grammatical, or punctuation errors in the text. On Day 4, the proactive interference effects on learning new material were similar for participants from both SD and RS. Technical terms are defined when first used, and subject-specific vocabulary is employed where appropriate. The study's results indicate that sleep after training enhances performance in the sequential domain of visuomotor sequence learning, but not in the motor domain.
Cousins, J. N., van Rijn, E., Ong, J. L., Wong, K. F., & Chee, M. W. (2019). Does splitting sleep improve long-term memory in chronically sleep deprived adolescents?. *npj Science of Learning*, *4*(1), 8. (54)	However, research has not yet established how learning is affected when sleep is divided between periods of nighttime and daytime sleep during a typical sleep-restricted school week.	The study compared the long-term memory of 58 teenagers who underwent two school weeks of suboptimal continuous (6.5 hours of night sleep opportunity) or divided sleep (5 hours of night sleep + 1.5 hours of day sleep at 14:00) simulations. After two nights of sound sleep, participants were tested on Day 5 in the late afternoon after encoding pictures during the first week. During the second week, participants learned about six different amphibian species in the morning and six different amphibians in the late afternoon for three consecutive days. The studies were conducted in the evening after a one-night break.	During the first week, the group with a split sleep schedule was able to identify more pictures. In the second week, they were able to recall more details about the species they had studied in the afternoon. However, there was no discernible difference between the groups for the species covered in the morning. This study demonstrates that a split-sleep schedule can improve learning after a nap opportunity, even when sleep is restricted, without compromising morning learning. The split-sleep schedule has been shown to be beneficial for students who experience chronic sleep deprivation, although it may not fully replace a full night's sleep.
Stiver, J., Fusco-Gessick, B., Moran, E., Crook, C., & Zimmerman, M. E. (2021). Variable objective sleep quality is related to worse spatial learning and memory in young adults. *Sleep Medicine*, *84*, 114-120. (55)	The aim of this study is to investigate the potential correlation between the learning and memory abilities of young adults in verbal and visuospatial domains and the objective intra-individual variability in sleep quantity and quality.	The study recruited 218 young adult college students from a university in the Eastern United States. Of these, 187 participants (mean age = 20.5, SD = 1.5; 70.6% female) provided full actigraphy and cognitive performance data. The study used wrist actigraphy to objectively measure the intraindividual means and variabilities of sleep quantity (total sleep time) and quality (percent wake after sleep onset) over a period of one to two weeks.	In young adults, there was a significant correlation between intraindividual variability in objective sleep quality and visuospatial learning and memory, beyond the impact of mean sleep quality.

		The study employed the Cogstate computerized test battery's International Shopping List and Groton Maze Learning tests to assess verbal and visuospatial learning, as well as memory.	
Smith et. al., 2004 (56)	To investigate changes in sleep following training.	The study compared students who were in the intensive exam period with those who did not have an exam.	It has been reported that there is an increase in the intensity of rapid eye movement (REM) sleep and associated eye movements.
Mednick SC et. al., 2013 (57)	The aim of this study is to determine which sleep period is associated with learning.	The subjects underwent a tissue discrimination test.	It has been reported that combining these two variables improves test performance by 79 percent.
Frank et. al., 2001 (58)	To investigate the relationship between neurons in the visual cortex and sleep.	For the initial 30 days of life, one eye remained closed.	The increase in primary visual cortex neurons has been linked to NREM sleep. Additionally, it has been demonstrated that plasticity increases after six hours of sleep when one eye is closed.
Best J et. al., 2007 (59)	To determine the relationship between nerve firing patterns and sleep.	Hippocampal cells firing in relation to the physical location of the rat were recorded.	They discovered that in both REM and NREM, the place cells that had fired during the initial entry remained active.
Stickgold R, et. al., 2000 (60)	It is aimed to determine which learning is affected by REM sleep deprivation.	After REM sleep deprivation was applied to the subjects, some tests were performed.	Associative learning has been found to negatively impact motor learning and have no effect on conscious learning, such as verbal learning.

Synaptic Plasticity

Synaptic plasticity is the fundamental mechanism underlying sleep, learning, and long-term memory formation. It refers to the strengthening or weakening of synapses in the connections between neurons. This process involves changes in receptor proteins, post-synaptic signalling mechanisms, and even alterations in the number and distribution of synapses between pairs of neurons. Sleep contributes to the synthesis of biomolecules that help retain information acquired during wakefulness [48].

Effects of sleep on synaptic plasticity

It has a positive effect on learning and memory processes that depend on synaptic plasticity. Conversely, sleep deprivation has a negative effect on these processes. Genes and proteins required for synaptic plasticity are synthesized during sleep. Both sleep and sleep deprivation affect synaptic connection structures and strength [49].

Differences between ınformation processing during sleep and wakefulness

Information processing during sleep is characterised by internal arousal, as opposed to external stimuli which are the basis for waking information processing. Therefore, to understand information processing during sleep, it is necessary to consider the internal functioning of sleep phenomena. Viewing information processing during sleep solely from the perspective of the waking state can result in inconsistent and disjointed results. Two fundamental questions arise regarding information processing during sleep. First, what kind of information processing does the brain allow during sleep? Second, what kinds of residues or effects of information processing events are carried over from wakefulness to sleep? During information processing in sleep, there is a cellular response to incoming information (at a later time and intensity than during wakefulness) and an active preparation of some information networks (especially cerebral structures) according to the brain's activity level [49]. To determine if information processing occurs during sleep, two conditions must be tested: 1. Recognition of a stimulus or task learned during wakefulness should also occur during sleep 2. Formation of new associations during sleep should be observed. It is important to note that subjective evaluations should be avoided and the language used should be clear, objective, and value-neutral. If we define learning as 'the process by which stimuli produce a change in behaviour', it is not possible to discuss this process during sleep. Therefore, instead

of using the term learning, it would be more appropriate to use the term 'information processing during sleep'. The initial source on this subject is dream analysis. According to these analyses, a significant number of dreams revolve around a few common themes. Individuals experience the source of a particular pathology through symbolic images in their dreams, where repressed experiences, emotions, or thoughts are reprocessed through various symbols. It has been reported that these individuals bring their subconscious to the level of consciousness during sleep and dreams, activating a recall and retrieval process, even if only temporarily [50]. A study was conducted on a group of children aged 5-13 over a period of five years, comparing their dream content and mental development with their level of mental development. A linear relationship was found between the participants' ability to represent and express their dream content, their symbolization methods, their ability to make sense of symbols, and their ability to reveal their dreams with logical expressions, and their mental development processes. The study suggests that information processing abilities, which develop accordingly as people get older, are reflected in their dreams up to a certain age, specifically 50. The study emphasises the correlation between dream content and cognitive functions, specifically memory functions. Rapid Eye Movement (REM) is associated with changes in emotion and thought, which make up the dream. The REM stage, during which most dreams occur, appears to aid in forgetting certain memories and experiences while enhancing the retention of others. During REM sleep, memory appears to be reprocessed [51]. The relationship between acetylcholine (Ach), REM sleep, and memory is suggested by the fact that Ach accelerates the stimulus-memory relationship during wakefulness and leads to the onset of REM. However, the function of other chemicals, such as norepinephrine, in REM sleep can make the processing of information appear strange and incomprehensible. This is a common feature of information processing. This fragment of text already meets the desired characteristics. Therefore, no changes have been made.

General results of studies on information processing during sleep

Studies on information processing during sleep can be categorised in various ways. Some studies have explored the impact of sleep stage deprivation on pre-sleep learning, while others have investigated the correlation between sleep stages and types of memory. Current research has analysed the content of dreams to identify differences between sleep stages and the intensity of information processing. Learning is the process by which a stimulus elicits a response in an organism. 'Sleep learning' is not supported by current research. Therefore, the aim of this study is to evaluate information processing during sleep. Although information processing during sleep and wakefulness share similarities, a fundamental difference is that wakefulness relies on external stimuli, whereas sleep relies on internal stimuli. Research on information processing during sleep consistently shows that it is closely linked to memory function and can even have a positive impact on it. Both human and animal studies have produced significant and similar results indicating that sleep deprivation has a detrimental effect on information processing while awake. Sleep deprivation negatively affects both targeted learning immediately following deprivation and general information processing the day after. This includes difficulties in remembering, an increased perception threshold, and distraction. Studies on sleep deprivation have shown that the timing and stage of sleep during which the deprivation occurs are crucial factors. This is because deprivation during different stages of sleep and at different times can have varying effects on information processing. Research suggests that although certain sleep stages, such as REM and NREM, are not specialized for specific types of memory, they are more closely linked to certain types of memory function. Sleep stages differ in terms of information processing and other characteristics that distinguish them from one another. Cognitive functions are supported by the integrity of sleep and its stages. Research has shown that the type of cognitive task presented before sleep, such as motor tasks, perceptual threshold, and memory tasks, affects the impact of sleep deprivation. It is important to note that sleep deprivation has varying effects on different cognitive tasks.

3. Conclusions

Sleep is closely linked to memory function and has a positive effect on it. Sleep deprivation has been shown to have a negative impact on information processing, as demonstrated by both human and animal studies.

Limitations of the Study

Limited generalizability, lack of precision and reliability, and limited exploration of heterogeneity when interpreting and updating research.

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Conflict of Interests

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Author Contributions

All authors contributed equally to the article.

Ethical Approval

None.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Consent to participate

None.

Informed Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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