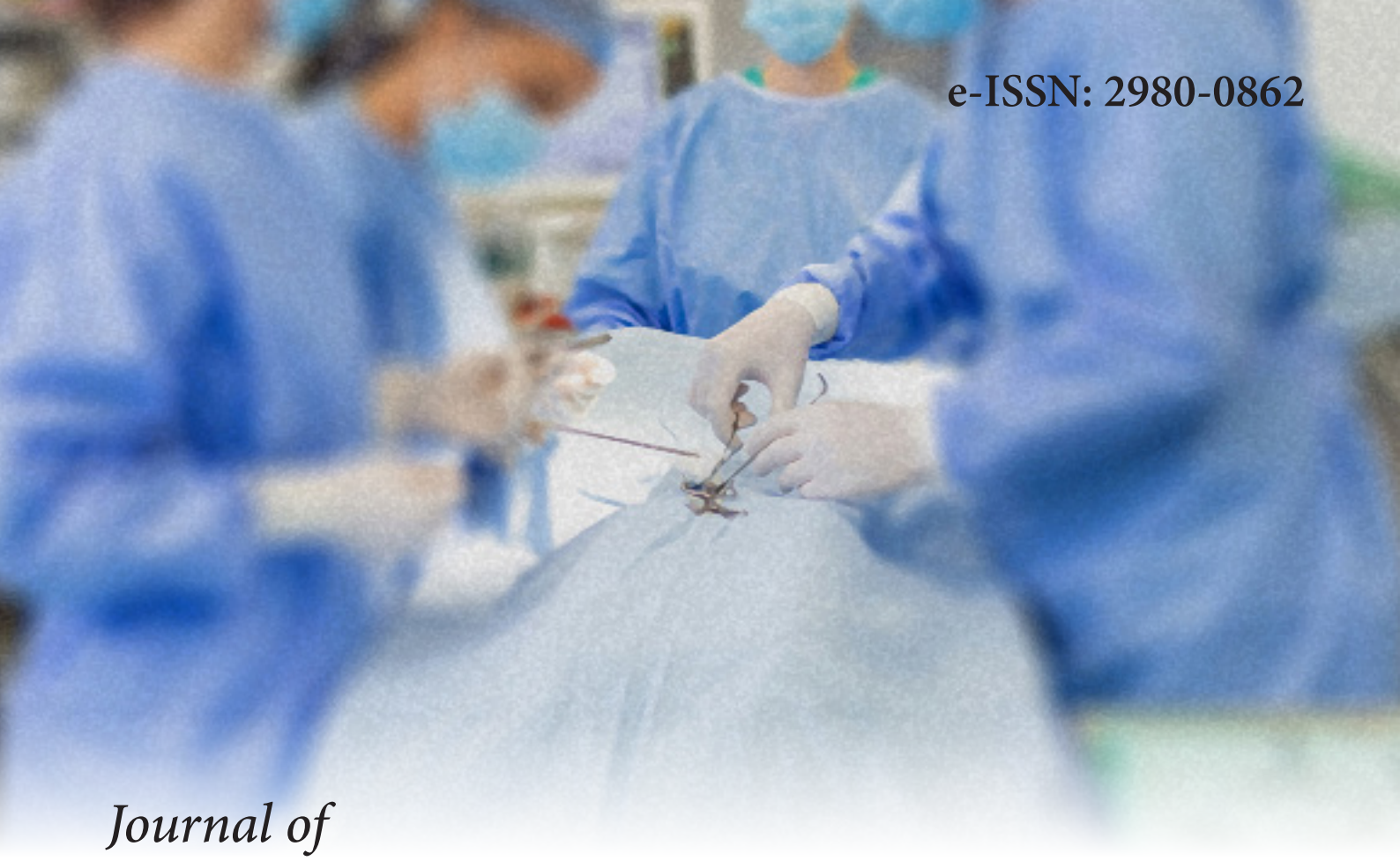

e-ISSN: 2980-0862

Journal of

Comprehensive Surgery

Volume: 3 Issue: 1 Year: 2025

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Dear Colleagues,

We are delighted to present the first issue of the third year of our journal, which aims to provide a multidisciplinary perspective on the surgical field. In a rapidly evolving world, we take pride in offering a comprehensive outlook on surgery alongside specialized field journals.

Over the past two years, our journal has successfully secured its place in international indexes, thanks to our dedicated editors, our reviewers for their impartial review of the manuscripts, authors, and the invaluable support of our readers. I extend my sincere gratitude to each of them for their contributions.

At the beginning of the new year, changes in our editorial team and board of directors will further strengthen our journal and pave the way for greater success. We are pleased to announce that this issue of JOCS includes four original research articles and a case report.

In the 3rd year of our journal, we aim to expand our reach, increase our scientific contributions in the field of surgery and be indexed not only in international databases but also in national databases.

Endless thanks to MHA and their team, as well as everyone who has contributed to the publication of the Journal of Comprehensive Surgery.

Best regards,

Assoc. Prof. Fatma KAVAK AKELMA

Editor-in-Chief

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Journal of Comprehensive Surgery

Original Article

DOI: 10.51271/JOCS-0046

The relationship between isolated head trauma during pregnancy and preterm birth

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Cite this article as: Esercan A, Şahin Y. The relationship between isolated head trauma during pregnancy and preterm birth. *J Compr Surg.* 2025;3(1):1-4.

Received: 04.12.2024 • **Accepted**: 07.01.2025 • **Published**: 23.02.2025

ABSTRACT

Aims: Traumatic brain injury is classified into three types. Blunt head trauma is the most common type. Studies found that after trauma high cortisol levels could cause preterm birth. In the literature, there was no study with isolated head trauma and preterm birth prediction. Our study aims to predict preterm birth in pregnancies with isolated head trauma.

Methods: In this prospective study, pregnant patients who applied to the emergency department of Şanlıurfa Training and Research Hospital with isolated head trauma between January 2018 and January 2024 were included in the study and followed up until the time of pregnancy termination (birth). All of the pregnant women with isolated head trauma (closed blunt trauma) over 18 years of age, and whose birth records are available in our hospital were included in the study. Their medical records and prognosis after blunt head trauma were followed up until birth.

Results: Out of a total of 2580 patients, 30 patients and 60 control group patients who experienced isolated head trauma during pregnancy were included. The initial mean gestational age of the patients included in the study was 26.43±6.53 in the trauma group and 24.32±6.09 gestational weeks in the control group. There was no statistical difference between groups according to the gestational age (p:0.13). Preterm birth was defined as birth before 37 gestational weeks. In the trauma group, 12 (40%) and 23 patients in the control group (38.3%) gave birth as preterm birth. No statistical difference was found (p:0.87) between the groups according to the preterm birth.

Conclusion: In mild head trauma, as all of the patient's Glasgow Coma Scale was 15, there was no risk increase in preterm birth. Studies with severe head trauma in pregnancy may be needed.

Keywords: Cervical dilatation, head trauma, preterm birth, placental abruption, vaginal bleeding

INTRODUCTION

Traumatic brain injury is one of the most common causes of disability, mortality, and morbidity at all ages all over the world.[1] As of 2005, research has shown that complications often occur after traumatic brain injury, such as neurological, psychosocial, and long-term disabilities.[2] This burdens the healthcare system and inspires the search for new treatments. The three kinds of traumatic brain injury are closed head, penetrating, and explosive trauma. Some symptoms may be observed months or even years after the injury, such as nausea, amnesia, seizures, and behavioral changes.[3]

Closed head trauma is the most common type of head trauma in the civilian population, usually resulting from blunt impact. It can damage the brain tissue and reduce blood flow due to direct neuronal damage to the area where the impact occurs or the vibrations caused by the impact. Penetrating brain trauma occurs when a penetrating object passes through the dura and damages the brain tissue. The consequences of lacerations and resulting intracranial bleeding and brain edema develop acutely and rapidly. It carries a higher risk of infection than closed-head trauma.[4] Explosive trauma, which was defined mainly after the explosions in Iraq and Afghanistan in the 2000s, occurs when an explosion near the skull creates fast and powerful shock waves that affect the brain. Results observed include damage to both gray and white matter, disruption of the blood-brain barrier, vasospasm, hyperemia, contusion, and cerebral edema; post-traumatic stress disorder is also common in survivors.[5]

Studies in both animals and humans have shown that traumatic brain injury causes the excessive release of excitatory amino acids such as glutamate and aspartate from presynaptic nerve terminals.[6] Excessive glutamate induces the failure of glutamate reuptake due to the dysfunction of glutamate transporters. Ligand-gated ion channels allow Na^+, K^+, and Ca^{2+} ionic flux upon binding to glutamate, causing membrane depolarization in neurons.[7] The NMDA receptor is also voltage-gated and is permeable to Ca^{2+} ions. Hyperactivation

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of AMPA and NMDA receptors by excessive glutamate has been shown to change ion homeostasis in postsynaptic neurons by allowing extracellular Ca^{2+} and Na^{+} ions to enter.[8] This intracellular Ca^{2+} activates various downstream signaling molecules, reactive oxygen species, and calcium-dependent mechanisms.[9]

Preterm birth is defined as live or stillbirth occurring at or above the 20th week of gestation and before the 37th week of gestation.[10] Ten percent of births are preterm. While 80% occur due to spontaneous reasons (spontaneous premature birth, premature rupture of membranes, placenta abruption, and cervical insufficiency), 20% occur due to medical reasons and termination of pregnancies due to maternal or fetal concern. Risk factors include previous premature birth, pregnancy with assisted reproductive techniques, multiple pregnancies, the threat of preterm labor in the current pregnancy, maternal or fetal life-threatening situations, Black race, cervical insufficiency, short cervix or history of conization, asymptomatic bacteriuria, periodontal disease, smoking and substance use, short pregnancy intervals, and stress.[11]

Stress can be divided into maternal and fetal stress. Fetal stress is characterized by uteroplacental insufficiency.[12] The literature shows that spontaneous preterm birth increases slightly (nearly two times) in cases of major maternal stress such as depression, post-traumatic stress disorder, or anxiety. This pathway is thought to be through the hypothalamic-pituitary-adrenal (HPA) axis. In a prospective study of pregnant women with depression, spontaneous preterm birth was twice as common as in the nondepressed control group.[13]

Stress induces the placental production and release of corticotropin-releasing hormone (CRH), released from the cause of hypothalamic stimulation for secretion of adrenocorticotropic hormone (ACTH) by the pituitary for earlier labor. Stress promotes the adrenal secretion of cortisol, inhibiting the negative feedback loop for hypothalamic CRH and pituitary ACTH.[14,15]

Our prospective cohort study focused on pregnant patients with isolated head trauma to follow up and determine whether preterm birth occurred.

METHODS

Ethics

Permission was obtained from the Harran University Clinical Researches Ethics Committee for the study (Date: 28.12.2023, Decision No: HRU/23.25.05). It conforms to the provisions of the Declaration of Helsinki. This observational prospective study had a Clinical Trial number of NCT06685549.

Pregnant patients who presented to the Emergency Department of Şanlıurfa Training and Research Hospital with isolated head trauma due between January 2018 and January 2024 were included in the study and followed up with until the time of pregnancy termination.

The Criteria for Inclusion in the Study

All of the pregnant women over 18 years of age with isolated head trauma (closed blunt trauma) who were evaluated with neurosurgical consultation or computed tomography/magnetic resonance (CT/MRI) and whose birth records are available at our hospital.

The exclusion criteria included patients with previous premature birth, pregnancies in the first trimester, pregnancies with assisted reproductive techniques, multiple pregnancies, the threat of preterm labor or abortus imminens in the current pregnancy, maternal or fetal life-threatening situations that may cause termination of the pregnancy, cervical insufficiency, short cervix or history of conization, asymptomatic bacteriuria, periodontal disease, and smoking and substance use. Patients who had trauma to the other parts of the body or placental abruption were also excluded. Additionally, the study did not include those with missing hospital records regarding birth and pregnancy follow-up.

Patient Data

We recorded the gestational week, age, parity, CT/MRI result of the patients' head trauma, whether they had surgery on the brain after the trauma, ward or intensive care hospitalizations, birth weeks, whether they had a risk of premature birth before birth, the baby's delivery method and weight, and neonatal intensive care unit admission.

Patients with a similar age and gestational age, who were not exposed to any trauma, who had no health problems, and who applied to the outpatient clinic for follow-up were randomized with a computer program and formed a control group.

Out of a total of 2,580 patients diagnosed with pregnancy and trauma, those with trauma other than isolated head trauma, first-trimester pregnancies, and those with other criteria that did not fit the study were excluded. After the exclusions, 30 patients remained.

Statistical Analysis

The data were evaluated in the SPSS 26.0 statistics program, and the percentages were calculated for the mean, standard deviations, and categorical data. The normal distribution of values was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov test). Student's T test was used for the variables with normal distribution to evaluate the statistical significance between the two independent groups. For the level of significance, $p<0.05$ was accepted.

RESULTS

Thirty patients and 60 patients in the control group who experienced isolated head trauma during pregnancy and met the study criteria were included in the study. The initial mean gestational age of the patients included in the study was 26.43±6.53 in the trauma group and 24.32±6.09 in the control group. There was no statistical difference between groups according to the gestational age (p=0.13). The mean age of the patients was 27.60±5.13 in the trauma group and 27.30±5.90 years in the control group. There was no statistical difference in age (p=0.81) or parity (p=0.92). The patients' demographic data are shown in **Table 1**.

Table 1. Patient demographics according to study group

	Trauma group	Control group	p/t values
Mean gestational age at trauma/ taken into study (for control)/ weeks	26.43±6.53	24.32±6.09	0.13/1.9
Mean age (years)	27.60±5.13	27.30±5.90	0.81/0.23
Mean parity	2.17±1.62	2.20±1.58	0.92/-0.09

While there was no statistical difference between groups according to the intensive care unit admission for the maternal status (p=0.85), the number of patients who were followed up in the ward for observation was statistically significantly higher in the trauma group (p=0.03). No maternal exitus was seen due to the head trauma. One out of 30 patients had a 9 mm subdural-epidural hematoma at the temporal lobe. Other patients had no intracranial bleeding. All patients' Glasgow Coma Scale (GCS) Scores were 15.

The mean gestational ages were 37.33±1.33 and 37.35±2.24 weeks at birth in the trauma and control groups, respectively (Figure). There was no statistically significant difference between the groups (p=0.97). The mean birth weights were 3077.83±541.35 and 3050.33±511.04 grams in the trauma and control groups, respectively, and there was no significant difference (p=0.81). In Table 2, the details of birth results in groups were mentioned.

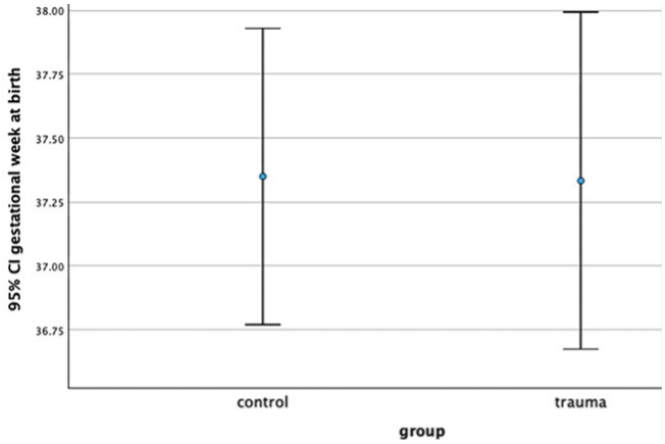

Figure. Gestational week at birth according to the groups (p: 0.97)

Table 2. The birth results in groups

	Trauma group	Control group	p/t values
Gestational week at birth	37.33±1.33	37.35±2.24	0.97/-0.03
Birth weight	3077.83±541.35	3050.33±511.04	0.81/0.23

Preterm birth was defined as birth before 37 gestational weeks. Seven patients (23.3%) in the trauma group and twelve patients in the control group (20%) gave birth preterm. No statistical difference was found (chi-square test, p=0.71, Table 3).

Table 3. Preterm birth among the groups (n)

	Trauma group (n=30)	Control group (n=60)	p
Preterm birth	6	12	
Preterm birth threat and preterm birth	1	0	0.71

The patient with a 9 mm subdural-epidural hematoma at the temporal lobe gave birth at the 38th gestational week and did not have a preterm birth threat.

Ten (33%) in trauma group and twenty-seven (45%) patients in control group had cesarean birth. The type of birth was not statistically different among the groups (p=0.28). There were no patients defined as placental abruption or fetal distress during the follow-up before birth. There was no correlation between the gestational week at trauma and the gestational week at birth (p=0.41).

DISCUSSION

The incidence of trauma in pregnancy is 6% and about 2-3% for severe trauma.[16] Our hospital is the center with the highest number of pregnancies and births in Turkiye, with 26,000 births per year. According to these statistics, although the expected number of pregnant women who experienced trauma should be approximately ten thousand in our six-year data, the number is less. These traumas are primarily the result of domestic violence and falling accidents,[17] so the lower number may be interpreted as domestic violence being hidden.

In the event of trauma, placental abruption and thorax or abdominal fluid are critical side effects so ultrasonographic examination is important in the evaluation of mortality. In our study, only pregnant women with head trauma were included. Obstetric ultrasound and, if necessary, cranial imaging were planned for all of them.[18]

In the literature, pregnant women with high levels of psychosocial stress have a 25%-60% increased risk for preterm birth compared with women reporting low levels of stress.[19] The pathophysiology is complex, but it is known that the HPA axis and the locus coeruleus norepinephrine systems play important roles by increasing cortisol activity. In some studies, increased cortisol levels were found to be related to preterm birth.[20]

In our study, although stress levels were high due to head trauma, there was no statistical difference or increase in preterm birth. Although these trauma patients were proven to have trauma and consulted with neurosurgeons, there was no effect on preterm birth.

The Revised Trauma Score is composed of the patient's systolic blood pressure, GCS Score, and respiratory rate.[21] Lower Scores were related to higher mortality. In our study, all of our patients Had High Scores, so our maternal and fetal results were fine, with no increase in preterm birth.

GCS is the best predictive factor for mortality and morbidity in traumatic brain injury. In our study, all patients' GCS Scores were normal, so the results were similar to the control group.

Limitations

Our study's strength is that it is the only study to focus on pregnant patients with isolated head trauma. The limitation is that our patients' GCS Scores were 15, so the results were similar to those of nontraumatic patients.

CONCLUSION

Despite our study, preterm birth is not expected from those with high GCS of pregnant women with isolated head trauma, studies with more pregnant women with isolated head trauma are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Harran University Clinical Researches Ethics Committee (Date: 28.12.2023, Decision No: HRU/23.25.05).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Availability of Data and Materials

Data is deposited at doi:10.6084/m9.figshare.26096599

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Journal of Comprehensive Surgery

Original Article

DOI: 10.51271/JOCS-0047

Effect of tramadol hydrochloride on ischemic colon anastomosis healing

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Cite this article as: Kaplan İ, Pehlivanlı F, Aydın O, Aydınuraz K, Daphan ÇE, Şahin Y. Effect of tramadol hydrochloride on ischemic colon anastomosis healing. *J Compr Surg.* 2025;3(1):5-8.

Received: 19.12.2024 ◆ **Accepted**: 15.01.2025 ◆ **Published**: 23.02.2025

ABSTRACT

Aims: This study aimed to investigate the possible effects of tramadol hydrochloride administration on the healing of colonic anastomosis after colonic ischemia-reperfusion injury in rats.

Methods: Twenty-four Wistar albino male rats were divided into the control group (rats underwent resection-anastomosis after ischemia-reperfusion injury in the colon and saline was given intraperitoneally, n=12); and the TRA group (rats underwent resection-anastomosis after ischemia-reperfusion injury in the colon and tramadol hydrochloride was given, n=12). After colon ischemia-reperfusion injury was produced, the distal part of the descending colon was cut to full thickness, and the lumen was completely closed one by one with 6/0 polypropylene sutures. Then, 0.5 ml saline was administered to the control group and 30 mg/kg tramadol hydrochloride was administered to the TRA group intraperitoneally every day for five days. After sacrificing all the rats, the burst pressures were recorded, and blood serum and colon tissue samples were analyzed biochemically.

Results: Biochemical analysis of blood serum samples revealed that IL-6 (p=0.026), MPO (p=0.001), CAT (p=0.024), and AST (serum p=0.002) levels were different between the two groups. Biochemical analysis of the tissue samples revealed that glutathione reductase (p=0.006), AST (p<0.001) and ALT (p=0.004) levels were different between the two groups.

Conclusion: At the end of this study, it was thought that tramadol usage as an analgesic drug may not have a negative or positive therapeutic effect on colon ischemia-reperfusion injury and colon anastomosis in rats. Therefore, it was thought that tramadol hydrochloride could be used as an analgesic drug option in pain management in such patients.

Keywords: Colon anastomosis, hypoxia-reperfusion injury, tramadol

INTRODUCTION

The colon is the part of the gastrointestinal tract most prone to ischemia. Colonic ischemia is more common in elderly patients due to atherosclerotic events and some other comorbid conditions. Therefore, colon resection and anastomosis have been performed more frequently in the same age group[1] Ischemic colitis may progress to transmural necrosis and develop into gangrenous colitis requiring surgical intervention by disruption of colonic blood flow due to occlusive or nonocclusive causes of mesenteric blood flow. Reactive oxygen radicals can cause reperfusion injury leading to lipid peroxidation and cell necrosis in case of reoxygenation after developing mucosal damage.[2] Although the safety of colorectal resection and anastomosis surgery has improved with advances in surgical technique, antibiotic prophylaxis, preoperative preparation, and postoperative period, major morbidity rates still range between 20-35% and 30-day mortality rates between 2-9%.[3] The most important complication in colorectal surgery is anastomotic leakage (5-15%) with a high mortality rate (10-32%).[4,5]

Agents that stimulate tissue healing or reduce inflammation are much more needed to prevent adverse anastomotic leakage, especially in tissues damaged by ischemia-reperfusion.[6] Studies are investigating the effect of drugs used for postoperative analgesia in patients undergoing segmentary colon resection and anastomosis under emergency or elective conditions. However, the effect of tramadol hydrochloride, which is considered a weak opioid analgesic causing serotonin and noradrenaline reuptake inhibition and used to treat moderate to severe pain in the postoperative period, is unknown on anastomotic healing.[6-8]

This study aimed to investigate the possible effects of tramadol hydrochloride administration on the healing of colonic anastomosis after colonic ischemia-reperfusion injury in rats.

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METHODS

Ethics

The study was conducted after the approval of the Kırıkkale University Animal Experiments Local Ethics Committee (Date: 24.12.2021, Decision No: 54). All procedures were carried out following the ethical rules and principles.

In this study, 24 Wistar albino male rats weighing 220-280 g were used. Rats were divided into groups by simple random sampling method as follows;

- Control group (resection-anastomosis was performed after ischemia-reperfusion injury was induced in the colon and saline was given intraperitoneally, n=12)
- TRA group (resection-anastomosis was performed after ischemia-reperfusion injury was induced in the colon and tramadol hydrochloride was given intraperitoneally, n=12)

Surgery

The same surgeon performed all surgical procedures. All rats were anesthetized intramuscularly with 50 mg/kg ketamine hydrochloride (Ketalar®, Pfizer). After a median abdominal incision of approximately 3 cm, the vascular structures, including the vessels and collaterals supplying all colon, were clamped with an atraumatic bulldog clamp. Blood flow was interrupted for 45 minutes and ischemia was induced in the entire colon. At the end of the time, the clamp was opened, blood flow was observed again in the colon, and reperfusion was waited for 45 minutes.[9,10] Following reperfusion, the distal part of the descending colon was cut to full thickness. The lumen was completely closed one by one with 6/0 polypropylene sutures (Figure 1). After the abdominal incision was sutured continuously, the rats were taken to their cages after the dressing procedure and the follow-up was started.

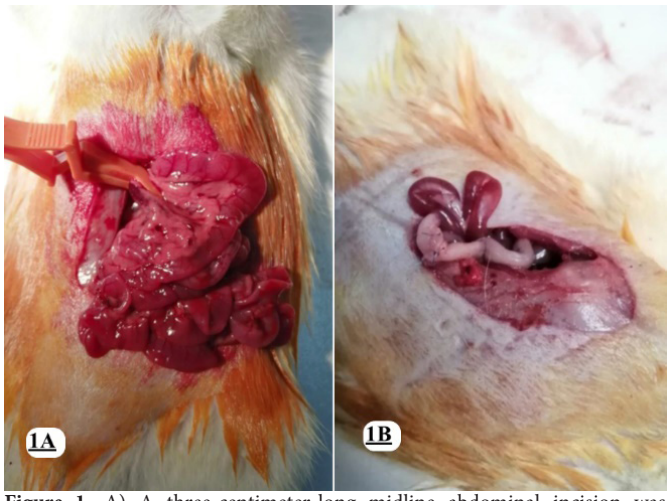

Figure 1. A) A three-centimeter-long midline abdominal incision was performed, and the vascular trunk of the colon was clamped with bulldog clamps to provide ischemia in the colon for 45 minutes. B) After the clamps were removed and reperfusion was allowed for 45 minutes, the descending colon was transected using a scalpel blade, and a single-layer colonic anastomosis was performed with 8 sutures using 6-0 polypropylene

In the postoperative period of the rats, 0.5 ml saline was administered intraperitoneally to the control group and 30 mg/kg tramadol hydrochloride was administered intraperitoneally to the TRA group every day for five days. On the sixth postoperative day, all rats were anesthetized with 50 mg/kg ketamine hydrochloride intramuscularly. The colonic anastomosis line was resected 3 cm each proximally and distally by entering the abdomen through the previously created median incision. After 8-10 ml blood sample was obtained from each rat vena cava, all rats were sacrificed by intracardiac blood puncture. The blood samples were centrifuged at 3000 rpm for 10 min and the serum samples were stored at -80°C.

Anastomotic Burst Pressure Measurement

The lumen of the resected intestinal segments of all rats was cleaned from fecal content with warm saline. Saline was infused into the lumen with an infusion pump (Braun® Infusomat Space) at a constant rate. A manometer connected to the infusion pump with a three-way cannula was used to measure the pressure as the pressure increased in the lumen. The pressure increase was monitored on the manometer monitor and the burst pressure value at the burst time was noted for each intestinal segment (Figure 2). After the burst pressures were recorded, the anastomotic line was stored at -80°C for biochemical analyses.

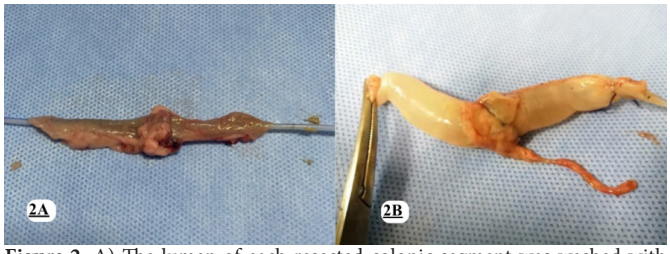

Figure 2. A) The lumen of each resected colonic segment was washed with saline for fecal removal. B) The system pressure was increased via saline infusion in a controlled manner, and the bursting pressure was measured when air bubbles were seen in the water-filled container

Biochemical Evaluation

Biochemical tests performed on tissue samples were aimed to evaluate wound healing, cross-linking of collagen fibrils, and endothelial damage. Tissues stored at -80° C were allowed to reach room temperature and homogenized with phosphate-buffered saline. Then, the homogenized tissues were centrifuged, and the supernatants were obtained. Then these supernatants were subjected to the ELISA kits' methods and tissue levels of hydroxyproline (Catalog No: E0511Ra, BT-Lab), myeloperoxidase (MPO) (Catalog No: Otto3048, Ottoscientific), malondialdehyde (MDA) (Catalog No: Otto1001, Ottoscientific) and caspase-3 (Catalog No: E1648Ra, BT-Lab) were measured using a spectrophotometer (Thermo Scientific Multiskan FC, 2011-06, USA).

On the other hand, frozen blood serum samples were also thawed at room temperature. Then, those serum samples were centrifuged, and the supernatants were obtained. Then, these supernatants were subjected to the ELISA kits' methods and serum tumor necrosis factor-α (TNF-α) (Catalog No: E0764Ra, BT-Lab), interleukin-6 (IL-6) (Catalog No: E0135Ra, BT-Lab), catalase (CAT) (Catalog No: E0869Ra, BT-Lab), glutathione reductase (Catalog No: E1085Ra, BT-Lab), superoxide dismutase (SOD) (Catalog No: RLD0123, REL ASSAY), and nitric oxide (NO) (Catalog No: E-BC-K035-S, Elabscience) were measured using a spectrophotometer (Thermo Scientific Multiskan FC, 2011-06, USA). Furthermore, serum aspartate aminotransferase (AST) (Catalog No: OttoBC127, Ottoscientific), and alanine aminotransferase (ALT) (Catalog No: OttoBC128, Ottoscientific) levels were measured using a fully automatic biochemistry device (Mindray brand BS300).

Statistical Analysis

Shapiro-Wilk test was performed to test the normal distribution of the study data. The parametric data was evaluated using the independent samples T test ($p<0.05$). The nonparametric data was analyzed using the Mann-Whitney U test ($p<0.05$).

RESULTS

The mean anastomotic burst pressure was measured at 130.4 (96-170) mmHg in the control group, and 106.6 (80-130) mmHg in the TRA group. However, anastomotic burst pressure values were not different between the groups ($p=0.183$) (Table).

Tissue hydroxyproline, MPO, MDA, and caspase-3 level values were not different between the groups ($p>0.05$). On the other hand, serum IL-6 ($p=0.026$), CAT ($p=0.024$), and AST ($p=0.002$) levels were different between the groups (Table).

DISCUSSION

Oxygenation is the most important factor in collagen synthesis produced by fibroblasts.[11,12] Studies showed that hypoxia occurring in the tissue after intestinal anastomosis adversely affects collagen synthesis and that the wound site heals faster in hyperoxia-treated tissue.[13] Increased reactive oxygen radicals in the damaged tissue after ischemia-reperfusion disrupt cellular functions, delay wound healing, and cause tissue necrosis, leading to anastomotic leaks. Prevention of anastomotic leaks can be aimed at preventing the generation of free oxygen radicals and accelerating wound healing.[14] In addition to hydroxyproline level, an important indicator of wound healing at the tissue level, collagen quality, and crosslinking properties have also been reported to be important in anastomotic wound healing.[14] In this study, burst pressure, a more reliable method comparing the rupture and tension method, was used to determine the wound healing of colon anastomosis. However, at the end of the study, it was found that tramadol hydrochloride administration did not affect burst pressure. In addition, hydroxyproline level values in tissue samples were similar between the two groups in our study. With these findings, it was thought that tramadol hydrochloride administration did not impair wound healing in terms of mechanical support in the tissue.

Activation of the cytokine network (such as IL-6 and TNF-α) has also been shown in intestinal ischemia-reperfusion injury models. In animal experiments, activated cytokines have also been reported to inhibit wound healing. Especially TNF-α stimulates the macrophages to synthesize IL-1, which inhibits wound healing. In addition, MPO can indicate the severity of inflammation and neutrophil migration.[15,16] In our study, MPO values measured at the colonic tissue were not different between the two groups. Furthermore, serum TNF-α level values were similar between the groups. However, serum IL-6 level values measured in the TRA group were lower than in the control group. With these findings, it was thought that tramadol hydrochloride could have a slightly anti-inflammatory effect on colon hypoxia-reperfusion injury in rats.

Catalase is the enzyme that converts hydrogen peroxide synthesized by peroxisomes into water and oxygen. Glutathione peroxidase and glutathione reductase also contribute to the degradation of lower concentrations of hydrogen peroxide to water and oxygen by establishing a GSH/GSSG balance. In addition, glutathione reductase has known functions such as neutralizing free radicals and reactive oxygen products, protecting membrane proteins, and detoxifying some metabolic end products by conjugation. SOD enzyme provides the reduction of superoxide radical to hydrogen peroxide. On the other hand, malondialdehyde level is considered a marker of oxidative stress and lipid peroxidation.[17-19]

In our study, tissue malondialdehyde level values were similar between the two groups. In addition, serum glutathione reductase, SOD, and NO level values were not different between the two groups. However, serum CAT level values were lower in the TRA group compared to the control group. With these findings, it was argued that the antioxidant activity of tramadol hydrochloride in colon tissue and blood serum was almost negligible.

Intestinal ischemia-reperfusion causes severe liver damage in both humans and animals. Studies have reported that tramadol decreases apoptosis in the liver and alleviates hepatic damage in liver ischemia-reperfusion injury.[20] In our study, serum AST level values, a hepatic damage indicator

Table. Comparison table of biochemical analysis of tissue and blood serum samples

		Control	TRA	
	Variable	Mean±SD/median (min-max)	Mean±SD/median (min-max)	p
	Burst pressure (mmHg)	130.4 (96-170)	106.6 (80-130)	0.183†
Tissue	Hydroxyproline	319.27 (153.34-417.27)	245.33 (89.25-1019.31)	0.242†
	Myeloperoxidase	44.25 (17.20-242.20)	30.55 (15.20-70.30)	0.178†
	Malondialdehyde	10.35 (3.28-46.19)	11.26 (2.75-32.13)	0.671†
	Caspase-3	0.32±0.14	0.29±0.06	0.539*
Serum	Tumor necrosis factor-α	18.56±2.84	18.06±2.83	0.669*
	Interleukin-6	5.40±1.28	4.33±0.89	0.026*
	Catalase	30.75 (8.90-50.17)	14.10 (9.68-37.16)	0.024†
	Glutathione reductase	5.22±1.18	4.43±1.37	0.148*
	Superoxide dismutase	387.17±108.04	404.83±72.23	0.642*
	Nitric oxide	11.95±2.60	11.98±1.80	0.975*
	Aspartate transaminase	104.25 (76.60-189.70)	139.30 (109.3-273)	0.002†
	Alanine transaminase	41.35 (28.70-58.10)	38.75 (25.90-108.40)	0.887†

*Independent samples T test, †Mann-Whitney U test, $p<0.05$, SD: Standard deviation, Min: Minimum, Max: Maximum

parameter in blood serum samples, were higher in the TRA group compared to the control group. However, serum ALT level values were similar between the two groups. With this finding, it was thought that AST values increased more in the TRA group than in the control group after colon ischemia-reperfusion injury. This increase was thought to be due to systemically administered tramadol hydrochloride.

On the other hand, caspase-3 is one of the effector caspases and is known to play a role in the apoptosis mechanism.[17] In our study, tissue caspase-3 level values were similar between the two groups. Thus, it was thought this experimental agent could not have an antiapoptotic effect on colon hypoxia-reperfusion injury in rats.

In conclusion, it was thought that this agent had no effect on collagen synthesis and had no anti-inflammatory, antioxidant, or antiapoptotic effect in colon ischemia-reperfusion injury in rats. In addition, the fact that the obtained burst pressure values were not found to be different between the two groups supported these thoughts. Thus, these findings thought that the use of tramadol as an analgesic agent did not create a negative or positive therapeutic effect in colon ischemia-reperfusion injury in rats. Therefore, it could be said that tramadol hydrochloride could be used as an analgesic drug option in pain management in such patients clinically.

Limitations

The study had some limitations. First, this study included the findings obtained at the end of 5 days of colon anastomosis following colon ischemia-reperfusion injury. Therefore, data regarding the chronic process were not included in this study. Second, the effects of tramadol hydrochloride were not compared to the other pharmacological agents in this study. Finally, histopathological (such as immunohistochemistry, electron microscopy) and biochemical (such as western blot) analysis methods that could reveal the anti-inflammatory, antioxidant, and possible anti-apoptotic mechanisms of action of tramadol hydrochloride in detail were not included in this study due to technical and/or financial limitations.

CONCLUSION

This study's results showed that tramadol hydrochloride usage as an analgesic drug may not have a negative or positive therapeutic effect on colon ischemia-reperfusion injury and colon anastomosis in rats. Therefore, it was thought that tramadol hydrochloride could be used as an analgesic drug option in pain management in such patients clinically.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the the Kırıkkale University Animal Experiments Local Ethics Committee (Date: 24.12.2021, Decision No: 54).

Informed Consent

Since experimental animals were used in this study, a written consent form was not required.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

This study was supported by the Scientific Research Projects Unit of the university to which the authors are affiliated (Project No: 2022/026).

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Journal of Comprehensive Surgery

Original Article

DOI: 10.51271/JOCS-0048

Comparison of the efficacy of extracorporeal shock wave lithotripsy, pneumatic lithotripsy, and laser lithotripsy in the treatment of proximal ureteral calculi

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Cite this article as: Özlük C, Polat F. Comparison of the efficacy of extracorporeal shock wave lithotripsy, pneumatic lithotripsy, and laser lithotripsy in the treatment of proximal ureteral calculi. *J Compr Surg.* 2025;3(1):9-14.

Received: 15.01.2025 ◆ **Accepted**: 11.02.2025 ◆ **Published**: 23.02.2025

ABSTRACT

Aims: This study aimed to compare the efficacy of extracorporeal shock wave lithotripsy (ESWL), pneumatic lithotripsy, and laser lithotripsy in the treatment of proximal ureteral calculi, focusing on stone-free rates, complication profiles, and the need for additional interventions.

Methods: A retrospective analysis was conducted on 150 patients with proximal ureteral calculi treated with ESWL, pneumatic lithotripsy, or laser lithotripsy. Patients were divided into three equal groups (50 per treatment arm). Demographic and clinical characteristics, procedural outcomes, and complication rates were evaluated. Stone-free status was assessed on postoperative day 1 via direct urinary system radiography and at 1 month using intravenous urography.

Results: For stones smaller than 10 mm, the stone-free rates were 93% in the ESWL group, 80% for pneumatic lithotripsy, and 84% for laser lithotripsy. In stones ≥10 mm, the rates dropped to 55.0%, 52.6%, and 75%, respectively. There were no statistically significant differences in the distributions of stone-free status, minimal residue, or the requirement for post-procedure URS across procedure types. A higher frequency of pusback was observed in the pneumatic lithotripsy group compared to the other groups (pneumatic lithotripsy: 31.6% vs. laser lithotripsy: 12.5% vs. ESWL: 0%, p=0.012). However, for stones smaller than 10 mm, this difference was not statistically significant. The mean operative duration was longest for laser lithotripsy compared to pneumatic lithotripsy and ESWL (pneumatic lithotripsy: 36.6±5.2 vs. laser lithotripsy: 62.8±11.1 vs. ESWL: 28.2±6.4 minutes, p=0.001). Complication rates were comparable across groups.

Conclusion: In smaller ureteral calculi, the three modalities exhibit comparable efficacy. For large ureteral stones, laser lithotripsy achieves better stone-free rates and requires fewer repeat interventions but has a longer operative time. Treatment decisions should be individualized according to stone size, patient factors, and available resources.

Keywords: Ureteral calculi, extracorporeal shock wave lithotripsy, lithotripsy, treatment outcome, ureteroscopy, complications

INTRODUCTION

Proximal ureteral stones constitute a significant portion of urolithiasis cases, and their treatment is crucial to prevent possible urinary system obstruction, pain, hydronephrosis, and potential renal dysfunction.[1] In managing ureteral stones, the main factors considered include stone size, location, structural characteristics, and the clinical condition of the patient.[2] Especially in proximal ureteral stones, the likelihood of spontaneous passage decreases as stone size increases, bringing invasive or semi-invasive treatment approaches to the forefront.[3]

Traditionally, for symptomatic proximal ureteral stones larger than 10 mm, treatment options such as extracorporeal shock wave lithotripsy (ESWL), ureteroscopic pneumatic lithotripsy, or laser lithotripsy have been recommended.[4,5] ESWL is widely accepted as a first-line method due to its favorable tolerability and non-invasive nature, while pneumatic and laser lithotripsy represent two commonly employed energy sources in ureteroscopic procedures.[6,7] Pneumatic lithotripsy effectively fragments hard and large stones, it carries a risk of fragment migration. On the other hand, laser lithotripsy is noted for providing more controlled fragmentation and achieving high success rates with both hard and soft stones.[8,9] Recent research indicates that, particularly for larger stones in the upper ureter, laser lithotripsy may offer higher stone-free rates compared to pneumatic lithotripsy.[10,11] However, studies comparing ESWL with pneumatic or laser lithotripsy have emphasized that while ESWL's non-invasive nature is an advantage, its success rates in larger or harder stones may be lower-sometimes requiring repeat procedures.[12] Although both pneumatic and laser lithotripsy can reduce the need for repeated sessions, thereby helping patients achieve stone-

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free status more quickly, one must also consider potential complications such as ureteral trauma.[9]

The existing literature on the management of proximal ureteral stones predominantly focuses on comparative analyses involving two treatment modalities, such as ESWL, pneumatic lithotripsy, or laser lithotripsy. However, studies that evaluate and compare the efficacy and safety profiles of all three methods simultaneously are scarce. Therefore, this study aimed to compare the efficacy of ESWL, pneumatic lithotripsy, and laser lithotripsy in the treatment of proximal ureteral calculi.

METHODS

This retrospective study was conducted at the at the Department of Urology, Gazi University Faculty of Medicine, between June 2009 and June 2012, in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The study was derived from a thesis completed prior to 2020 and received institutional approval. The need for informed consent was waived under the approval of the local ethics committee due to the retrospective design.

Patients diagnosed with proximal ureteral calculi and treated with either ESWL, pneumatic ureterorenoscopy (URS), or laser URS during the study period were retrospectively screened for eligibility. Patients were excluded if they were on continuous anticoagulant therapy, had ureteral strictures, multiple stones, anatomical anomalies, or chronic kidney disease. After applying these exclusion criteria, 150 patients were included in the study, with 50 patients in each treatment group.

All patients included in the study had radiopaque stones confirmed by preoperative non-contrast computed tomography evaluation. The localization of upper ureteral stones was defined as the region between the ureteropelvic junction and the bony pelvis. Stone size was calculated as described in the European Association of Urology (EAU) guidelines.[13]

Surgical Methods

The ESWL procedure was performed without anesthesia. The Siemens Lithostar Modularis 140 (SN:792SPV0001) lithotripter was used for stone fragmentation, with C-arm fluoroscopy employed for targeting. Following fragmentation, stone fragments were removed in some cases using a basket or forceps. URS procedures were performed under general or spinal anesthesia using a 10F rigid ureterorenoscope (Karl Storz, Germany). For laser lithotripsy, a Dornier Medilas H20 laser lithotripter (SN: H20-1205, Germany) was used, operating at a pulse energy of 120 mJ and a frequency of 8 Hz at a wavelength of 595 nm. For pneumatic lithotripsy, an Elmed Vibrolith pneumatic lithotripter (SN: 1038VB672, Germany) was used, set at a pressure of 2 bar and a frequency of 10 Hz. During URS, stones were fragmented into pieces ≤2 mm in size. Normal saline was used as the irrigation fluid during the procedure.

To prevent renal colic caused by any remaining fragments or ureteral edema, a 4.8 Fr ureteral catheter was placed in all patients at the end of the procedure. In uncomplicated cases, this catheter was removed on postoperative day 1, whereas in complicated cases it remained in place for 48-72 hours.

Endpoints

Successful treatment was defined as having no fragments larger than 2 mm. If the residual fragment size exceeded 2 mm, the patient was deemed not stone-free, necessitating additional forceps or basket retrieval. In this study, achieving fragmentation to 2 mm or less was considered equivalent to being stone-free.

Complications potentially associated with each treatment method included ureteral perforation, ureteral mucosal laceration, stone migration, hematuria, urinary tract infection, postoperative fever, steinstrasse, and pain. Stone-free status was evaluated on the first postoperative day using a direct urinary system radiography and again at one month via intravenous urography (IVU).

In all groups, post-procedure URS was performed in patients who were found to have residual stone fragments larger than 2 mm on follow-up imaging (direct radiography on postoperative day 1 or IVU at one month) or who had persistent (e.g., ongoing pain, obstruction, or infection) suggesting inadequate fragmentation or incomplete stone clearance.

Statistical Analysis

All data were analyzed using SPSS Statistics Software, version 15 (SPSS, Inc., Chicago, IL, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean±standard deviation values, while non-normally distributed variables are given as median (min-max) values. Accordingly, student T test and Mann-Whitney U test were used for comparisons between two groups. ANOVA test (post-hoc: Bonferroni test) or Kruskal-Wallis H test (post-hoc: Dunn's test) were used for comparisons between more than two groups. Categorical variables were presented as numbers and percentages, and comparisons between groups were performed using chi-square and Fisher exact tests. Significance was accepted at $p<0.05$ (*) for all statistical analyses.

RESULTS

Table 1 summarizes the demographic and clinical characteristics of the treatment groups. The median age was comparable across all groups (pneumatic lithotripsy: 44 vs. laser lithotripsy: 41 vs. ESWL: 42 years; p=0.960). While the proportion of males was higher in all groups, there was no statistically significant difference among the groups (pneumatic lithotripsy: 72% vs. laser lithotripsy: 58% vs. ESWL: 68%, p=0.355). Stone location was more frequently observed on the right side, and its distribution was similar across all groups.

Double-J ureteral catheter usage was significantly lower in the ESWL group compared to the other groups (pneumatic lithotripsy: 64% vs. laser lithotripsy: 72% vs. ESWL: 18%, p<0.001). The median stone size did not differ significantly among the groups. The mean operation duration was longer in the laser lithotripsy group compared to the other groups (pneumatic lithotripsy: 36.6±5.2 vs. laser lithotripsy: 62.8±11.1 vs. ESWL: 28.2±6.4 minutes, p=0.001). Additionally, the ESWL group exhibited a shorter duration of hospital stay compared to the other groups (pneumatic lithotripsy: 24 hours vs. laser lithotripsy: 12 hours vs. ESWL: 1 hour, p=0.001) (Table 1).

While the complication rates were comparable among the groups, there were no significant differences in the types of complications observed. The frequency of pusback was higher in the pneumatic lithotripsy group compared to the other groups, while it was not observed in the ESWL group (pneumatic lithotripsy: 22% vs. laser lithotripsy: 12% vs. ESWL: 0%, p=0.001). In the overall population, no significant differences were observed in other outcome findings (Table 2).

Among patients with stones less than 10 mm, there were no statistically significant differences in the distributions of stone-free status, pushback, minimal residue, or the requirement for post-procedure URS across procedure types (Table 3).

Table 1. Demographic and clinical findings of the patients

Variables	Pneumatic lithotripsy n=50	Laser lithotripsy n=50	ESWL n=50	p-value
Age, years	44 (3-77)	41 (10-91)	42 (18-72)	0.960
Gender, n (%)				
Female	14 (28.0)	21 (42.0)	16 (32.0)	0.355
Male	36 (72.0)	29 (58.0)	34 (68.0)	
Stone location, n (%)				
Right	26 (52.0)	29 (58.0)	25 (50.0)	0.778
Left	24 (48.0)	21 (42.0)	25 (50.0)	
Double-J ureteral catheter, n (%)	32 (64.0)	36 (72.0)	9 (18.0)	<0.001*
Stone size, mm	8 (5-15)	9 (5-30)	7 (5-16)	0.060
Operation duration, minutes	36.6±5.2	62.8±11.1	28.2±6.4	0.001*
Hospital stay, hours	24 (1-48)	12 (1-48)	1 (1-24)	0.001*

Data are shown as mean±standard deviation or median (minimum-maximum) or number and percentage (%). *p<0.05 shows statistical significance. Bold characters indicate differences between groups. Abbreviations: ESWL: Extracorporeal shock wave lithotripsy

Table 2. Distribution of postoperative complications and outcomes according to procedure types

Variables	Pneumatic lithotripsy n=50	Laser lithotripsy n=50	ESWL n=50	p-value
Complications, n (%)				
No	31 (62.0)	33 (66.0)	27 (54.0)	0.501
Yes	19 (38.0)	17 (34.0)	23 (46.0)	
Fever	5 (10.0)	4 (8.0)	4 (8.0)	0.999
Migration	6 (12.0)	3 (6.0)	6 (12.0)	0.556
Infection	2 (4.0)	2 (4.0)	3 (6.0)	0.999
Leak	-	-	1 (2.0)	0.999
Hematuria	9 (18.0)	11 (22.0)	18 (36.0)	0.107
Pain	18 (36.0)	15 (30.0)	18 (36.0)	0.791
Steinstrasse	-	-	2 (4.0)	0.326
Outcomes, n (%)				
Stonefree	35 (70.0)	40 (80.0)	39 (78.0)	0.563
Pushback	11 (22.0)	6 (12.0)	-	0.001*
Minimalresidue	1 (2.0)	2 (4.0)	6 (12.0)	0.147
Post-procedure URS	3 (6.0)	2 (4.0)	5 (10.0)	0.600

Data are shown as number and percentage (%). *p<0.05 shows statistical significance. Abbreviations: ESWL: Extracorporeal shock wave lithotripsy, URS: Ureterorenoscopy

Table 3. Comparison of postoperative outcomes among procedure types based on stone size

Outcomes	Pneumatic lithotripsy	Laser lithotripsy	ESWL	p-value
Stones <10 mm, n (%)	**n=31**	**n=26**	**n=30**	
Stonefree	25 (80.6)	22 (84.6)	28 (93.3)	0.364
Pushback	5 (16.1)	3 (11.5)	-	0.063
Minimal residue	-	1 (3.8)	2 (6.7)	0.406
Post-procedure URS	1 (3.2)	-	-	0.999
Stones ≥10 mm, n (%)	**n=19**	**n=24**	**n=20**	
Stonefree	10 (52.6)	18 (75.0)	11 (55.0)	0.238
Pushback	6 (31.6)	3 (12.5)	-	0.012*
Minimal residue	1 (5.3)	1 (4.2)	4 (20.0)	0.272
Post-procedure URS	2 (10.5)	2 (8.3)	5 (25.0)	0.286

Data are shown as number and percentage (%). *p<0.05 shows statistical significance. Abbreviations: ESWL: Extracorporeal shock wave lithotripsy, URS: Ureterorenoscopy

Among patients with stones ≥10 mm, there were no statistically significant differences in the distributions of stone-free status (pneumatic lithotripsy: 52.6% vs. laser lithotripsy: 75.0% vs. ESWL: 55.0%, p=0.238) across procedure types. The frequency of pusback was higher in the pneumatic lithotripsy group compared to the other groups, while it was not observed in the ESWL group (pneumatic lithotripsy: 31.6% vs. laser lithotripsy: 12.5% vs. ESWL: 0%, p=0.012). There were no statistically significant differences in the distributions of minimal residue (pneumatic lithotripsy: 5.3% vs. laser lithotripsy: 4.2% vs. ESWL: 20.0%, p=0.273), and the requirement for post-procedure URS (pneumatic lithotripsy: 10.5% vs. laser lithotripsy: 8.3% vs. ESWL: 25.0%, p=0.286) across procedure types (**Table 3**).

DISCUSSION

Guidelines by both the American Urological Association (AUA) and the European Association of Urology (EAU) indicate that for stones <10 mm, ESWL and URS yield stone-free rates of approximately 90% and 80%, respectively; for stones ≥10 mm, these rates decrease to 68% and 79%.[14] Their meta-analyses further confirm that ureteroscopy outperforms ESWL for stones ≥10 mm in the upper ureter.[14] Similarly, in a large series of patients undergoing URS for upper ureteral stones, a stone-free rate of 91.7% and a low complication rate of 1.8% have been reported.[15] A previous study comparing ultrasonic, electrohydraulic, pulsed-dye laser, and pneumatic lithotripsy in URS have documented an overall success rate of 87.8%; success rates for each modality have been reported as 79.6%, 72%, 86.7%, and 92.7%, respectively.[16] A meta-analysis comparing URS and ESWL for the management of large (>10 mm) proximal ureteral stones revealed that URS achieved a higher stone-free rate, whereas ESWL was associated with a higher retreatment rate. Nonetheless, no significant differences were observed between the two techniques regarding mean operative time, auxiliary procedure rates, or complication rates.[5] In our study, treatment success was defined as achieving stone-free status; any residual fragments and need for repeated interventions were considered a failure. For stones <10 mm, the stone-free rates in the ESWL, pneumatic, and laser lithotripsy groups were 93.3%, 80.6%, and 84.6%, respectively, without statistically significant differences among them. However, for stones ≥10 mm, the rates decreased to 55%, 52.6%, and 75%, respectively. Laser lithotripsy tended to show high success rate than other treatment groups. These findings highlight the impact of stone size on the effectiveness of different treatment modalities.

We observed that the re-intervention rate among patients with stones ≥10 mm treated with ESWL was 25%, compared to 10.5% for pneumatic lithotripsy and 8.3% for laser lithotripsy. Conversely, second procedure rates were markedly lower in cases involving stones <10 mm. Our findings align with previous reports that ESWL might be more suitable for smaller stones, given that larger or impacted stones can yield higher rates of residual fragments and possible steinstrasse.[5,17-19] In response to the drawbacks associated with ESWL-particularly the need for repeated sessions and the associated increased morbidity-endoscopic approaches have gained prominence and, in many centers, have become the first-line treatment for ureteral stones.[20] Historically, ESWL was recommended for upper ureter stones, whereas URS was primarily indicated for mid and distal ureteral stones.[21] However, the development of small-caliber semirigid and flexible ureteroscopes, alongside advances in holmium laser technology, has enabled safer and more effective ureteroscopic intervention at all ureteral levels.[22] Indeed, single-session stone-free rates with flexible ureteroscopy have been reported to reach 81-94% in various series, bringing outcomes closer to those of ESWL, particularly for upper ureteral stones.[14,23-25]

Although ESWL is less invasive, patients must sometimes endure extended periods awaiting spontaneous fragment passage, which can be accompanied by colic, possible additional sessions, or even salvage URS.[26] Meanwhile, URS-whether pneumatic or laser-often can provide a definitive solution in a single session. Consequently, many patients prefer ureteroscopic approaches to avoid the uncertainty and repeated visits associated with ESWL, particularly when stones are large or symptomatic.[27] Nonetheless, institutional factors such as the availability of endoscopic equipment, laser fibers, and the surgeon's experience also play roles in treatment selection.[28,29]

Pneumatic lithotripsy effectively fragments even hard calculi. However, its high-impact mechanical force can drive stone fragments proximally (pushback), leading to longer procedure times, additional interventions, and potentially higher morbidity.[30] In our series, the laser lithotripsy group had the longest mean operative time, which we attribute partly to a steeper learning curve, the delicate nature of laser fragmentation, and the slightly larger stone sizes in that group compared to the other arms. Also, we noted a 12% rate of significant upward stone migration with pneumatic lithotripsy, consistent with other publications.[30-33] Because most pneumatic systems are used with rigid ureteroscopes, retrieving migrated fragments can be technically challenging-especially for upper ureter stones. Laser lithotripsy, often employing holmium: YAG technology, emits energy localized primarily on the stone surface rather than surrounding tissues or irrigation fluid. It is compatible with small-caliber and flexible ureteroscopes, thus broadening its utility for upper ureter or intrarenal stones.[34,35] Beyond stone fragmentation, holmium lasers can assist with coagulation and even the excision of ureteral strictures or other obstructive lesions, offering a "multipurpose" advantage during endoscopic procedures.[36]

Complication rates for ESWL range from 1.5% to 35% in various series.[37] Post-ESWL complications, such as sepsis, steinstrasse, hematuria, and flank pain, do occur but are generally lower than the potential injuries seen in URS (e.g., perforation, mucosal tears).[38] According to the 2007 AUA guidelines, URS complications include a 1-2% risk of stricture, 3-6% ureteral injury, 2-4% urinary tract infection/sepsis, and 0% steinstrasse.[14] Consistent with the literature, our study documented the most frequent postoperative complaints as fever, mucosal lesions, and stone migration-especially in the pneumatic group. In the ESWL group, minimal extravasation was observed in one patient, managed successfully with temporary stenting and no further intervention required. Interestingly, the overall complication distribution also seems tied to surgeon expertise. In our series, laser lithotripsy tended to show fewer complications than pneumatic lithotripsy, potentially reflecting the surgeon's familiarity with the laser device and the localized mechanism of holmium laser energy. This notion is supported by other studies demonstrating that surgeon experience can play a pivotal role in minimizing complications and optimizing outcomes.[38-40]

Limitations

This study has several limitations. The retrospective nature of the study may introduce inherent biases, such as selection bias and the inability to control for all confounding variables. The study was conducted at a single center, which may limit the generalizability of the findings to other institutions or patient populations with different clinical practices, technological access, or surgeon expertise. The study primarily focused on short-term outcomes, such as stone-free rates and complications within the immediate postoperative period. We evaluated stone-free status in the short term using direct urinary system radiography and intravenous urography, which may underestimate final stone-free rates, as the EAU guidelines recommend a longer follow-up-up to three months-for possible delayed fragment passage. Longer-term follow-up is necessary to assess late complications, such as ureteral stricture formation, and to determine the recurrence rates of stones after treatment. Additionally, a longer follow-up period with additional imaging modalities, such as ultrasonography or non-contrast computed tomography, could have provided a more precise assessment of stone-free rates.

CONCLUSION

ESWL remains a valuable non-invasive option, offering shorter hospital stays and minimal procedural risk. However, its efficacy decreases with increasing stone size, often necessitating multiple sessions and additional interventions, which may offset its initial advantages. Pneumatic lithotripsy is effective for stone fragmentation but carries a higher risk of stone migration due to its mechanical impact, particularly in proximal ureteral stones. This migration often leads to extended operative times and additional procedures. Laser lithotripsy demonstrated better stone-free rates, especially for stones ≥10 mm, with lower complication rates compared to other modalities. Despite requiring longer operative times, its precision and ability to manage complex stone scenarios make it a highly effective treatment option.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was produced from a thesis before 2020, and institutional approval was received.

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Comprehensive Surgery

Original Article

DOI: 10.51271/JOCS-0049

Construction of three-dimensional cartilage autograft and evaluation of the superiority of interperichondrial implantation

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Cite this article as: Avşar Y, Aygıt AC. Construction of three-dimensional cartilage autograft and evaluation of the superiority of interperichondrial implantation. *J Compr Surg.* 2025;3(1):15-21.

Received: 30.01.2025 • **Accepted**: 18.02.2025 • **Published**: 23.02.2025

ABSTRACT

Aims: This study aimed to develop a three-dimensional (3D) cartilage autograft using diced cartilage and fibrin tissue glue and to compare the outcomes of interperichondrial implantation versus subcutaneous implantation in terms of graft viability, biomechanical properties, and histopathological characteristics.

Methods: Eleven albino rabbits underwent auricular cartilage harvesting, with a 3×2 cm segment dissected bilaterally. After dicing, the cartilage fragments were combined with fibrin tissue glue and molded into two 3D dorsal nasal grafts. One graft was implanted into the interperichondrial pocket of the right ear, and the other was placed subcutaneously in the right dorsal region. Two control sites were created: subcutaneous fibrin-only implantation on the left dorsal region and an empty interperichondrial pocket on the left ear. The rabbits were sacrificed at eight weeks, and the grafts were evaluated macroscopically, physically, and histopathologically.

Results: Two animals were excluded due to graft loss from flap necrosis. In the remaining rabbits, the interperichondrial group exhibited superior shape retention, less volume loss, and higher elasticity compared to the subcutaneous group ($p<0.05$). Histopathological assessment showed significantly greater chondrocyte viability ($p<0.05$) and new cartilage formation ($p<0.05$) in the interperichondrial group, coupled with lower vascularization ($p<0.05$) and reduced fibrosis ($p<0.05$). By contrast, the subcutaneous group exhibited prominent vascularization, dense fibrous encapsulation, and more pronounced shape and volume loss. No significant intergroup differences were observed for fibrin residue or ossification ($p>0.05$). The control grafts (fibrin-only and empty interperichondrial sites) demonstrated no cartilage formation.

Conclusion: Diced cartilage grafts combined with fibrin tissue glue are better supported in the interperichondrial environment than in the subcutaneous tissue. Interperichondrial implantation not only preserves graft shape and volume but also enhances chondrocyte viability and cartilage regeneration, emphasizing its potential as a clinically valuable strategy in reconstructive cartilage grafting.

Keywords: Cartilage engineering, diced cartilage, fibrin glue, interperichondrial implantation, subcutaneous implantation, perichondrium, rabbit model, cartilage regeneration

INTRODUCTION

Cartilage defects represent a significant clinical challenge due to the tissue's limited regenerative capacity and the high incidence of degenerative joint diseases worldwide.[1] Autologous cartilage grafting is often preferred in clinical practice to restore functional tissue, as it reduces immunological complications and leverages the patient's inherent biological properties.[2] Among available techniques, diced or minced cartilage grafts have gained popularity for various reconstructive purposes including defect filling, contour correction, and augmentation.[3]

Although three-dimensional (3D) cartilage constructs can be produced by isolating chondrocytes and culturing them in biocompatible polymer scaffolds, such approaches are time-consuming, labor-intensive, and costly, requiring specialized laboratory facilities.[4,5] These practical barriers can limit the widespread clinical application of engineered cartilage tissues.[6,7] To overcome these challenges, replacing isolated chondrocytes with diced or minced cartilage fragments and utilizing readily available bio-polymers, such as fibrin tissue glue, could streamline the generation of 3D cartilage grafts, making the process more feasible and cost-effective.[8,9]

Since cartilage has a very limited ability to regenerate, additional biological support may be needed to preserve graft viability and strength. The perichondrium, an envelope of dense connective tissue surrounding cartilage, contains progenitor cells and supports vascularization at the interface, which can

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be crucial for graft survival.[10,11] Consequently, implanting 3D cartilage constructs interperichondrially-i.e., between layers of perichondrium-has been proposed as a method to enhance nutrient diffusion, mechanical stabilization, and overall tissue remodelling.[12-14]

In this study, we aimed to explore an alternative approach to 3D cartilage grafting by utilizing diced cartilage instead of chondrocytes. To achieve this, we selected a rabbit model and employed fibrin tissue glue as a biopolymer scaffold to enhance graft cohesion and integration. Given the limited regenerative capacity of cartilage, we hypothesized that perichondrial support would be critical for maintaining graft viability and structural integrity. Therefore, we compared the outcomes of interperichondrial implantation and subcutaneous implantation in terms of graft survival, biomechanical properties, and histopathological characteristics. By systematically evaluating these grafts through visual, physical, and histological assessments, we aimed to determine the superiority of interperichondrial implantation and provide insights into optimizing clinical cartilage grafting techniques.

METHODS

This experimental study was conducted at the Department of Plastic and Reconstructive Surgery, Trakya University Faculty of Medicine, using 11 albino rabbits. The experimental protocol was approved by the Trakya University Faculty of Medicine Ethics Committee (Date: 06.02.2003, Decision No: 03). All procedures were carried out in accordance with the ethical rules and the principles. Histopathological examinations were carried out at the Department of Pathology, Trakya University Faculty of Medicine.

Surgical Procedure

Anesthesia was induced using 2% xylazine hydrochloride (Rompun, Bayer, Leverkusen, Germany) at 0.5 ml/kg and 10% ketamine hydrochloride (Ketalar, Pfizer) at 0.5 ml/kg. A 1/3 segment of each auricular cartilage (3×2 cm in size) was excised bilaterally following perichondrial dissection and preserved in 0.9% saline solution. Interperichondrial implantation sites were prepared in the same regions.

The harvested cartilage grafts were diced and combined with fibrin tissue glue (Tisseel, Baxter, Austria) to form two three-dimensional dorsal nasal grafts. A two-part mold made of polysiloxane (Zetaplus, Zhermack, Italy) was used to shape the grafts (Figure 1).

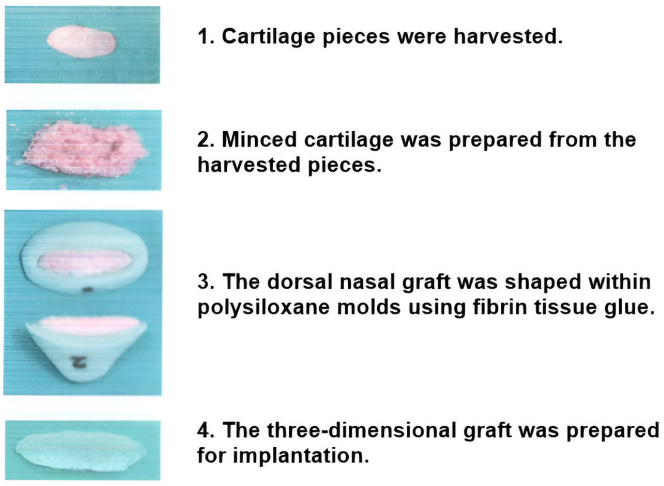

Figure 1. Construction of the three-dimensional cartilage graft

Graft Groups

The first graft was placed in the interperichondrial area of the right ear (interperichondrial graft group) (Figure 2), while the second graft was placed in the subcutaneous area of the right dorsal region (subcutaneous graft group).

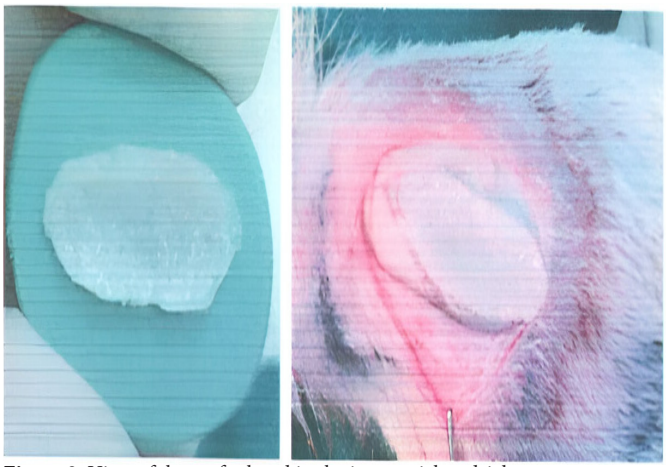

Figure 2. View of the graft placed in the interperichondrial area

In the left dorsal region, a shaped fibrin tissue adhesive without diced cartilage was placed into the subcutaneous area, while the interperichondrial area of the left ear was left empty. These two regions served as control groups (Figure 3).

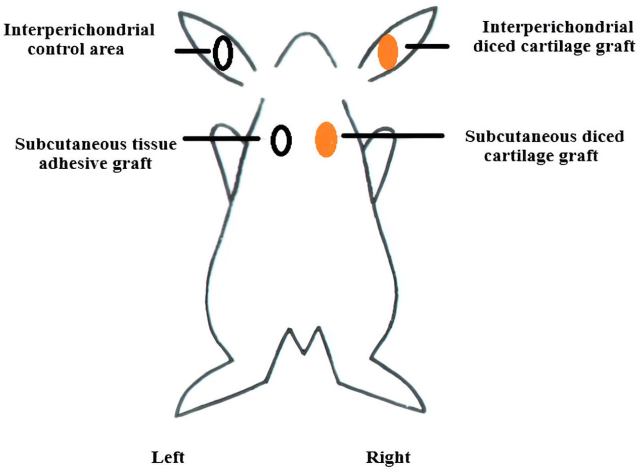

Figure 3. Implantation area of cartilage grafts and control groups

Sample Collection

The rabbits were sacrificed 8 weeks postoperatively, and the placed cartilage structures were retrieved for evaluation. The harvested samples were assessed based on visual, physical, and histopathological criteria. Shape and volume loss percentages were determined by two independent observers. Elasticity measurements were conducted and compared between the two groups. Interobserver agreement was assessed, followed by a direct comparison of the interperichondrial and subcutaneous implantation groups.

Retrieved specimens were fixed in 10% formalin for 24 hours. Sections were stained with hematoxylin-eosin (H&E) for general histological evaluation. Masson's trichrome staining was used to assess fibrotic tissue formation. Samples were examined under a light microscope, and six parameters were analyzed: viability, new cartilage formation, residual fibrin tissue glue, vascularization, fibrosis, and ossification.

Statistical Analysis

All data were analyzed using Minitab Release 13 software package version (Minitab Inc. State College, PA, USA). The Wilcoxon signed-rank test and Kappa test were employed to evaluate inter-observer differences, while the Mann-Whitney U test and Chi-square analysis were used for intergroup comparisons. Significance was accepted at $p<0.05$ (*) for all statistical analyses.

RESULTS

All rabbits gained weight throughout the study and exhibited no signs of distress findings. However, in two rabbits, graft extrusion was observed in the auricular region due to flap necrosis during the first week, leading to graft loss. These cases were excluded from the study.

Macroscopic examination of the retrieved samples revealed distinct differences between the interperichondrial and subcutaneous grafts. The structures obtained from the interperichondrial space were white in color and lacked a surrounding capsule, whereas the grafts retrieved from the subcutaneous region appeared white-blue and were encapsulated by a thin fibrous membrane, which made them easily separable from the surrounding tissues. In the control groups, the fibrin tissue glue placed in the left dorsal subcutaneous region was completely resorbed by the 8th week, and no cartilage formation was observed. Similarly, in the interperichondrial control sites of the left ear, no cartilage formation was detected in any of the animals by the end of the study period (Figure 4).

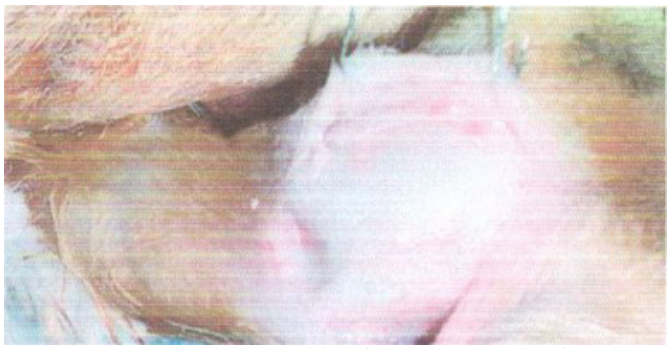

Figure 4. Interperichondrial area of the left ear without cartilage formation

When comparing the macroscopic morphology of the interperichondrial and subcutaneous graft groups, the interperichondrial graft group exhibited better structural organization and greater preservation of shape and volume (Figure 5). Conversely, the grafts retrieved from the subcutaneous region appeared more fibrotic and fragile, with noticeable shape and volume loss (Figure 6). Elasticity was also reduced in the subcutaneous graft group compared to the interperichondrial graft group. Statistical analysis confirmed significant differences between the two groups in terms of volume loss, shape loss, and elasticity ($p<0.05$ for all) (Table 1). Interobserver analysis showed no significant discrepancies in the evaluation of these parameters.

Histopathological assessment further demonstrated that chondrocyte viability was higher in the interperichondrial graft group compared to the subcutaneous graft group ($p=0.014$) (Table 2). Moreover, the interperichondrial graft group exhibited lower vascularization ($p=0.014$) and fibrosis ($p=0.001$), but greater new cartilage formation (p-0.002)

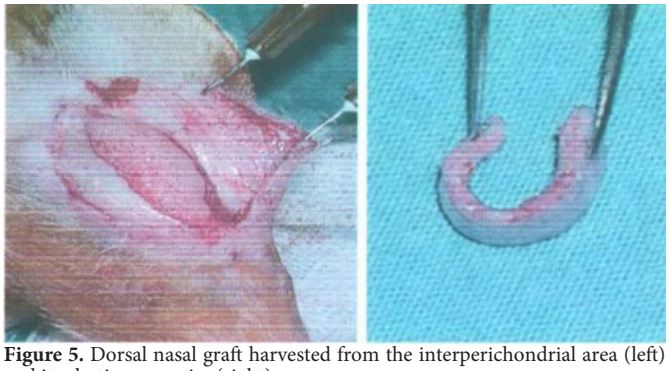

Figure 5. Dorsal nasal graft harvested from the interperichondrial area (left) and its elastic properties (right)

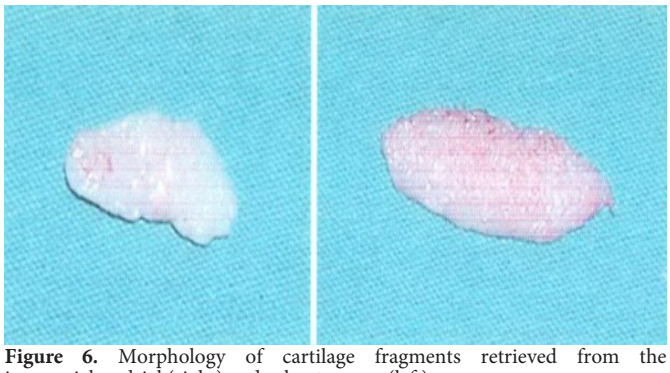

Figure 6. Morphology of cartilage fragments retrieved from the interperichondrial (right) and subcutaneous (left) areas

Table 1. Visual and physical evaluation of the obtained structures

Graft area	Subject	Observer	Volume loss (%)	Shape loss (%)	Elasticity
Interperichondrial	1	1	8	8	+++
		2	7	7	+++
	2	1	8	7	+++
		2	6	5	++++
	3	1	5	8	++++
		2	5	5	++++
	4	1	8	7	+++
		2	7	3	++++
	5	1	4	4	++++
		2	4	5	++++
	6	1	5	5	++++
		2	4	3	++++
	7	1	7	5	+++
		2	6	5	+++
	8	1	9	8	++++
		2	4	3	+++
	9	1	5	3	++++
		2	9	8	+++
Subcutaneous	1	1	20	30	+++
		2	16	20	+++
	2	1	30	40	++
		2	8	15	+++
	3	1	7	10	+++
		2	12	20	+++
	4	1	19	32	++
		2	22	36	++
	5	1	12	20	+++
		2	18	30	+++
	6	1	15	35	++
		2	19	28	+++
	7	1	20	40	+++
		2	8	15	++
	8	1	15	32	+++
		2	7	10	+++
	9	1	8	15	+++
		2	22	35	++

Table 2. Histopathological evaluation of the obtained structures

Graft area	Subject	Viability	Fibrin tissue glue residue	Vascularity	New cartilage formation	Fibrosis	Ossification
Interperichondrial	1	Good	No	Good	Good	Low	No
	2	Good	No	Good	Moderate	Low	No
	3	Good	No	Moderate	Good	Low	No
	4	Moderate	No	Good	Moderate	Low	No
	5	Good	No	Moderate	Good	Low	No
	6	Good	No	Low	Good	Orta	No
	7	Moderate	No	Good	Moderate	Orta	No
	8	Good	No	Moderate	Good	Low	No
	9	Good	No	Good	Good	Low	No
Subcutaneous	1	Moderate	No	Good	Low	Severe	No
	2	Low	No	Good	yok	Severe	No
	3	Moderate	No	Good	Low	Moderate	No
	4	Moderate	No	Good	Low	Severe	No
	5	Good	No	Good	Moderate	Moderate	No
	6	Moderate	No	Moderate	Low	Severe	No
	7	Moderate	No	No	Low	Severe	No
	8	Moderate	No	Low	Low	Severe	Yes
	9	Low	Yes	Moderate	No	Moderate	Yes

(Figure 7, Table 2), whereas the subcutaneous graft group showed increased vascularization and dense fibrosis (Figure 8, Table 2). However, no significant differences were noted between the groups in terms of fibrin tissue glue residue and ossification (p>0.05) (Table 2).

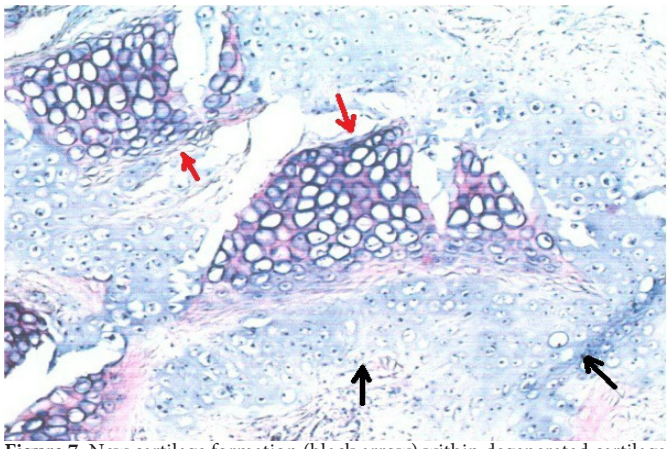

Figure 7. New cartilage formation (black arrow) within degenerated cartilage fragments (red arrow) (Hematoxylin-Eosin, x50)

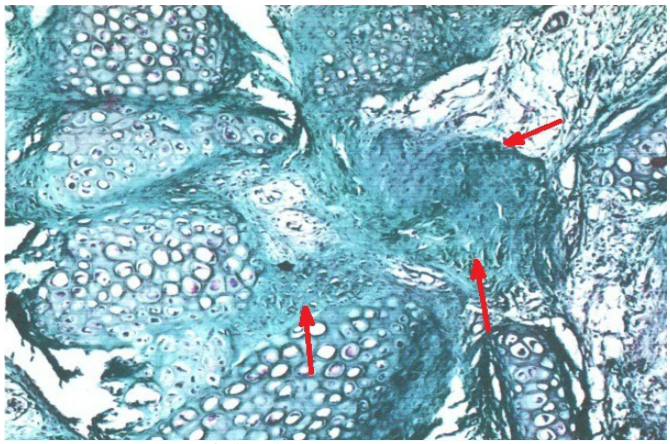

Figure 8. Formation of abundant connective tissue (red arrow) observed among degenerated cartilage fragments (Masson's Trichrome Staining, x50)

DISCUSSION

The findings of this study highlight the importance of the perichondrial environment in promoting the viability and structural integrity of 3D cartilage grafts composed of diced cartilage and fibrin tissue glue. Our results showed that interperichondrial implantation yielded superior macroscopic and histological outcomes compared to subcutaneous placement, suggesting that the unique biological and mechanical features of the perichondrium play a pivotal role in cartilage regeneration.

An ideal cartilage structure can be engineered by culturing chondrocytes within synthetic or biological polymer scaffolds, a technique widely explored in tissue engineering literature.[15,16] However, this method is both time-consuming and costly, requiring specialized laboratory facilities and extensive processing. Additionally, the amount of viable tissue obtained is often insufficient for clinical use, and these constructs are prone to volume loss over time, limiting their long-term effectiveness.[17,18] Due to these drawbacks, engineered cartilage is not readily available for immediate intraoperative application, making its routine use in surgical procedures challenging.[19]

The perichondrium has long been recognized as an essential component for cartilage repair, attributable to its reservoir of progenitor cells, local growth factors, and the capacity to support vascularization at the graft-host interface.[20] However, its precise mechanism of fostering cartilage tissue engineering remains an active area of investigation. In the interperichondrial environment, diced cartilage fragments appear to benefit from an enhanced chondrogenic niche, as evidenced by higher chondrocyte viability, less fibrosis, and greater new cartilage formation in our study. These observations align with previous reports indicating that perichondrial grafting or enveloping may help maintain the chondrogenic phenotype and facilitate tissue remodelling.[21-24]

Conversely, the subcutaneous environment offers a comparatively higher vascular density and reduced mechanical support, often leading to fibrotic encapsulation of grafted tissues.[25] In our study, the subcutaneous grafts exhibited greater shape and volume loss as well as higher vascularization and fibrosis, findings that mirror clinical challenges encountered when cartilage grafts are placed in non-perichondrial sites.[4,26] Excessive vascular ingrowth has been associated with a propensity for fibrocartilage formation or even ossification in certain contexts, potentially compromising the long-term functional properties of the implant.[1] Although we did not observe significant ossification in our subcutaneous grafts, the increased fibrotic response likely impairs biomechanical resilience, diminishing the potential for durable cartilage repair.

In histopathological assessment, seeing a chromatin-containing nucleus in living cartilage cells indicates viability.[27] While necrotic areas may be present within the newly generated graft from diced cartilage due to inadequate nourishment, the remaining viable chondrocytes possess strong proliferative abilities and a marked capacity for new cartilage formation.[28] Additionally, growth factors secreted from the perichondrial surface, including epidermal growth factor, fibroblast growth factor, and insulin-like growth factors, play a crucial role in new cartilage formation.[23,29] We demonstrated that cartilage grafts obtained from the interperichondrial space more closely resemble native cartilage in terms of visual, physical, and histopathological characteristics. Previous studies have also shown that the presence of the perichondrium significantly enhances graft survival and new cartilage formation.[30,31] In contrast, cartilage fragments lacking perichondrium tend to be fragile and exhibit significant chondrocyte loss. Notably, in grafts with perichondrial support, the healing process is characterized by new cartilage formation rather than fibrotic tissue development.[31] However, in highly vascular implantation sites, the presence of macrophages and partial graft resorption should be anticipated.[32]

In this study, vascularization was evaluated using H&E staining, which provides general insights into tissue morphology and blood vessel presence. However, immunohistochemical staining (IHC) with endothelial markers such as platelet endothelial cell adhesion molecule (PECAM-1), also referred to as cluster of differentiation 31 (CD31), vascular endothelial growth factor (VEGF), and alpha smooth muscle actin (α-SMA) offers a more detailed and quantitative assessment of vascularization.[33] Robust CD31 staining indicates the presence of mature microvessels infiltrating the graft, reflecting effective angiogenesis. In graft analyses, $CD34^+$ cells can denote angiogenic activity or immature vessels forming.[34] VEGF expression in the graft or surrounding tissue signifies an active drive for new vessel formation. It plays a primary role in initiating angiogenesis and can even promote vascular invasion into cartilage.[35] In graft histology, α-SMA positivity around capillaries indicates maturation and stabilization of neovessels by pericyte recruitment.[34,36] Collectively, these markers provide a detailed picture of graft revascularization. Using such markers in combination enhances the histological evaluation of cartilage graft viability and integration by quantifying microvessel density and the maturity of the vascular network.

Previously, synthetic polymers like polyglycolic acid/polylactic acid, calcium alginate, and polyethylene oxide were used to join small pieces of diced cartilage. However, these materials have drawbacks, including poor resorption, fibrosis formation, and immunogenicity concerns.[37,38] The use of fibrin tissue glue as a bio-scaffold proved advantageous for molding and stabilizing the diced cartilage fragments.[39] Similar to other scaffolds such as collagen matrices or hyaluronic acid derivatives, fibrin provides a provisional matrix conducive to cellular adhesion and nutrient exchange.[40,41] Nevertheless, it is ultimately resorbed, underscoring the importance of having a robust chondrogenic milieu-such as the interperichondrial space-for sustained graft survival and cartilage formation. Our control group findings, showing complete resorption of fibrin without cartilage formation in the absence of diced cartilage, further corroborate the necessity of a cartilage-derived cellular component and an appropriate biological niche.

Autologous 3D cartilage grafts support high chondrocyte viability and robust extracellular matrix production, which are crucial for long-term graft success. Studies constructing 3D cartilage (for example, packing diced cartilage into molds) report that the resulting graft retains living chondrocytes and abundant cartilage-specific matrix (collagen II, glycosaminoglycans), with mechanical properties akin to native tissue.[42] Cartilage grafts nurtured by perichondrium show significantly greater chondrocyte survival than those without. An experimental comparison demonstrated ~87% viable chondrocytes in grafts wrapped with perichondrium, versus only ~41% in grafts wrapped in a non-perichondrial material (fascia) under otherwise identical subcutaneous conditions.[26] In practical terms, a graft surrounded by perichondrium establishes a microcirculation faster, which is crucial for the survival of larger or three-dimensional cartilage pieces that rely on diffusion.[43] On the other hand, mechanical testing of engineered 3D cartilage implants (e.g., auricular grafts) has shown stiffness and flexibility comparable to native ear cartilage, indicating they can endure physiological stresses.[42] Grafts supported by perichondrium tend to retain their volume and mechanical strength over time.[44] Due to these factors, interperichondrial implantation is considered superior when feasible. In practice, surgeons may create a pocket between perichondrial layers or preserve the graft's native perichondrium and secure it in a vascular bed to capitalize on these benefits.

Limitations

This study has several limitations. First, our sample size was relatively small, and two grafts were lost in the early phase due to flap necrosis. Additionally, although the rabbit model is widely used in preclinical research due to its manageable size and cost-effectiveness, interspecies differences in immune response and regenerative capacity may influence the direct translation of these findings to human clinical practice. Future work could involve extending the follow-up period to assess long-term structural integrity and biomechanical performance of the constructs, as well as exploring adjunctive techniques, such as growth factor delivery or preconditioning of cartilage fragments, to further enhance graft outcomes.

CONCLUSION

Our study provides meaningful insights into the design of clinically translatable 3D cartilage grafts. By capitalizing on the favorable characteristics of diced cartilage fragments

and fibrin glue, and harnessing the biological potential of the perichondrium, we present a potentially more feasible and cost-effective alternative to traditional chondrocyte-based tissue engineering approaches. Interperichondrial implantation offers distinct advantages in preserving graft shape, volume, and chondrocyte viability, emphasizing its potential as a preferred strategy in clinical cartilage repair and reconstructive applications.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Trakya University Faculty of Medicine Ethics Committee (Date: 06.02.2003, Decision No: 03).

Informed Consent

Because the study was designed using an albino rabbit, no written informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Journal of Comprehensive Surgery

Case Report

DOI: 10.51271/JOCS-0050

Approach to anal sphincter dysfunctions in a patient with endorectal pull-through procedure

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Cite this article as: Ulusoy Tangül S, Şenaylı A. Approach to anal sphincter dysfunctions in a patient with endorectal pull-through procedure. *J Compr Surg.* 2025;3(1):22-24.

Received: 28.12.2024 • **Accepted**: 05.02.2025 • **Published**: 23.02.2025

ABSTRACT

A seven-year-old male patient was examined in our pediatric surgery outpatient unit with abdominal distension. He had been operated on for congenital megacolon in the newborn period in another center. After a period of follow-up, he had been re-operated because of a diagnosis of insufficient pull-through, and a second pull-through had been performed. Following this procedure, myectomy and temporary colostomy procedures were reported in a different hospital. After all these treatments, he still had a distension episode, even associated with enterocolitis. In our clinic, we medically treated enterocolitis four times in 5 months. According to the council decision in our department, we decided to use a medically used Botulinum toxin to evaluate the possibility of internal anal sphincter achalasia (IASA), and therefore we injected Botulinum toxin into the internal sphincter under anesthesia. Following the procedure, the patient was brought to our attention only once in 4 months with distension. This data encouraged us to diagnose the disease and planned to perform partial sphincterotomy and internal sphincter myectomy. Nine months after the myectomy, the patient was not hospitalized and had a mild distension once. There is a significant improvement in his life quality; as a clear result, we observed and experienced that sphincter-related problems must be taken into account in incurable postoperative obstructive situations related to Hirschsprung's disease.

Keywords: Hirschsprung's disease, internal anal sphincter, achalasia

INTRODUCTION

Persisting obstructive diseases may lead to fecal stasis, which may progress to cases of enterocolitis associated with Hirschsprung's disease.[1] It is known that 11-55% of enterocolitis attacks may occur after surgery, and obstructive problems may continue.[1-5] Many methods have been tried to treat this condition.[1] These include redoing pull-through metronidazole treatment, preventive rectal irrigations, and the use of probiotics.[1,2,5]

Another method described for treatment is *Botulinum* toxin injection (Botox), which Langer described in 1997.[1,3] *Botulinum* toxin injection can be applied if complaints of enterocolitis continue despite trying the other methods mentioned above.[2,4] However, there are doubts about *Botulinum* toxin use.[5] Due to the effectiveness of *Botulinum* toxin, in cases where the injection is beneficial, continued injections will be required to maintain this therapeutic effect.[2] In other words, it is not a sustainable practice for every patient at all times. Alternatives to Botox are the topical application of nitric oxide to the anal canal, posterior myotomy, redo pull-through, or diverting colostomy.[2]

Posterior myectomy has been a recognized practice, especially for internal anal sphincter achalasia (IASA), for over 50 years.[6] Hurst first described internal anal sphincter achalasia in 1934.[6] It is a problem with the relaxation mechanism of the sphincter. It has been detected in 2.9-4.5% of children with chronic constipation, even without any other disease.[6,7] It is stated that this amount is a level that cannot be underestimated.[7] It is stated that it is characterized by the absence of the rectoanal inhibition reflex (RAIR).[6]

In the end, whatever procedures are performed, continuity of IASAs is possible, although all alternative treatments are used.[6] Besides, these applications also have their characteristic complications.[2]

In our case, we use the *Botulinum* toxin as a diagnostic tool rather than a treatment instrument for IASA. The report aimed to share our experience of diagnosing IASA with *Botulinum* toxin, and we discussed our findings with literature.

CASE

A seven-year-old male patient was hospitalized with abdominal distension and inflammatory findings. A high level of C-RP was found at 91 mg/ml (n: 0.15-5), and leucocytosis 18.65 U/L (n: 4.6-10.2) was detected. A plain abdomen X-Ray showed distension and obstruction (**Figure**). Enterocolitis was diagnosed as an exploding stool with a nasty smell that was found in a rectal digital examination. Broad-spectrum antibiotics and other procedural treatments for inflammation were performed.

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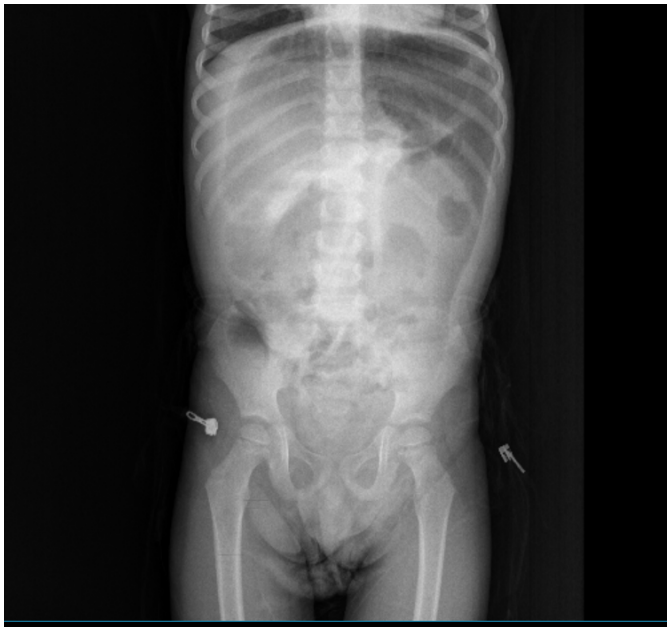

Figure. Abdominal distension in plain abdomen X-Ray

The patient had surgical procedures for congenital megacolon disease in some other hospitals. Endorectal Pull-through had been performed twice in a center and myectomy was also done in the same hospital. Pathology specimen of excised bowel obtained in the second pull-through, which was done as an expectation of remnant for an aganglionic segment, had resulted as usual. Unfortunately, as complaints continued, a colostomy was performed in another hospital. After a year, colostomy was closed in that hospital. However, he again suffered from the same problem.

In our hospital, encouraged after the patient's history, we thought that continuing problems despite all these performed procedures had to be related to sphincter mechanisms. To test our hypothesis, based on the literature, we decided to use medically used *Botulinum* toxin. We did not evaluate anorectal function with anal manometry because, in our facility, there is any. Also, a financial status of the family is not suitable to have an anorectal manometry in a different city. As a result, they requested this procedure to ease this social problem. After Botox, distension and clinical findings altered, were not totally disposed of, but were significantly reduced. In four months, the patient had mild complaints without needing clinical hospitalization.

We found this result satisfying enough to perform posterior partial sphincter myectomy. Myectomy containing internal sphincter muscles was performed in lithotomy position to the posterior region between four and eight o'clock location. The patient has been in a healed situation nine months after the surgery. Parents called the outpatient clinic by phone to ask for slight suffering and for some other complaints that were not related to the disease. Since the hospital discharge, they did not need to bring the patient for further examination.

DISCUSSION

After Hirschsprung's disease surgeries, even if the surgery is successful, complaints related to obstructive attacks such as distension, excessive gassiness, vomiting, and cramps may be encountered.[1] Obstruction findings that develop after pull-through may be due to technical reasons (structure, folding of the pull-through segment, Soave cuff) or functional reasons (anus internal sphincter hypertonicity).[1] It has been shown that there is no relationship between obstructive findings after surgery and the timing of the surgery.[4] In other words, there is an impression that postoperative Hirschsprung-related enterocolitis[1] may develop slightly fewer amounts in patients operated on at older ages than in the neonatal period.[4]

Internal anal sphincter achalasia (IASA) is at least one of the causes of childhood constipation and fecal obstruction.[6] IASA can also be caused by any functional or physical problem.[6] Although the exact cause is unknown, it is thought that IASA is caused by deterioration in the innervation of the muscles, nitrergic nerve deficiency, cholinergic hyperplasia, and abnormal peptidergic innervation.[6] This pathological condition may be encountered during Hirschsprung's' disease, but similar findings may occur without Hirschsprung's' disease.[6] The difference between them is that symptoms occur later in patients with constipation than in Hirschsprung's' disease.[7] In contrast, some studies state that patients with IASA have fecal incontinence; others state that the inability to defecate is evident.[7]

If this condition is left untreated, it can cause problems including enterocolitis, systemic inflammation, and mortality.[1] Studies have shown that enterocolitis attacks are reduced by approximately 17-76% with Botox.[1,5,7] There is no consensus regarding the amount and location of the injection.[1,6] There are studies with amounts between 30-200 units/ml and studies performed between 4-8 regions.[1,4] However, it is stated that symptoms may return within 3-6 months.[1] As another approach, it has been said that *Botulinum* toxin, nitroglycerin ointment, or calcium channel blockers can be used after the surgical procedure until the surgical area heals.[4]

There is also literature expressing negative opinions about the application. A study determined that Botox in the first month postoperatively did not reduce the likelihood of developing enterocolitis in patients who underwent Swenson surgery.[4] In a study, a group of patients who underwent posterior internal anal sphincter myectomy was compared with a group of patients who received *Botulinum* toxin, and similar results were reported.[6] In some studies, it has been stated that there is no need to perform Botox, as it has been stated that the expected effect of disrupting the anal sphincter appears over the years and only weakly.[7] For this reason, as general literature information, it has been claimed that procedures such as sphincterotomy or myectomy have begun to be performed instead of *Botulinum* injection.[4]

Various complications may occur with Botox. These include temporary incontinence, pelvic floor muscle paresis, rectal prolapses, and perianal abscess.[1,2] In addition, despite *Botulinum* toxin, there may be no benefit, and problems that may lead to repeat surgery may continue.[2]

The patient applied to our clinic after all IASA-related procedures such as redo pull-through, diverting colostomy, and posterior myectomy had been performed. However, there was no history of using nitric oxide topical cream. We injected the sphincter with *Botulinum* toxin to see whether the problem was IASA. When the patient showed significant clinical improvement, we decided that IASA caused it. Since the economic situation of the family would not buy it for continuous use of *Botulinum* toxin, we decided to perform a sphincter myectomy. It was observed that the patient's clinical well-being continued during follow-up.

CONCLUSION

Although there is enough information in the literature about the use of *Botulinum* toxin, it is clear that there needs to be a standard regarding what situations, at what intervals, and in what dosages it should be used. In our clinical experience, we have come to the understanding of identifying the IASA problem, if any, and combining it with sphincter myectomy application rather than using it as a treatment protocol. Such a method of use has also been suggested in the literature and has clinical use. This method is realistic in decision-making, and I believe that such use of *Botulinum* toxin will contribute to the search for treatment protocols.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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