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Electromyographic and Clinical Investigation of the Effect of Platelet-Rich Plasma on Peripheral Nerve Regeneration in Patients with Diabetes after Surgery for Carpal Tunnel Syndrome

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Abstract

Background Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. Studies have shown that results of CTS surgery are poorer in patients with diabetes. In this study, the effect of platelet-rich plasma (PRP) on nerve regeneration was investigated through clinical and electromyographic findings in patients with diabetes who underwent CTS surgery.

Methods A retrospective analysis of 20 patients with diabetes who had surgically decompressed CTS was conducted. Patients were divided into two groups. The study group received PRP treatment following surgery. The control group did not receive any treatment. Patients were assessed using electromyography and the Boston Carpal Tunnel Syndrome Questionnaire preoperatively as well as postoperatively at 3-month, 6-month, and 1-year follow-ups visits.

Results There was a decrease in complaints and an improvement in sensory and motor examinations in both groups. The Boston Carpal Tunnel Syndrome Questionnaire scores did not show any statistically significant differences between the two groups. However, electromyographic findings showed that there were statistical differences between preoperative and postoperative (3 months, 6 months, and 1 year) results in both groups. When the two groups were compared using preoperative and postoperative (3 months, 6 months, and 1 year) electromyographic values, no statistically significant differences were seen.

Conclusion Single injections of PRP did not have a significant impact on median nerve regeneration following CTS surgery in patients with diabetes. The effectiveness of multiple PRP injections can be investigated in patients with diabetes in future studies.

Keywords
- diabetes mellitus
- carpal tunnel syndrome
- median nerve
- nerve regeneration
- platelet-rich plasma

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Carpal tunnel syndrome (CTS) is the result of compression of the median nerve at the wrist and is the most frequently observed entrapment neuropathy. It was first described by Paget in a case of distal radius fracture.[1] Its frequency of occurrence in the general population is between 3.8 and 5.8%.[2] It is observed more commonly in women, primarily between ages 45 and 59 and between ages 75 and 84.[3] Patients with CTS usually present with complaints of numbness in the hand while carrying items. Tingling, numbness, and pain in the hands that wake patients up from their sleep at night, as well as aches and weakness that keep people from performing daily activities, are the most frequent complaints. The physiological basis of CTS is ischemic damage that occurs in the median nerve as a result of increased internal carpal tunnel pressure.[4] Various modalities have been described for the treatment of CTS. Wrist splints and corticosteroid injections are suggested for minor or moderate CTS treatment. Severe CTS cases do not respond to conservative treatment and may require surgical decompression. Any mass, disease, or situation that causes compression of the median nerve may cause CTS. Although CTS is most frequently seen idiopathically, numerous diseases and conditions can cause CTS, such as rheumatoid arthritis, diabetes mellitus (DM), radius fractures, and obesity.[4–6]

A correlation between DM and CTS has been identified in several studies. The prevalence of CTS in people with diabetes is 15 to 33%,[7] and the life-long CTS risk in patients with type 1 diabetes is 80%.[8,9] It is known that the results of surgical decompression in patients with diabetes are worse when compared with the nondiabetic population.[10,11] This can be explained by the sensorimotor neuropathy observed in patients with diabetes. Demyelination and structural changes in the nerve, as seen in diabetic neuropathy, results in a decline in the speed of neural transmission and a decrease in action potentials. Additionally, accompanying growth factor deficiency and the weakened immune system response in patients with diabetes contribute to their poor outcomes.[12,13]

Platelet-rich plasma (PRP) is a plasma component containing highly concentrated platelet-based growth hormones that is prepared by centrifuging autologous blood.[14] Platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β1 and TGF-β2), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), and endothelial growth factor, which are released with platelet activation, provide the regenerative effects of PRP. In numerous in vivo and in vitro studies, it has been shown that PRP has neuroprotective and neurotrophic effects.[15–17] The aim of this study was to evaluate the effects of PRP on median nerve regeneration for CTS cases treated surgically by retrospectively comparing patients with diabetes who received PRP treatment after surgery and those who did not..

Methods

The study was approved by the institutional ethical committee (IRB #4668). Informed consent was obtained from all patients. Ten patients with DM who were injected with PRP through a drainage tube on the incision line were included in the study group. Injections were administered on postoperative day 1 following surgical decompression. Ten patients with DM who did not receive any additional treatment after decompression surgery were included in the control group. Since a drainage tube was routinely placed after every CTS operation to prevent postoperative hematoma formation around the nerve and avoid pressure on the median nerve, the PRP was injected through the mini-vacuum drain and the drain was removed afterwards, so that it would not suction the administered PRP, rather than spraying it directly on the nerve during surgery. Since only one compartment was released during surgery and the mini-vacuum drain was fixed to its place after insertion, PRP was administered directly onto the median nerve. Patients with rheumatologic disease, thyroid disorder, connective tissue disease, or a history of carpal bone fracture were not included in the study. All patients were followed with a postoperative hand splint for 1 week. Splinting at night was suggested for the following 6 months. Patients' files were scanned for preoperative and postoperative (3 months, 6 months, and 1 year) motor and sensory examinations, as well as results of electromyography, pain assessment and provocation tests, preprandial blood glucose, microalbuminuria, accompanying nephropathy, retinopathy, and hemoglobin A1c levels. The results of the Boston Carpal Tunnel Syndrome Questionnaire and the Health Assessment Questionnaire (HAQ) were statistically analyzed.

Surgical Method

Operations were performed under general anesthesia or axillary nerve block with an upper extremity tourniquet. Following a short carpal tunnel incision, dermal and subdermal adipose tissues were passed and the transverse carpal ligament (TCL) was reached. The median nerve and flexor tendons that coursed underneath the TCL were protected with an elevator and the TCL was incised. The recurrent motor and palmar cutaneous branches of the median nerve were identified and preserved. Following the release of the forearm fascia proximally, the tourniquet was deflated. Following hemostasis, a mini-vacuum drain was inserted for drainage in each patient and the skin was sutured. Postoperatively, the patients wore a neutral-position wrist splint continuously for a week and then only at night for 6 months. Sutures were removed within 10 to 14 days. Patients were encouraged to use their hands for daily activities after a week and were allowed to perform strenuous activities such as lifting weights after a month.

Preparation of Platelet-Rich Plasma

On postoperative day 1, 9 mL of venous blood was obtained from each patient and placed in kits with 1 mL of sodium nitrate as an anticoagulant, then centrifuged for 5 minutes at 1,200 revolutions per minute (rpm) at 25°C to separate the erythrocytes and plasma containing the platelets. After the first round of centrifugation, the plasma component containing the erythrocytes at the top of the tube was separated and discarded. Afterwards, the sample was placed in the

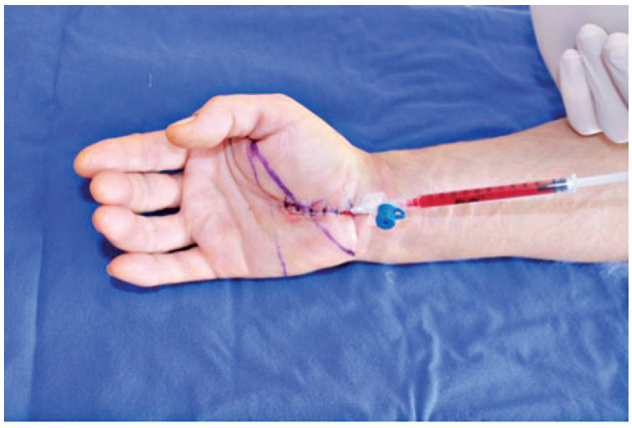

Fig. 1 The injection of platelet-rich plasma (PRP) from the surgical incision line. A patient on postoperative day 1. PRP treatment was applied from the incision line after surgical release of the transverse carpal ligament.

Table 1 Patient demographics

Variables	Study group	Control group
Age (average)	48. 3	49
Sex (female/male)	9/1	8/2
Follow-up time (average)	13 mo	13 mo
Affected hand (right/left)	7/3	4/6
Dominant hand (right/left)	7/3	8/2
DM treatment (OAD/insulin)	6/4	7/3
HbA1c	7	7.2
DM type (½)	0/10	0/10
Duration of DM (y)	3.5	3.9

Abbreviations: DM, diabetes mellitus; HbA1c, hemoglobin A1c; OAD, oral antidiabetic drug.

centrifuge again for another 10 minutes at 1,200 rpm to separate poor plasma from rich plasma, thereby obtaining 2 mL of PRP. The PRP (2 mL) was introduced through the mini-vacuum drain. The drain was removed afterwards so that the injected PRP would stay in the injected site. The dressing and wrist splint were reapplied (►**Fig. 1**).

Electrophysiological Assessment

On needle electromyography, median nerve distal motor latency (between wrist and abductor pollicis muscle), compound muscle action potential (CMAP) (sensory neuron action potentials in the first and third digits from the beginning of the last monophasic negative muscle response to its peak value), motor transmission velocity (between elbow and wrist), and sensory nerve action potential (SNAP) values were recorded and the results were compared between preoperative and postoperative follow-up periods in each group and also between both groups.

Statistical Assessment

SPSS software version 22.0 (IBM Corp., Armonk, NY) was used for the statistical analysis. The distribution of variables was measured with the Kolmogorov–Smirnov test. The Mann–Whitney *U* test was used to analyze quantitative data. The Wilcoxon test was used to analyze repeated measurements. *p*-Values < 0.05 were considered to indicate statistical significance.

Results

The average age of the study group was 48.3 years and the average age of the control group was 49 years. There was no statistically significant difference between the ages of the two groups ($p > 0.05$). Eighty-five percent of the patients in the study were female ($n = 17$) and 15% were male ($n = 3$). The average follow-up period was 13 months. Eight of the patients had unilateral CTS in their dominant hand and three of them had unilateral CTS in their nondominant hand. All patients had type 2 DM. Six of the 10 patients in the study group and 7 patients in the control group were on oral antidiabetic treatment, and 4 patients in the study group and 3 in the control group were using insulin. One patient in the control group developed minimal wound dehiscence and was treated with medical dressings and healed completely. There were no statistically significant demographic differences between the two groups (►**Table 1**). Provocation tests and cold intolerance examinations were performed for both groups at postoperative 3 months, 6 months, and 1 year, and showed statistically significant differences when compared with the preoperative results.

Statistical assessment results from the preoperative symptom severity score of the Boston Carpal Tunnel Syndrome Questionnaire for both groups showed a significant drop ($p < 0.05$) in comparison with the postoperative 3-month, 6-month, and 1-year results. However, there were no statistically significant differences ($p > 0.05$) between the two groups when comparing the decrease in symptom severity scores for the postoperative follow-up period (3 months, 6 months, and 1 year) and the preoperative period (►**Table 2**).

In the study group, a statistically significant decrease ($p < 0.05$) was observed in the functional status scores of the Boston Carpal Tunnel Syndrome Questionnaire during the postoperative follow-up period (3 months, 6 months, and 1 year) compared with the preoperative period. No statistically significant changes were observed ($p > 0.05$) in the functional status scores at postoperative month 3 when compared with preoperative results in the control group; however, a statistically significant decrease ($p < 0.05$) was seen in the functional status scores at the 6-month and 1-year follow-up period compared with the preoperative scores (►**Table 3**).

In the study group, the decreased (i.e., improved) functional status scores at postoperative month 3 and month 6 were higher than the control group and reached statistical significance ($p < 0.05$). No statistically significant differences were observed ($p > 0.05$) between the two groups' functional status score change in postoperative year 1 when compared with the preoperative results.

Table 2 Comparison of Boston Carpal Tunnel Questionnaire, Symptom Severity Score in both groups preoperatively and at 3 months, 6 months, and 1 year postoperatively

	Study group							Control group							*p-Value*
	Main			Median (Min-Max)				Main			Median (Min-Max)				
Symptom severity scale															
Preop	37.0	±	6.6	39.0	26.0	–	45.0	25.0	±	4.9	25.0	20.0	–	33.0	***0.016***
Postop month 3	24.0	±	4.2	23.5	18.0	–	30.0	15.5	±	3.0	15.5	11.0	–	20.0	***0.006***
Postop month 6	19.0	±	1.8	18.5	17.0	–	22.0	7.5	±	1.0	7.5	6.0	–	9.0	***0.004***
Postop year 1	14.0	±	2.0	14.0	11.0	–	16.0	12.0	±	1.8	11.5	10.0	–	15.0	0.087
Change															
Postop month 3	−13.0	±	9.6	−17.0	−22.0	–	1.0	−9.5	±	4.5	−10.0	−16.0	–	−4.0	0.378
Change	***0.046***							***0.028***							
Postop month 6	−18.0	±	5.4	−20.0	−23.0	–	−9.0	−17.5	±	5.5	−17.0	−26.0	–	−11.0	0.748
Change	***0.027***							***0.028***							
Postop year 1	−23.0	±	6.4	−26.0	−29.0	–	−13.0	−13.0	±	3.7	−13.0	−18.0	–	−8.0	0.024
Change	***0.027***							***0.027***							

Abbreviations: Preop, preoperative; Postop, postoperative.
Note: Mann–Whitney *U* test/Wilcoxon test. Statistically significant *p*-values (<0.05) are in bold and italics.

Table 3 Comparison of Boston Carpal Tunnel Questionnaire, Functional Status Scale in both groups preoperatively and at 3 months, 6 months, and 1 year postoperatively

	Study group							Control group							*p-Value*
	Main			Median (Min-Max)				Main			Med(Min-Max)				
Functional Status Scale															
Preop	24.2	±	3.0	25.0	20.0	–	27.0	17.0	±	3.6	18.0	10.0	–	20.0	***0.005***
Postop month 3	14.0	±	1.4	14.0	12.0	–	16.0	13.5	±	2.7	12.0	11.0	–	17.0	0.462
Postop month 6	10.0	±	1.4	10.0	8.0	–	12.0	10.0	±	1.4	10.0	8.0	–	12.0	1.000
Postop year 1	9.0	±	1.4	9.0	7.0	–	11.0	6.7	±	1.6	6.5	5.0	–	9.0	***0.035***
Change															
Postop month 3	−10.2	±	3.2	−10.0	−15.0	–	−6.0	−3.5	±	4.0	−3.5	−8.0	–	2.0	***0.016***
Change	***0.028***							0.115							
Postop month 6	−14.2	±	3.1	−14.5	−19.0	–	−10.0	−7.0	±	4.1	−8.0	−10.0	–	1.0	***0.006***
Change	***0.027***							***0.045***							
Postop year 1	−15.2	±	2.9	−16.5	−18.0	–	−11.0	−10.3	±	4.1	−12.0	−13.0	–	−2.0	0.072
Change	***0.027***							***0.026***							

Abbreviations: Preop, preoperative; Postop, postoperative.
Note: Mann–Whitney *U* test/Wilcoxon test. Statistically significant *p*-values (<0.05) are in bold and italics.

When analyzing the HAQ scores for both groups, there was a statistically significant drop in both study and control groups ($p < 0.05$) postoperatively (3 months, 6 months, and 1 year) when compared with the preoperative period. The postoperative 6-month HAQ score decline in the study group was higher than the control group and reached statistical significance ($p < 0.05$). No statistically significant differences in the score decrease were observed ($p > 0.05$) between the two groups at the 3-month and 1-year postoperative follow-ups when compared with the preoperative period.

In the electromyographic results, a statistically significant decrease ($p < 0.05$) in motor latency values in the study and control groups at all three postoperative time points (3 months, 6 months, and 1 year) was found when compared with the preoperative results. However, a statistically significant difference was not found when the decrease in motor latency values in the study and control groups were compared with each other at these three time points.

When the two groups were compared preoperatively and at 3 months and 1 year postoperatively, the CMAP values did not

Table 4 Comparison of CMAP values in both groups preoperatively and at 3 months, 6 months, and 1 year postoperatively

	Study group							Control group							*p-Value*
	Mean			Median (Min-Max)				Mean			Median (Min-Max)				
CMAP															
Preop	6.9	±	2.9	6.8	3.2	–	12.1	5.9	±	2.7	6.8	0.3	–	8.5	0.778
Postop month 3	6.4	±	2.5	7.2	1.3	–	10.1	5.8	±	3.5	6.4	1.0	–	13.0	0.377
Postop month 6	8.1	±	1.8	7.3	6.3	–	11.4	4.7	±	1.8	5.3	1.2	–	6.8	***0.001***
Postop year 1	7.9	±	2.1	8.4	3.1	–	11.4	6.4	±	4.5	4.3	1.4	–	14.0	0.398
Changing values															
Postop month 3	−0.5	±	3.9	0.1	−10.8	–	5.2	0.0	±	2.8	−0.1	−3.7	–	6.5	0.647
Difference	0.919							0.878							
Postop month 6	1.2	±	2.1	0.7	−1.1	–	5.9	−1.1	±	2.0	−1.6	−3.7	–	2.9	***0.011***
Difference	0.154							0.114							
Postop year 1	1.0	±	2.5	0.5	−2.5	–	5.9	0.5	±	3.9	0.9	−3.7	–	7.5	0.573
Difference	0.266							0.878							

Abbreviations: CMAP, compound muscle action potential; Preop, preoperative; Postop, postoperative.
Note: Mann–Whitney *U* test/Wilcoxon test.Statistically significant *p*-values (<0.05) are in bold and italics.

show any statistically significant difference ($p > 0.05$). The 6-month CMAP value in the study group showed a statistically significant increase ($p < 0.05$) in comparison with the control group (►**Table 4**). The SNAP values increased at 3 months, 6 months, and 1 year postoperatively compared with the preoperative period, but there was not a statistically significant difference ($p > 0.05$) between the two groups (►**Table 5**).

Discussion

DM is the leading cause of secondary CTS. The reported prevalence of CTS in people with diabetes is 15% and this rate increases to 30% in patients with diabetes who have developed polyneuropathy.[18] According to a study analyzing patients with and without diabetes, the recuperation of CTS patients with diabetes who underwent decompression surgery was observed to be worse than the patient group without diabetes.[8,11] In the study conducted by Mojaddidi et al, the median nerve distal motor latency in the group with diabetes was significantly prolonged and the myelinated nerve density was significantly decreased.[19]

In recent years, numerous studies have been conducted to improve nerve regeneration. Ma et al have researched whether curcumin, which increases nerve regeneration, is effective in diabetic conditions. Nerve damage was developed in a streptozotocin-induced diabetes rat model. Four weeks after daily intraperitoneal curcumin injections, immunohistochemical evaluation showed that high doses

Table 5 Comparison of SNAP values in both groups preoperatively and at 3 months, 6 months, and 1 year postoperatively

	Study Group							Control group							*p-Value*
	Mean			Median (Min-Max)				Mean			Median (Min-Max)				
SNAP															
Preop	12.2	±	9.2	12.0	0.5	–	33.0	13.4	±	6.8	14.4	3.9	–	23.0	0.481
Postop month 3	25.8	±	10.9	22.5	16.3	–	45.2	23.7	±	12.0	23.3	7.5	–	47.9	0.778
Postop month 6	22.9	±	12.5	17.7	10.8	–	42.0	16.2	±	8.9	16.1	3.4	–	28.1	0.341
Postop year 1	30.3	±	8.9	27.0	22.5	–	52.0	25.3	±	16.2	24.5	5.6	–	51.3	0.418
Changing values															
Postop month 3	13.6	±	8.4	12.0	−1.9	–	29.1	10.3	±	14.0	7.3	−8.1	–	43.0	0.260
Change	***0.004***							***0.022***							
Postop month 6	10.7	±	10.4	9.0	0.1	–	34.0	2.8	±	9.9	3.6	−16.7	–	14.1	0.218
Change	***0.003***							0.241							
Postop year 1	18.1	±	5.0	19.0	8.4	–	24.8	11.9	±	17.5	9.1	−13.6	–	46.4	0.231
Change	***0.003***							***0.038***							

Abbreviations: Postop, postoperative; Preop, preoperative; SNAP, sensory nerve action potential.
Note: Mann–Whitney *U* test/Wilcoxon test. Statistically significant *p*-values (<0.05) are in bold and italics.

of curcumin increased nerve regeneration in the diabetic rat model.[20] Yasui et al researched the effects of neuregulin-1 in facial nerve regeneration. Following the facial nerve damage induced in rat subjects, hydrogel soaked in neuregulin-1 was applied to the rats and it was observed that nerve regeneration significantly increased.[21] In the experimental study by Lichtenfels et al, the regenerative effect of PRP on peripheral nerve damage was researched. In the study, consisting of four groups, 10-mm segments were cut from the sciatic nerve in the first group and then sutured after being rotated 180 degrees. In the remaining three groups, a 10-mm gap was created in the sciatic nerve and a silicone conduit was placed. In three different groups, saline, PRP, and platelet-rich fibrin (PRF) were deposited inside the silicone conduit. A histopathologic evaluation demonstrated significant recovery in the control, PRP, and PRF groups after 2 months.[16]

In an experimental study by Küçük et al, the effect of PRP on nerve regeneration in rat subjects was researched. The sciatic nerve was identified and a full-thickness cut was made and repaired. A dissolvable sponge containing physiological saline solution was placed in the repaired area in the control group and a dissolvable sponge containing PRP was placed in the repaired area in the study group. The electrodiagnostic and histopathologic assessments, which were done after 12 weeks, showed a statistically significant difference between the two groups in terms of CMAP amplitudes, the number of axons, and the angle of climb; a regenerative effect of PRP was thus observed.[22]

PRP is a plasma product with proven anti-inflammatory and regenerative effects that is prepared from centrifuged autologous blood that contains higher concentrations of platelets than normal blood. Because of the multitude of growth factors that it contains, PRP is used in numerous fields such as bone, muscle, peripheral nerve, and connective tissue recuperation.[23,24]

The impact of numerous growth factors, such as PDGF, TGF-β, IGF-1, FGF, and VEGF (released from the α granules of platelets), on nerve regeneration has been proven.[15,25] There are IGF receptors in the axonal termination of peripheral nerve systems, Schwann cells, and motor neurons. IGF is activated in two ways[1]: phosphatidylinositol 3-kinase (PI3K) activates protein kinase B, which increases neural regeneration[2]; mitogen-active protein kinase ensures cell regeneration and differentiation. Studies have proven that IGF-2 is neurotrophic in both methods. The TGF-β isoforms TGF-β2 and TGF-β3 increase Schwann cell proliferation and differentiation. It is also known that FGF-β and VEGF increase neural tissue regeneration.[23,26] Park and Kwon researched the effect of PRP in a rat model with experimentally induced median nerve damage. The damage was induced by injecting dextrose solution to the median nerve and PRP was injected afterwards. After 12 weeks, electrophysiologic and histologic studies were done to compare PRP with a control group and it was found that PRP had a positive impact on median nerve recuperation.[27] In the study done by Zayni et al, a single PRP injection was compared with two consecutive PRP injections in patients with patellar tendinopathy. According to this study, the patients who were treated with two consecutive PRP injections had better recovery-related findings than the single injection group.[28] Görmeli et al compared the effect of single and multiple PRP injections, as well as hyaluronic acid injections and saline injections in patients with osteoarthritis and reported that the patients treated with multiple PRP injections had better results than the other groups.[29]

PRP was used in this study because of its advantages, such as ease of application, ready availability from autologous blood, and lack of complications. When short- and long-term postoperative results were compared, it was observed that there was significant nerve regeneration in the PRP group when compared with preoperative data, whereas, when compared with the control group, PRP was not observed to have a significant impact on median nerve regeneration when applied following CTS surgery. Although multiple PRP injections have shown positive effects on regeneration in various fields, this study used a single-dose PRP injection based on the promising results of earlier studies using conservative CTS treatments.[30–33] Only one previous study was found that investigated the effects of PRP as an adjuvant treatment in addition to surgery. Trull-Ahuir et al compared single injections of PRP and platelet-poor plasma after carpal tunnel surgery and came to the conclusion that PRP was effective as an adjuvant therapy.[34] Although the current study found PRP to be ineffective, it could be used as a pilot study for further investigations of PRP treatment in addition to surgery in CTS patients with diabetes. The effectiveness of multiple PRP injections can also be researched in the future.

In conclusion, when short- and long-term postoperative results were compared between the two groups, it was observed that a single injection of PRP did not have a significant impact on median nerve regeneration in patients with diabetes following CTS surgery. The effectiveness of multiple PRP injections can be investigated in future studies.

Author Contributions

Conceptualization: T.Y., Ö.Ö., Ö.Ç. Data curation: A.E.Ş., Ö.Ç. Formal analysis: T.Y., Ö.Ç. Methodology: T.Y., Ö.Ö., A.E.Ş. Project administration: A.E.Ş. Visualization: T.Y.,Ö.Ö. Writing-original draft: A.E.Ş. Writing-review and editing: T.Y.,Ö.Ç.

Ethical Approval

The study was approved by the institutional ethical committee (IRB #4668).

Patient Consent

Informed consent was obtained from all patients.

Conflict of Interest

None declared.

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