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Vagus Nerve Stimulation in Drug-resistant Epilepsy: A Single-center Experience

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Abstract

Objective: Vagus nerve stimulation (VNS) has been increasingly used in recent years as an alternative treatment method for drug-resistant epilepsy (DRE). In this study, we aimed to analyze the data of patients diagnosed with DRE and treated with VNS, who are being followed up at the Muğla Sıtkı Koçman University Faculty of Medicine, Department of Neurology, and to review our experience.

Methods: This is a study including patients who were still under follow-up as of October 31, 2024, and had undergone VNS implantation at least one year prior. Demographic characteristics, epilepsy history, and VNS-related data were collected and recorded in the follow-up form. The effectiveness of VNS was evaluated according to the McHugh classification, based on changes in seizure duration, severity, and frequency.

Results: Of the 40 patients, 42.5% (n=17) were female and 57.5% (n=23) were male. The mean age was 37.2±11.2 years. The average duration of epilepsy was 24.7±10.7 years. The median seizure frequency prior to VNS implantation was 20 per month (minimum: 1 to maximum: 600). The median values for VNS output current and VNS magnet current were 1.50 and 1.75 milliamperes, respectively. The median values for VNS duty cycle, VNS OFF time (minutes), and VNS ON time (seconds) were 10, 5, and 30, respectively. According to the McHugh classification, 22.5% (n=9) were classified as class 1A, 30% (n=12) as class 2A, 10% (n=4) as class 2B, 17.5% (n=7) as class 3A, 7.5% (n=3) as class 3B, and 12.5% (n=5) as class 5.

Conclusion: Following VNS implantation, more than 50% reduction in epileptic seizures was observed in 62.5% of patients, while less than 50% reduction was seen in 25% of patients. VNS is an important treatment option for patients with DRE.

Keywords: Epilepsy treatment, seizure, seizure frequency

INTRODUCTION

The definition of drug-resistant epilepsy (DRE) was published by the International League Against Epilepsy in 2010: failure to suppress seizure activity or persistence of seizures for more than 12 months or for a period three times the longest inter-seizure interval reported previously, despite effective use of two or more appropriately selected anti-seizure drugs in monotherapy, alternating monotherapy or in combination, at therapeutic doses.[1] The etiology of DRE can often include mesial-temporal sclerosis, tuberous sclerosis, Sturge-Weber syndrome, cerebral tumors, hamartomas, arteriovenous malformations, structural malformations, cerebral infection sequelae, or trauma. Various diets, such as the ketogenic diet, the medium-chain triglyceride diet, the modified Atkins diet, and the low glycemic index diet, are used in its treatment. Surgical treatments, such as focal resection, corpus callosotomy, or hemispherectomy, are among the options for patients with partial or multifocal epilepsy. Stimulation methods are another treatment option for patients who do not respond to medical treatment or are not suitable for surgical treatment. Vagal nerve stimulation (VNS), deep brain stimulation of the anterior nucleus of the thalamus, and responsive neurostimulation can be applied to these patients.[2-4]

VNS, one of the methods used in the treatment of DRE, was first implanted as a device in a human in 1988. VNS, which was approved for use in focal-onset DRE in patients over 12 years of age in Europe in 1994 and in the United States of America (USA) in 1997, has become

increasingly popular in recent years.[5,6] With the development of technology and accumulation of clinical experience, VNS has been actively used in many epilepsy centers. The expected results included a decrease in seizure frequency, severity, and duration in patients.

In this study, we aimed to examine the data of patients with VNS at our center.

METHODS

This study was planned according to the Declaration of Helsinki. Approval was obtained from Muğla Sıtkı Koçman University Faculty of Medicine Clinical Research Ethics Committee (no: 13/XI, date: 07.09.2022). The study included patients over the age of 18 years who were diagnosed with DRE and underwent VNS; who applied to the outpatient clinic of the Muğla Sıtkı Koçman University Faculty of Medicine, Department of Neurology, between September 1, 2022, and October 31, 2024; who were still being followed up in our clinic on October 31, 2024; and who had at least one year after VNS implantation.

All patients included in the study were systematically evaluated by a psychiatrist prior to VNS implantation. During this assessment, the individuals' mental health status, capacity for treatment adherence, and psychiatric suitability for the interventional procedure were comprehensively evaluated. The presence of an active psychotic episode, uncontrolled mood disorder, or acute suicidal ideation was considered a temporary contraindication for VNS, and psychiatric stabilization was ensured before proceeding with the intervention in such cases. Aside from these conditions, the presence of stable severe psychiatric disorders (e.g., schizophrenia, bipolar disorder) or intellectual disability was not considered a barrier to accessing treatment. This approach was adopted in line with the principle that individuals with epilepsy have a fundamental right to access effective and evidence-based treatment options. The evaluation process was carried out by a multidisciplinary team composed of neurologists, neurosurgeons, and psychiatrists, allowing for a holistic assessment of each patient's medical, surgical, and psychiatric suitability.

VNS surgeries were performed at the same hospital and the department of neurosurgery. The surgical procedures for all patients were performed on the left vagus nerve using the surgical technique described by Reid.[7] The incision point is the midway between the chin and the sternal notch, with 1/3 of the incision lying medial to the sternocleidomastoid muscle (SCM) and 2/3 remaining lateral to the SCM transversely. The head is fixed with extension, kept straight, or rotated 15 degrees towards the opposite side for surgery by using intraoperative ultrasonography for identifying the best vagus nerve position inside the carotid sheath. After the VNS leads were placed on the left vagus nerve microsurgically, the system was connected with a VNS generator placed in a pocket opened approximately 5 cm inferior to the left clavicle. Generator replacements were performed from the previous incision over the generator and involved using a full power battery. The age, sex, occupation, marital status, education level, history of epilepsy, medications used, VNS application time and duration, VNS battery status, post-VNS utilization status, seizure frequency, seizure severity and duration, and VNS device setting information of the patients were collected and recorded in the follow-up form. The battery operating cycle, duty cycle, current intensity, stimulus frequency, pulse width, and battery impedance values were recorded under the VNS device setting information title. The effectiveness of VNS was evaluated according to the McHugh classification, using changes in seizure duration, severity, and number. Data from 45 patients were examined in this study. Four of the 45 patients continued their follow-up in different cities, and one patient exited for other reasons than epilepsy. The data from 40 patients were statistically evaluated, and in the light of these data, our VNS experience at the Muğla Sıtkı Koçman University Faculty of Medicine, Department of Neurology, was reviewed and discussed.

MAIN POINTS

- Following vagus nerve stimulation (VNS) implantation, a reduction in epileptic seizures greater than 50% was observed in 62.5% of patients.
- VNS is an important treatment option for patients with drug-resistant epilepsy.
- No side effects were observed after VNS implantation in most patients.
- Epilepsy patients who receive VNS can cope with several VNS side effects, as these side effects are tolerable compared to the benefits.

Statistical Analysis

The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Descriptive statistics for continuous variables were presented as mean±standard deviation or median [minimum (min)-maximum (max)] values, depending on the distribution. Categorical variables were summarized using frequencies (n) and percentages (%). All statistical analyses were performed using RStudio version 2024.09.0 (Posit Software, Public Benefit Corporation, Boston, Massachusetts, USA).

RESULTS

The data of 40 patients, who visited the outpatient clinic of our center between September 1, 2022, and October 31, 2024, and who were implanted with VNS due to the diagnosis of DRE, were statistically evaluated (Tables 1, 2). Of the 40 patients included in the study, 42.5% (n=17) were female and 57.5% (n=23) were male. The mean age was 37.2±11.2 years. 70% (28) of the patients were single, and 30% (12) were married. When the educational levels of the patients were examined, 25% (10) were illiterate, 27.5% (11) were primary school graduates, 25% (10) were high school graduates, and 22.5% (9) were university graduates. Of the 40 patients, 60% (n=24) were unemployed, 27.5% (n=11) worked in the service sector, 5% (n=2) worked as farmers, 5% (n=2) worked as teachers, and 2.5% (n=1) worked as civil servants. 25% (10) of patients were illiterate, 27.5% (11) were primary school graduates, 25% (10) were high school graduates, and 22.5% (9) were university graduates. Focal-onset epileptic seizures were observed in 82.5% (33) of the patients, while 17.5% (7) had multifocal-onset seizures. The median age at the onset of epilepsy was 8 years (range, 0-46 years). The mean duration of epilepsy was 24.7±10.7 years. Our patients used 16 different anti-seizure drugs. Levetiracetam was a preferred anti-seizure drug in 72.5% (29) of patients, carbamazepine in 57.5% (23) of patients, and another drug in 40% (16) as shown in Table 3. The median seizure frequency of the patients before VNS implantation was 20 seizures per month (min: 1, max: 600). The median age at VNS implantation

Table 1. Descriptive statistics of categorical variables

Variable name	n (%)
Marital status	
Single	28 (70)
Married	12 (30)
Occupation	
Farmer	2 (5)
Service sector	11 (27.5)
Unemployed	24 (60)
Civil servant	1 (2.5)
Teacher	2 (5)
Education level	
Illiterate	10 (25)
Primary school	11 (27.5)
High school	10 (25)
University	9 (22.5)
VNS battery percentage	
18-25	1 (2.5)
25-50	9 (22.5)
50-75	8 (20)
75-100	22 (55)
Epilepsy onset	
Focal	33 (82.5)
Multifocal	7 (17.5)
McHugh classification	
1A	9 (22.5)
2A	12 (30)
2B	4 (10)
3A	7 (17.5)
3B	3 (7.5)
V	5 (12.5)

VNS: Vagus nerve stimulation

Table 2. Descriptive statistics of numerical variables

Variable	Value
VNS implantation duration (years)	2.50 (1.00-4.00)
VNS output current (mA)	1.50 (0.75-2.25)
VNS magnet current (mA)	1.75 (1.00-2.50)
VNS impedance	2,569.88±387.14
Duty cycle	10 (10-35)
On time (sec)	30 (21-30)
Off time (min)	5 (1.10-5.00)
Age at epilepsy onset	8 (0-46)
Duration of epilepsy	24.73±10.76
Number of seizures in 1 month pre-VNS	20 (1-600)
Avg. reduction in seizure frequency	50 (0-100)
Avg. reduction in seizure severity	50 (0-100)
Avg. reduction in seizure duration	50 (0-100)
Age at VNS implantation	32 (26-39.75)

Descriptive statistics are shown as mean±standard deviation or median (minimum-maximum).
Avg: Average, mA: Milliampere, Min: Minutes, Sec: Seconds, VNS: Vagus nerve stimulation

in our patients with follow-up was 32 years (range: 26 to 39.75). The median time since implantation was 2.50 years (min: 1, max: 12 years). When the VNS settings of our patients were examined, the median of VNS output current and VNS magnet current were 1.50-1.75 milliamperes (mA). The median VNS duty cycle, VNS off time (minutes), and VNS on time (seconds) were 10, 5, and 30, respectively. After VNS implantation, the median decrease in seizure frequency, seizure duration, and seizure severity was determined to be 50%. The results related to patients' epileptic seizures after VNS implantation were evaluated according to the McHugh classification. Of the patients, 22.5% (9) were classified as class 1A, 30% (12) as class 2A, 10% (4) as class 2B, 17.5% (7) as class 3A, 7.5% (3) as class 3B, and 12.5% (5) as class 5. No side effects were observed after VNS in 70% of the patients (28). Fourteen side effects were observed in 12 patients, with some patients developing more than one side effect (Table 4). The

Table 3. Frequency and percentage distribution of medications used

Medication	n (%)
LEV	29 (72.5)
CBZ	23 (57.5)
LTG	16 (40)
VPA	14 (35)
LCM	13 (32.5)
ZNS	12 (30)
CLZ	11 (27.5)
TPM	9 (22.5)
PRG	4 (10)
OXC	4 (10)
PB	4 (10)
GBP	4 (10)
CLB	3 (7.5)
PRM	2 (5)
PHB	1 (2.5)
ETX	1(2.5)

The second column shows the number (n) and percentage (%) of patients using each medication among the 40 patients. Since patients used multiple drugs, the total percentage exceeds 100%.
CBZ: Carbamazepine, CLB: Clobazam, CLZ: Clonazepam, ETX: Ethosuximide, GBP: Gabapentin, LCM: Lacosamide, LEV: Levetiracetam, LTG: Lamotrigine, OXC: Oxcarbazepine, PB: Phenobarbital, PHB: Phenytoin, PRG: Pregabalin, PRM: Primidone, TPM: Topiramate, VPA: Valproic Acid, ZNS: Zonisamide

Table 4. Frequency and percentage distribution of side effects

Side effects	Total patients (n, %)	Patients with side effects (n, %)
None	28 (70.00)	-
Paresthesia	4 (10.00)	4 (28.57)
Dyspnea	2 (5.00)	2 (14.29)
Pain	1 (2.50)	1 (7.14)
Hoarseness	3 (7.50)	3 (21.43)
Hypotension	1 (2.50)	1 (7.14)
Delayed wound healing	3 (7.50)	3 (21.43)

The distribution of observed side effects is shown both across the total sample of 40 patients, (multiple side effects allowed, total percentage >100%) and among the 14 patients who reported side effects

most common side effect after VNS implantation was paresthesia occurring in 4 patients, while hoarseness was observed in 3 patients. In addition, 3 patients experienced delayed healing of the surgical wound after VNS implantation.

DISCUSSION

In recent years, VNS has been increasingly used as an alternative treatment for DRE that does not respond to medical treatment. The idea that seizures can be stopped by stimulating the vagal nerve was first proposed by Leonard Corning in the 1880s. In the 1980s, Zabara[8] performed VNS in a dog and demonstrated that seizures could be stopped. VNS implantation in humans was first attempted in 1988 and the first results were presented at the annual meeting of the American Epilepsy Society in 1989. This study was published by Penry and Dean[5] in 1990, and VNS was proposed as a new treatment option for patients with focal-onset epilepsy who were resistant to medication.[9,10] VNS was approved for clinical use in Europe in 1994. In 1997, VNS was approved by the Food and Drug Administration for use in focal-onset DRE patients over the age of 12.[6]

VNS is a neuromodulatory therapy used in addition to anti-seizure medications to manage DRE. The synergistic effects of VNS and anti-seizure medication combinations are used to achieve seizure control and improve quality of life. A recent study has shown that the use of VNS in combination with anti-seizure medications, especially with synaptic vesicle glycoprotein 2A (SV2A) modulators and slow sodium channel inhibitors, provides higher success rates in seizure control. These combinations have been shown to be effective in reducing seizure frequency (64.0% and 61.8%, respectively) and even in achieving seizure freedom (19.8% and 19.7%).[11] In another study, the combined use of VNS and SV2A modulators significantly enhanced HrQoL and reduced depression scores, indicating favorable synergistic effects of these combinations.[12] When the most frequently used drugs by our patients were examined, it was seen that the 5 most frequently used drugs, consistent with the literature, were levetiracetam, carbamazepine, lamotrigine, valproic acid, and lacosamide.

When evaluating the treatment efficacy of VNS, the primary goal was to determine a decrease in seizure frequency and severity. Reducing in anti-seizure drug use, decreasing in the frequency of interictal epileptiform discharges, and increasing in quality of life are seen as secondary goals. In a study by Vonck et al.,[13] 195 patients were followed up for 33 months, and a 55% decrease in seizure numbers was shown with VNS. A study conducted by Spanaki et al.[14] reported that the reduction rate in the number of seizures was 72%. A study conducted in Türkiye showed that 52.9% of patients had a reduction in seizures of more than 50%, while 35.3% had less than 50% reduction.[15] VNS had positive effects not only on seizure frequency but also on seizure duration, seizure severity, and postictal period. In a study of 48 patients, a decrease in seizure or postictal period severity was observed in 19 patients. This situation reveals that in addition to the number of seizures, seizure duration, severity, and postictal period characteristics should be taken into consideration when evaluating efficacy. The McHugh et al.[16] classification is frequently used to measure efficacy according to these criteria. In this practical classification, an 80-100% decrease in seizure frequency is classified as class 1, a 50-80% decrease as class 2, and a decrease below 50% is classified as class 3. An improvement in ictal or postictal activity is marked with suffix A, and its absence is marked with suffix B. Benefits with magnets alone are class 4, and no benefit is observed in class 5. Of the patients, 22.5% (9) were in class 1A, 30% (12) in class 2A, 10% (4) in class 2B, 17.5% (7) in class 3A, 7.5% (3) in class 3B, and 12.5% (5) in class 5 (Figure 1). In other words, a more than 50% decrease in epileptic seizures was observed in 62.5% of the patients, whereas a less than 50% decrease was observed in 25% of the patients. No change was observed in epileptic seizures in 12.5% of the patients.

After implantation, the VNS was adjusted according to the principle of min. side effects and maximum benefit for the patient. The most commonly used working principle is a 30-second operation (VNS on time) and a 5-minute break (VNS off time), and the duty cycle value is 10%. Duty cycle is calculated with the following formula: [on time+2×(2 sec triangular ramps)] / [on time+(off time×60)]×100%. If the patient's seizure control cannot be achieved in the current working order of VNS, the duty cycle value can be increased by shortening the off-time period.[17] The pulse width is usually 500 µs. The current frequency was typically determined to be 30 hertz (Hz). The current intensity can start at 0.25 mA and gradually increase to 3.5 mA. Magnet-induced stimulation is usually 0.25 mA more intense than continuous stimulation.[18] In our clinic, 2 weeks after the implantation surgery, VNS is activated with the VNS output current set at 0.75 mA and the VNS magnet current at 1.00 mA; then, they are increased to 1.00 mA and 1.25 mA, respectively, on the same day. Then, in the following check-ups, battery settings are adjusted according to the patient's seizure control and tolerance. When the VNS settings of the patients we followed in our clinic were examined, the median values of VNS output current and VNS magnet current were determined as between 1.50-1.75 mA, in accordance with the literature. In addition, the median values of the VNS duty cycle, VNS off time (minutes), and VNS on time (seconds) were found to be 5-10 min and 30 s, respectively, in accordance with the literature.

The battery life depends on many parameters. Stimulation settings, magnet usage, and battery model affect battery life. Depending on the battery model used, the period varied between four and twelve years. During follow-up, five of our patients had their VNS batteries depleted and therefore had their batteries replaced.

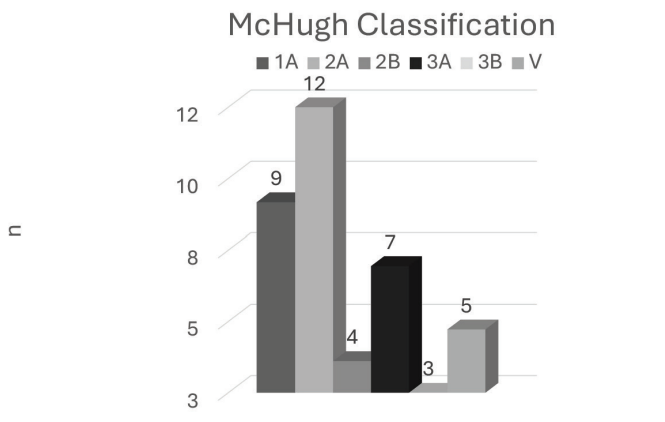

Figure 1. Bar plot for McHugh classification distribution

During implantation, patients may develop intraoperative complications. The most common of these are vocal cord injury, peritracheal hematoma development due to damage to vascular structures, clavicle or esophageal injury, pneumothorax, and vagal nerve injury.[19] VNS implantation was performed in 39 of our patients at our center, and delayed wound healing was observed in 3 patients. No additional surgical complications were noted. The side effects that occur due to stimulation in working VNS include hoarseness, episodes of coughing, paresthesia in the neck region, dyspnea, chest pain, burning sensation in the throat, numbness in the jaw, sore throat, and difficulty swallowing. The cause of cough, hoarseness, and dyspnea is laryngopharyngeal dysfunction due to stimulation of the inferior laryngeal nerve. Side effects, such as earache, headache, weight gain, or weight loss, are less commonly seen due to VNS. While these side effects are more common in the first period of VNS implantation, they are expected to decrease over time. Cardiac arrhythmias are among the complications that can be observed in the long term after VNS implantation. Electrode breakage was the most common complication associated with the equipment used. It usually develops years after surgery because of deformities that form over time. Migration of the electrode from the vagus nerve is also a common equipment-related complication.[9,20] Epilepsy patients who receive VNS can cope with many of the side effects of VNS, and these side effects are tolerable compared to the benefits experienced by the patients. No side effects were observed after VNS implantation in most patients. However, paresthesia was observed in four patients, hoarseness in three patients, dyspnea in two patients, and pain and hypotension episodes in one patient (Figure 2). In our patients, side effects such as paresthesia, hoarseness, dyspnea, and pain were observed in accordance with the literature and were tolerated by the patients. Their effects decreased over time. The use of VNS for blood pressure regulation in patients with resistant hypertension has been investigated recently but remains promising for future development.[20] However, the blood pressure-lowering effect of VNS has been reported in different animal studies.[21,22] In the literature, hypotension is not frequently reported as a side effect in epileptic patients receiving VNS. The hypotension episodes that occurred in our patient were rare.

Although implanted metallic devices are a relative contraindication to magnetic resonance imaging (MRI) scanning, 1.5 or 3.0 Tesla MRI scans can be performed under certain conditions in a patient implanted with a VNS.[23] During the follow-up of 3 of our patients, MRI was required. In these patients, the battery settings were checked and noted before the MRI scan. Subsequently, the patients' VNS settings were set to output current (mA); 0.0, magnet current (mA) 0.0, and MRI scans were performed. After the MRI scan, the patients' battery settings were adjusted to be the same as those before the MRI scan. No side effects or complications occurred in any patient during the procedure.

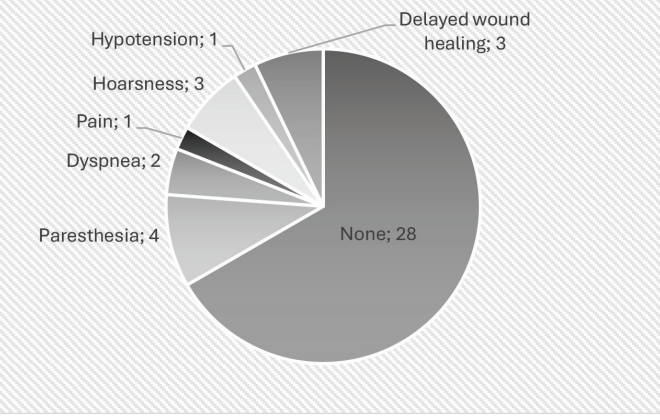

Figure 2. Pie plot for adverse effect distribution

Certain procedures must be performed prior to the planned surgical procedures in patients with VNS implants. It is generally considered safer to deactivate the VNS before elective surgical procedures to avoid possible complications. It is recommended that bipolar electrocautery devices be used instead of monopolar electrocautery devices during surgery. It is also recommended to place the electrosurgical electrodes as far away from the VNS generator and cables as possible.[24] Two of our patients underwent surgery during their follow-up. Before the surgery, the patients' VNS settings were set to output current (mA): 0.0, magnet current (mA): 0.0. In other words, the VNS was deactivated. Electrocautery was avoided if possible during surgery, and if electrocautery was necessary, bipolar electrocautery devices were used. After surgery, the VNS settings were adjusted to match the pre-surgery settings. No side effects or complications occurred in any patient during the procedure.

Polytherapy in pregnant women with DRE may affect maternal and fetal health. However, studies examining the effects of VNS on maternal and fetal health are limited and include small sample sizes. In a mini-review, a total of 44 pregnancies in 38 patients were examined; two pregnancies (2/44, 4.5%) resulted in miscarriage, and congenital malformations in two pregnancies (2/42, 4.8%) were attributed to polytherapy. The rest of the pregnant women reported no postpartum complications or unhealthy fetuses.[25] One of our patients became pregnant during the follow-up period after VNS implantation. The VNS device was monitored openly throughout her pregnancy, and it was turned off during the cesarean section due to the surgical procedure. No complications occurred in our patient or in her baby during or after delivery.

Study Limitations

One of the limitations of this study is the small sample size due to the limited number of patients who underwent VNS implantation. In addition, having our patients were over 18 years of age limited our ability to evaluate the effects of VNS implantation in different age groups.

CONCLUSION

In this study, we investigated the effectiveness of VNS in 40 adult patients were under regular follow-up, and reviewed our VNS experience. VNS, which is widely used in many epilepsy centers with the development of technology and the accumulation of clinical experience, is an effective treatment method for DRE. The frequency and duration of VNS side effects are tolerable for patients.

Ethics

Ethics Committee Approval: Approval was obtained from Muğla Sıtkı Koçman University Faculty of Medicine Clinical Research Ethics Committee (no: 13/XI, date: 07.09.2022).

Informed Consent: Written informed consent was obtained from all participants.

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Footnotes

Author Contributions: Surgical and Medical Practices: İ.Ö., G.G., D.M.Ş., S.B., G.K. Concept: İ.Ö., M.B.Ç., T.A.Ç., G.G., G.K. Design: İ.Ö., E.D., D.M.Ş., F.C.T., S.B., Data Collection or Processing: İ.Ö., M.B.Ç., T.A.Ç., E.D., F.C.T., Analysis or Interpretation: İ.Ö., F.C.T., Literature Search: İ.Ö., M.B.Ç., V.S.B., G.K. Writing: İ.Ö., M.B.Ç., T.A.Ç., E.D., G.G., D.M.Ş., F.C.T., S.B., G.K.

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