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Research

Evaluating the Efficacy and Associated Factors of Vagus Nerve Stimulation in Medically Refractory Epilepsy Patients

Medikal Tedaviye Dirençli Epilepsi Hastalarında Vagus Sinir Stimülasyonunun Etkinliğinin ve İlişkili Faktörlerin Değerlendirilmesi

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ABSTRACT

Objective: This study investigated seizure control rates and factors associated with treatment response in a series of patients with medically refractory epilepsy who underwent vagus nerve stimulation (VNS).

Methods: We conducted a retrospective observational study of 82 patients who received VNS implantation between 2007 and 2024. Demographic data, epilepsy characteristics, and preoperative and postoperative outcomes, including seizure frequency, were analyzed. Seizure outcomes were assessed using the International League Against Epilepsy and Engel classifications, and statistical analyses were performed to identify factors associated with seizure control.

Results: The average follow-up duration was 67.1 months. At 12 months post-VNS, 73.18% of patients achieved more than a 50% reduction in seizure frequency, with 36.59% experiencing a 75-100% reduction. Higher response rates were observed among patients with a history of epilepsy surgery. No significant associations were found between treatment response and age, gender, or epilepsy type.

Conclusion: VNS implantation is an effective treatment option for seizure control in patients with medically refractory epilepsy. This study highlights factors potentially associated with better outcomes, suggesting that VNS may be particularly beneficial in specific patient subgroups. Further research with larger, prospective studies is recommended to confirm these findings.

Keywords: Vagus nerve stimulation, seizure control, medically refractory epilepsy, neuromodulation, treatment response

ÖZ

Amaç: Bu çalışmada, vagus sinir stimülasyonu (VNS) uygulanan medikal tedaviye dirençli epilepsi tanılı hastaların nöbet kontrol oranları ve tedavi yanıtıyla ilişkili faktörler araştırıldı.

Gereç ve Yöntem: 2007 ile 2024 yılları arasında VNS implantasyonu uygulanan 82 hastada retrospektif bir gözlemsel çalışma yürüttük. Demografik veriler, epilepsi özellikleri ve nöbet sıklığı dahil olmak üzere ameliyat öncesi ve sonrası sonuçlar analiz edildi. Nöbet sonuçları Uluslararası Epilepsi ile Savaş Derneği ve Engel sınıflandırmaları kullanılarak değerlendirildi ve nöbet kontrolüyle ilişkili faktörleri belirlemek için istatistiksel analizler yapıldı.

Bulgular: Ortalama takip süresi 67,1 aydı. VNS'den 12 ay sonra hastaların %73,18'i nöbet sıklığında %50'den fazla azalma elde etti ve %36,59'u %75-100 azalma yaşadı. Epilepsi cerrahisi öyküsü olan hastalarda daha yüksek yanıt oranları gözlendi. Tedavi yanıtı ile yaş, cinsiyet veya epilepsi türü arasında önemli bir ilişki bulunamadı.

Sonuç: VNS implantasyonu, medikal tedaviye dirençli epilepsi hastalarında nöbet kontrolü için etkili bir tedavi seçeneğidir. Bu çalışma, daha iyi sonuçlarla ilişkili olabilecek faktörleri vurgulayarak, VNS'nin belirli hasta alt gruplarında özellikle yararlı olabileceğini öne sürmektedir. Bu bulguları doğrulamak için daha büyük, prospektif çalışmalarla daha fazla araştırma yapılması önerilmektedir.

Anahtar Kelimeler: Vagus siniri stimülasyonu, nöbet kontrolü, medikal tedaviye dirençli epilepsi, nöromodülasyon, tedavi yanıtı

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INTRODUCTION

Epilepsy, with a prevalence of approximately 0.5-1% according to the World Health Organization, is a neurological disorder affecting nearly 50 million people globally, with a bimodal incidence distribution showing higher rates in both young and elderly populations (1,2). According to the International League Against Epilepsy (ILAE), epilepsy that remains uncontrolled despite the appropriate dosage and combination of at least two well-tolerated antiepileptic drugs is classified as medically refractory epilepsy, comprising about 30-40% of all epilepsy cases (3,4). Although focal epilepsies arising from focal epileptogenic lesions may be amenable to surgical intervention, only 10-30% of these patients benefit from resective surgeries, posing a significant challenge in seizure management for epileptologists and epilepsy surgeons (5,6).

Neuromodulation surgery serves as a crucial alternative for patients with medically refractory epilepsy who are either unsuitable for resective surgery or do not achieve desired outcomes postoperatively (7-9). Vagus nerve stimulation (VNS) was one of the first three neuromodulation methods approved by the United States Food and Drug Administration in 1997 (8). VNS therapy can be applied in patients with medically refractory epilepsy who are not suitable for resective surgery, those with multiple or bilaterally independent symptomatic localization-related epilepsy syndromes, cryptogenic or symptomatic generalized epilepsy accompanied by diffuse epileptogenic anomalies, or those who have undergone unsuccessful intracranial epilepsy surgeries.

In this study, we aim to assess long-term outcomes, specifically the effects on seizure frequency, anti-epileptic drug use, and quality of life in patients who underwent VNS implantation between 2007 and 2024, and to discuss our findings in the context of the existing literature, thus underscoring the significance of VNS implantation in seizure control for patients with medically refractory epilepsy.

METHODS

Participant Analysis

This study was conducted retrospectively, following approval from University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Ethics Committee (decision no: 162, date: 19.04.2023) and in compliance with the Helsinki Declaration. The study was designed as a retrospective observational study. We included 82 patients with medically refractory epilepsy who underwent VNS implantation between 2007 and 2024, as recommended by the local epilepsy surgery council, comprising adult, or pediatric epileptologists, neurosurgeons, psychiatrists, or child, psychiatrists, psychologists, and neuroradiologists. Only patients with at least 12 months of follow-up were included, while cases lacking regular follow-up were excluded.

Preoperative demographic data were recorded, including age, sex, handedness, age at seizure onset, seizure type, epilepsy etiology, magnetic resonance imaging (MRI) findings, video-electroencephalography (vEEG) findings, positron emission tomography (PET) findings, neuropsychological assessment results, the number of antiepileptic drugs used prior to VNS implantation, duration of epilepsy, seizure frequency, and the year of VNS implantation. Postoperatively, patients were followed by an adult or pediatric epileptologist. Data recorded during the postoperative follow-up included the number of anti-epileptic drugs, seizure frequency at the 3rd, 6th, and 12th months, recorded complications, time until battery replacement, and subjective assessments by the caregiver.

Seizure type and epilepsy etiology were categorized based on the 2017 ILAE classification (10). For all patients with a follow-up period longer than one year, seizure outcomes were evaluated by the epilepsy surgery council using both ILAE and Engel classifications, as both classifications offer unique categorical characteristics that contribute to the study (11).

Seizure reduction in the postoperative period was monitored using seizure diaries maintained by a single evaluator. Seizure reduction data were generated based on the change in seizure frequency at the end of the first year compared with the frequency prior to VNS implantation. Seizure reduction rates were categorized as 0-25%, 25-50%, 50-75%, and 75-100%, according to existing literature assessments (12-14). A reduction of more than 50% in seizure frequency was considered the target therapeutic response. This classification aimed to capture the degree of change in seizure frequency. It is not comprehensively represented in the ILAE and Engel classifications.

Surgical Procedure

The VNS implantation is a well-defined procedure (15). During the VNS implantation surgery, the patient is positioned supine with the head rotated 45 degrees to the right and slightly extended to minimize the risk of bradycardia. This positioning targeting the left vagus nerve. The first incision is planned horizontally at the midpoint between the clavicle and mastoid process, where it intersects the medial border of the sternocleidomastoid muscle. The second incision is made parallel to the left pectoral muscle, 3-5 cm inferior

to the clavicle. Following the standard anterior cervical exposure, the left vagus nerve is isolated for a minimum length of 3 cm, distal to the cardiac branches and proximal to the recurrent laryngeal nerve. Helical electrodes are then placed around the 3 cm exposed segment of the vagus nerve (Figure 1). The electrode cable is routed through a subcutaneous tunnel to the pectoral area. Subsequently, the VNS generator is positioned subcutaneously or subpectorally using the second incision and connected to the electrode cable. In all patients, the LivaNova Demipulse model device was used. The VNS generator is programmed externally with a handheld wand, and total impedance is measured to complete the surgery.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Appropriate tests were selected to evaluate the relationships between prognostic parameters and categorical and continuous variables. The associations between prognostic parameters (ILAE score, Engel score, postoperative medication changes, and postoperative seizure reduction) and categorical variables such as gender, epilepsy surgery, MRI lesion 1 (presence/absence), MRI lesion 2 (single/multiple foci), EEG focus status, and epilepsy type (focal/generalized) were analyzed using the chi-square test. This test was applied to assess the independence between categorical variables, with p-values below 0.05 considered statistically significant.

Pearson correlation analysis was applied to assess the relationships between prognostic parameters and continuous variables such as the duration of epilepsy (years), age at seizure onset, and epilepsy frequency (number of seizures per day). The Pearson correlation test examines the linear relationship between two continuous variables, with the strength and direction of the association evaluated using the correlation coefficient (r). In all analyses, a p-value of less than 0.05 was considered the threshold for statistical significance.

The chi-square test was also used to evaluate the association between epilepsy surgery and postoperative seizure reduction. The distribution of continuous variables was reported as mean±standard deviation, while categorical variables were presented as frequencies and percentages.

RESULTS

The mean age of patients included in our study was 25.94 years (range: 5-53 years). The average follow-up duration was 67.1 months (range: 12-199 months). The mean age at seizure onset was 6.39 years, and the mean duration of epilepsy was 19.46 years (range: 2-41 years). The average number of seizures per day was 3.68, and the mean number of anti-epileptic drugs used was 3.23 (Table 1).

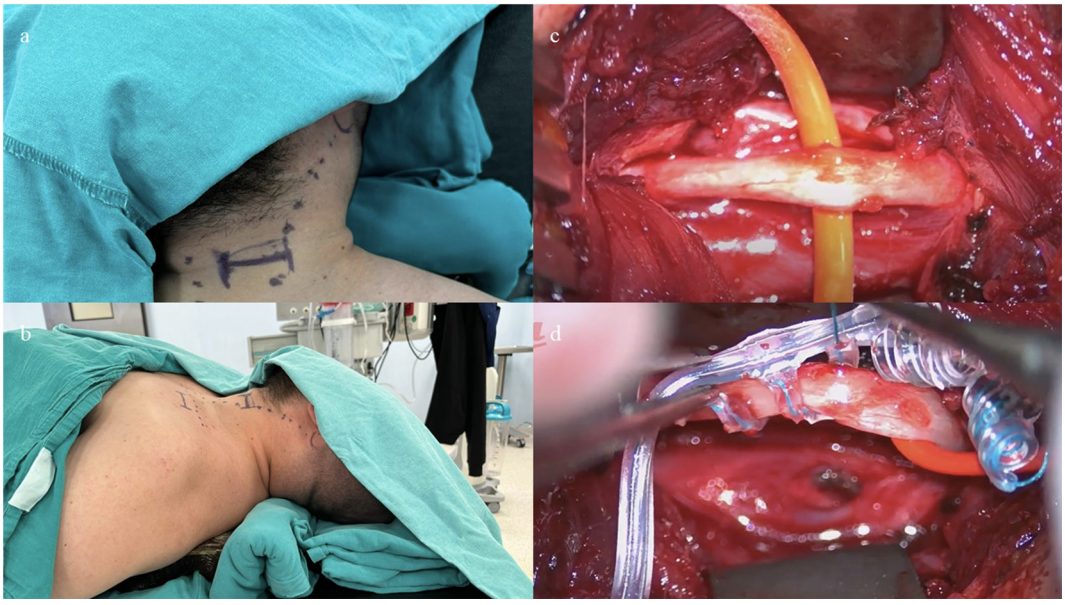

Figure 1. Vagus nerve stimulation (VNS) implantation procedure. This figure illustrates the standard procedure for VNS implantation. a: The patient is positioned supine, with the head rotated 45 degrees to the right and slightly extended to target the left vagus nerve. b: The first horizontal incision is planned at the midpoint between the clavicle and mastoid process, intersecting the medial border of the sternocleidomastoid muscle. The second incision is made parallel to the left pectoral muscle, approximately 5-8 cm below the clavicle. c: Following anterior cervical exposure, the left vagus nerve is isolated over a minimum length of 3 cm, distal to the cardiac branches and proximal to the recurrent laryngeal nerve. d: Helical electrodes are placed around the exposed vagus nerve segment

In terms of categorical data, 34.15% of patients were female, and 65.85% were male. The percentage of patients with a known epilepsy etiology was 54.88%, while 45.12% had an unknown etiology. Among the patients, 26.83% had focal epilepsy, and 73.17% had generalized epilepsy. The proportion of patients who underwent epilepsy surgery was 18.29%, and 81.71% had not undergone surgery. MRI revealed lesions in 54.88% of patients, with 45.12% showing no lesions (Table 1).

In the postoperative ILAE score distribution, 74.39% of patients were classified as ILAE 4, 20.73% as ILAE 5, 3.66% as ILAE 6, and 1.22% as ILAE 3. In terms of the Engel score distribution, 70.73% of patients were classified as Engel 3-A, 10.98% as Engel 4-B, 9.76% as Engel 2-B, 3.66% as Engel 4-A, 3.66% as Engel 4-C, and 1.22% as Engel 2-D (Figure 2).

Postoperative anti-epileptic drugs were reduced in 24.39% of patients, while remaining unchanged in 75.61%. The rates of seizure reduction were as follows: 75-100% reduction in 36.59% of patients, 50-75% reduction in 36.59%, 25-50% reduction in 8.54%, and 0-25% reduction or an increase in seizures in 18.28% of patients. Overall, 73.18% of patients were classified as responsive to treatment (Figure 2).

Statistical analyses showed no significant associations between gender and ILAE score, Engel score, postoperative medication changes, or postoperative seizure reduction ($p>0.05$). Similarly, there were no significant associations between epilepsy type (focal/generalized) and prognostic parameters ($p>0.05$). However, a significant association was found between epilepsy surgery and postoperative seizure reduction ($p=0.025$), with patients who had undergone surgery showing greater seizure reduction. MRI findings did not show a significant association with prognostic parameters. MRI findings of single versus multiple foci exhibited borderline significant associations with Engel score and postoperative seizure reduction but did not reach statistical significance ($p=0.079$ and $p=0.098$). No significant associations were observed between EEG focus status (single focus/multiple foci) and prognostic parameters ($p>0.05$). Additionally, no significant associations were found between age at seizure onset and duration of epilepsy and prognostic parameters ($p>0.05$). A borderline association was observed between the duration of epilepsy and Engel score, but it did not reach statistical significance ($p=0.080$). No significant association was found between seizure frequency per day and prognostic parameters ($p>0.05$).

Table 1. Clinical and demographic characteristics of patients before VNS implantation

Characteristic	Value
Age (mean, min-max)	25.94 (5-53)
Follow-up duration (mean, min-max, months)	67.1 (12-199)
Age at seizure onset (mean, min-max, years)	6.39 (0-23)
Duration of epilepsy (mean, min-max, years)	19.46 (2-41)
Number of antiepileptic drugs (mean, min-max)	3.23 (1-5)
Seizures per day (mean, min-max)	3.68 (0.1-10)
Gender (female/male, %)	34.15 / 65.85
Epilepsy etiology (known/unknown, %)	54.88 / 45.12
Type of epilepsy (focal/generalized, %)	26.83 / 73.17
History of epilepsy surgery (yes/no, %)	18.29 / 81.71
MRI findings (present/absent, %)	54.88 / 45.12

VNS: Vagus nerve stimulation, MRI: Magnetic resonance imaging

In terms of complications, a total of 5 patients (6.1%) developed wound site complications during the treatment period. Three of these occurred after the initial surgery, and two after generator replacement. All complications developed in the generator site. In one patient who developed a wound site complication after generator replacement, the abscess progressed, necessitating the removal of the entire system. Methicillin-resistant *Staphylococcus aureus* growth was identified in this case. The remaining patients recovered without sequelae following surgical revision and antibiotic therapy. Additionally, in one patient, the system was removed at the end of the third year due to unsuccessful seizure control (ILAE 6). Furthermore, 5 patients (6.1%) experienced hoarseness, and 3 patients (3.7%) developed coughing symptoms; all of these symptoms resolved with follow-up and medical treatment.

DISCUSSION

Since the introduction of VNS implantation as a novel treatment for drug-resistant epilepsy in the 1990's, numerous studies have been conducted. These studies generally consider a reduction of over 50% in seizure frequency in patients with drug-resistant epilepsy as a positive response to VNS therapy, with reported efficacy increasing over time Studies have demonstrated that VNS implantation provides significant seizure control in the treatment of refractory epilepsy. In a meta-analysis conducted by Wang et al. (14), which included 16 studies covering 1,080 patients, the treatment response rate varied between 38.89% and 73.21%. Another meta-analysis by Toffa et al. (16) reported a response rate ranging from 45% to 65%. More recent large single-center series reported by Boluk et al. (6) showed the highest reduction rate of 75.6% at the end of the 18th month, independent of seizure type; LoPresti et al. (17) documented a 52% seizure reduction, and Alexopoulos et al. (18) reported a reduction of 58.7%.

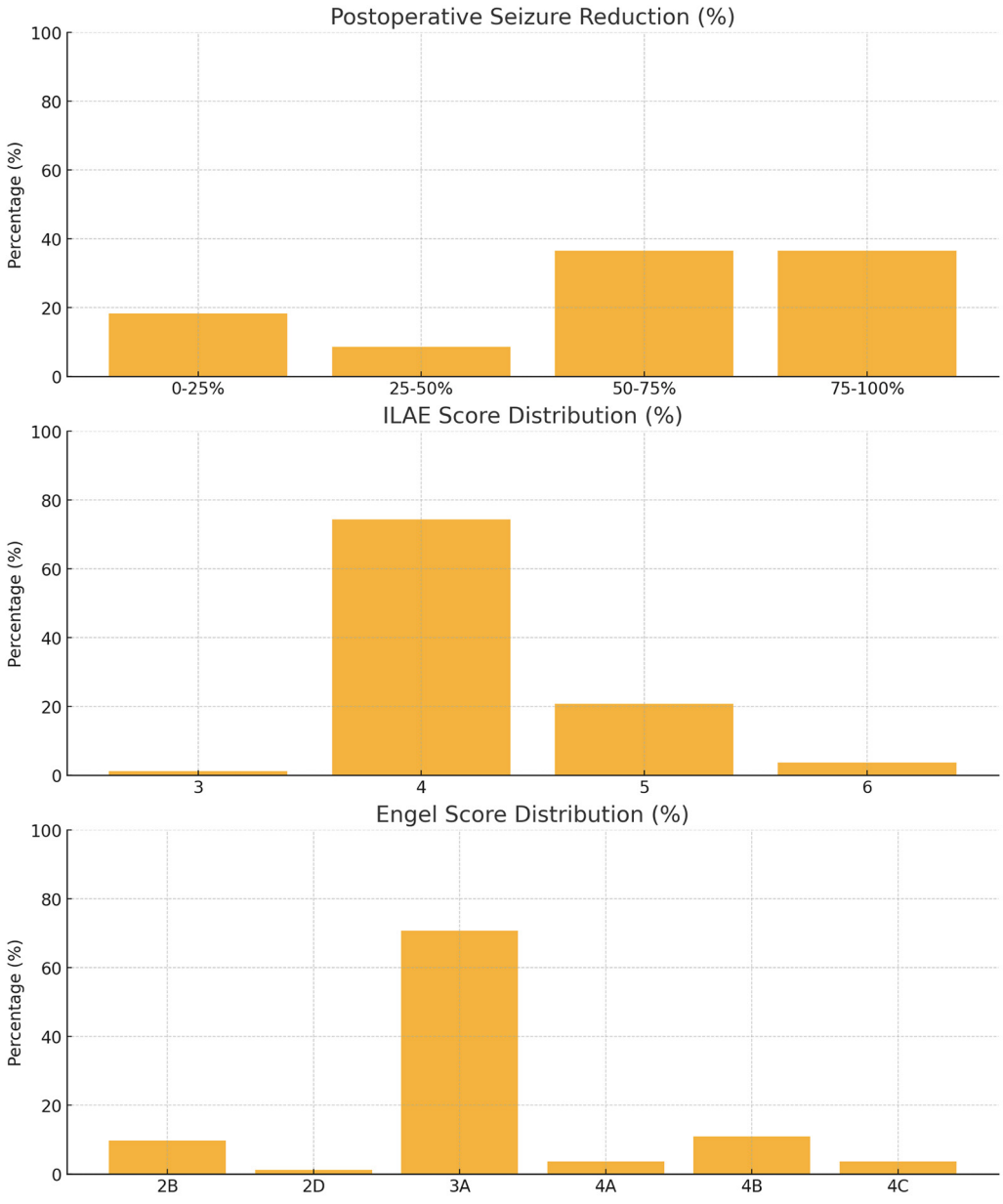

Figure 2. Distribution of postoperative outcomes following VNS implantation. This figure illustrates the distribution of postoperative outcomes in patients. The ILAE classification: • Grade 1: Completely seizure-free; no auras • Grade 2: Only auras; no other seizures • Grade 3: One to three seizure days per year; ±auras • Grade 4: Four seizure days per year to 50% reduction of baseline seizure days; ±auras • Grade 5: Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ±auras • Grade 6: More than 100% increase of baseline seizure days; ±auras. The Engel classification: • 1A: Completely seizure-free since surgery • 1B: Non-disabling simple partial seizures only • 1C: Some disabling seizures after surgery, but free of disabling seizures for at least 2 years • 1D: Generalized convulsions only with medication changes • 2A: Initially free of disabling seizures but rare disabling seizures now • 2B: Rare disabling seizures from the start • 3A: Worthwhile seizure reduction (≥50%) • 3B: <50% reduction in disabling seizures • 4A: No worthwhile improvement • 4B: No change • 4C: Worsening seizures

Consistent with the literature, our series demonstrated the efficacy of VNS implantation therapy, with a reduction in seizures of more than 50% in 73.18% of patients by the end of the 12th month. We selected the 12-month mark to allow the neuromodulation effect to develop fully, to observe the efficacy of VNS before potential long-term seizure-increasing factors could arise. Additionally, more than 75% seizure reduction was achieved in half of these patients, highlighting the significant improvement in quality of life provided by this therapy.

Some studies reporting on the efficacy and safety of VNS have indicated that initiating VNS implantation therapy within the first five years of epilepsy progression, and in the pediatric age group, results in higher effectiveness (16,19,20). In our study, we observed no significant differences in treatment response with respect to age and gender. We believe this may be due to the substantially higher number of adult patients compared to pediatric patients in our cohort. The alignment of our results with adult patient series in the literature supports this view. In a series of 45 pediatric patients who underwent VNS implantation, Soleman et al. (19) emphasized that early implantation at age five or younger, led to significantly greater improvements in quality of life and cognitive outcomes compared to VNS implantation performed after age five. In a meta-analysis by Englot et al. (20) involving 1,489 patients, the treatment response rate was reported as 49.2% in adults, while this rate increased to 55.3% in the pediatric age group and reached 62% in pediatric patients younger than six years. In contrast, some studies conducted in adult patient groups have reported that initiating VNS implantation therapy in the early stages following an epilepsy diagnosis enhances treatment response; however, patient age does not produce a significant difference in treatment efficacy (14,21,22).

Research have not established a clear relationship between epilepsy type and treatment response; however, various studies have reported significant differences in response periods between focal and generalized epilepsy. In our study, we did not observe a difference in treatment response between focal and generalized epilepsies, as reported in previous research. However, as our study was not specifically designed to assess the therapeutic effect between epilepsy types, statistical data on this topic were not included. Drees et al. (23) compared treatment response durations and early response rates between focal and generalized epilepsy patient groups, finding that the rate of super-responders was significantly higher in the generalized epilepsy group, although initially higher among patients with focal epilepsy (23).

Before initiating VNS implantation therapy, the resectability of lesions in all patients should be assessed (17,24). In our cohort, we utilized MRI, PET, and vEEG evaluations to assess epileptic foci to exclude candidates for resective epilepsy surgery prior to VNS implantation. However, 18.3% of our patients had a history of resective or ablative epilepsy surgery. The response to VNS in these patients was significantly better than in others within our study. As suggested in a similar study, this may be related to the reduction in epileptogenic load (25). Nonetheless, as demonstrated in our series, we emphasize that resective surgery should be the primary treatment choice in refractory epilepsy whenever feasible. Even if seizure control is not achieved due to insufficient resection, repeated resective surgery may yield better outcomes than VNS. Thorough patient selection evaluations can prevent the high number of unsuitable candidates noted in recent literature (17,26).

In our study, we were unable to determine the impact of etiological factors and vEEG findings on treatment response. However, consistent with the literature, we observed a near-significant improvement in treatment response among patients with multiple foci compared to those with a single focus on MRI. In the literature, LoPresti et al. (17) evaluated the relationship between seizure etiology and treatment response and found no significant association between seizure etiology and genetics. However, they reported a higher treatment response in patients with positive MRI findings. They identified brain atrophy as associated with poorer outcomes, whereas, unexpectedly, dysplastic hippocampus and periventricular leukomalacia were linked to better treatment responses. In light of our results, we believe that VNS implantation therapy may be more effective and should be considered earlier in patients with refractory epilepsy who have a history of epilepsy surgery or are not candidates for resective surgery, but present with multiple foci.

Complications of VNS are another factor influencing outcomes. Known complications of VNS include wound site complications, hoarseness, sore throat, coughing, dizziness, arrhythmias, vocal cord paralysis, sleep apnea syndrome, pneumothorax, muscle spasms, chronic diarrhea, and Horner syndrome (27). In the literature, wound site complications have been reported at rates of 2-7%, hoarseness at 37%, and coughing at 7%. Our case series aligns with the literature regarding the frequency of these complications (28-30).

Study Limitations

This study has several limitations that should be considered when interpreting the findings. First, as a retrospective study, it is susceptible to recall and selection biases, given its reliance on existing records rather than prospective data collection. Additionally, with a sample size of 82 patients, the results may not be generalizable to larger, more diverse populations.

Another limitation is the absence of a control group, which restricts our ability to attribute improvements solely to VNS therapy without accounting for potential placebo effects or the natural progression of epilepsy. Although we aimed to examine the effect of VNS on different types of epilepsy, the study was not specifically designed to assess differences

in efficacy across epilepsy types or etiologies, limiting our conclusions regarding which subtypes may benefit most from VNS. Moreover, other potential confounding factors, such as concurrent treatments, lifestyle influences, and adherence to antiepileptic medications, may have impacted seizure outcomes but were difficult to fully control in this retrospective setting.

Finally, as we exclusively used the LivaNova Demipulse model for VNS implantation, the findings may not be directly applicable to other VNS models or newer devices with potentially varying efficacy and safety profiles. Future studies with larger, prospective, and controlled designs could help address these limitations, enhancing the understanding of VNS's long-term impact across diverse patient populations.

CONCLUSION

In this retrospective study of VNS implantation therapy, we demonstrate its high efficacy in seizure control, which is consistent with the literature, and its positive impact on patients' quality of life. For seizures persisting after successful resective surgery, VNS remains highly effective in reducing seizure severity and frequency. For patients with refractory epilepsy, VNS implantation therapy should be considered the primary treatment option for patients who are not candidates for resective or ablative epilepsy surgery or whose seizures remain uncontrolled despite these surgical interventions.

ETHICS

Ethics Committee Approval: This study was conducted retrospectively, following approval from University of Health Sciences Türkiye, Başakşehir Çam ve Sakura City Hospital Ethics Committee (decision no: 162, date: 19.04.2023) and in compliance with the Helsinki Declaration.

Informed Consent: Since this research was retrospective, patient consent was not required in this research.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: O.H., O.B., B.E., B.T., Concept: O.H., O.B., T.Ö.K., N.B.G., B.E., B.T., Design: O.H., O.B., T.H., B.E., B.T., Data Collection or Processing: O.B., T.Ö.K., T.H., N.B.G., Analysis or Interpretation: O.H., O.B., B.E., Literature Search: O.H., O.B., T.Ö.K., T.H., N.B.G., Writing: O.H., O.B., T.Ö.K., T.H., N.B.G., B.E., B.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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