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Research Article

Vagus Nerve Stimulation in Adults With Drug-Resistant Epilepsy: Efficacy, Adverse Effects and Outcomes

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Summary

Background: Vagus nerve stimulation (VNS) is an adjunctive therapy for patients with drug-resistant epilepsy (DRE) excluded from ablative surgery or who have had such surgery with no optimal outcome. In this study, we provide an analysis of efficacy, side effects and seizure outcomes after VNS implantation for patients with DRE.
Method: We retrospectively examined 17 adult cases (M/F: 12/5) with DRE that received VNS treatment in our center from 2001 to May 2014 and analyzed the following parameters: age of patient receiving VNS, seizure frequency before and after VNS as well as treatment duration and etiological parameters of epilepsy.
Results: The well response rate was 58.8% (10/17). The mean age at the time of receiving VNS was 17.4 years, seizure frequency before and after VNS were 28.5/16.4. Epilepsy was caused by a structural or metabolic disorder of the brain: neoplasm, infarct, trauma, mesial temporal sclerosis and encephalitis, in eleven patients (64.7%). The well response rate was (7/11) 63.6% in this group. The well response rate was 50% (3/6) in the genetic or unknown etiology group. The EEG lateralization has the best predictive value for efficacy (p:0.007). In 2 patients with focal motor seizures, 75% and 86.6% seizure reductions were achieved whereas the percentage was 66.7% in the patient with startle epilepsy.
Conclusions: VNS is a safe and effective adjunctive treatment for DRE, the best results observed in patient with focal motor and startle epilepsy. Patients with bilateral epileptiform abnormality were seen to have better prognosis with VNS.

Key words: VNS, DRE, vagal nerve stimulation

Dirençli Epilepside Vagal Sinir Uyarımı: Etkinliği, Yan etkileri, Prognozu

Özet

Giriş: Vagal sinir uyarımı (VSU), cerrahi uygulanamayan ya da cerrahi ile iyi sonuç alınamamış olan ilaca dirençli epilepside (İDE) etkin bir tedavi seçeneğidir. Bu çalışmada İDE hastalarında VSU sonrası etkinliği, yan etkileri ve prognozu belirlemeyi hedefledik.
Yöntem: Merkezimizde 2001- 2014 yılları arasında değerlendirilmiş İDE hastalarında VSU uygulanmış 17 (E/K: 12/5) erişkin hastayı değerlendirdik. Hastanın VSU uygulandığı sıradaki yaşı, VSU öncesi ve sonrası nöbet sıklığını, tedavi süresi ve etiyolojik özellikleri değerlendirdik.
Bulgular: İyi cevap oaranı %58.5 (10/17) idi. Ortalama VSU uygulama zamanı 17.4 yıldı. VSU öncesi ve sonrası nöbet sıklığı ortalaması 28.5/16.4 idi. On bir hastada (%64.7) epilepsi

nedeni yapısal bozukluklara: neoplazm, enkakt, travma, meziyal temporal skleroz ve ensefalit, bağlıydı. Bu grupta iyi cevap oranı %63.6 (7/11) idi. Genetik ve nedeni bilinmeyen epilepsi grubunda iyi yanıt oranı %50 (3/6) idi. Etkinlik konusunda en iyi prediktif değer EEG odağıydı (p: 0.007). Startle epilepsisi ve fokal motor nöbeti olan 2 hastada nöbet sıklıkları %75 ve %86.6 iken nöbet sıklığı VSU ile %66.7 oranında azaldı.
Sonuç: VSU, İDE hastalarında güvenli ve etkin bir tedavi seçeneğidir. En iyi sonuç fokal motor ve startle epilepsi hastalarında elde edilir. İki yanlı epileptiform anomali bulgusu olan hastalarda VSU en iyi prognoza sahiptir.

Anahtar Kelimeler: VSU, İDE, vagal sinir uyarımın

INTRODUCTION

According to World Health Organization reports, over 50 million patients worldwide have epilepsy, 85% of whom are in developing countries. Thirty percent of patients with epilepsy are drug resistant (1). Some patients can undergo surgery, but others do not have that option. Vagal nerve stimulation (VNS) is reported to be effective on adults and adolescents older than 12 years with intractable partial seizures who cannot undergo surgery (2). The efficacy of VNS in reducing seizure frequency is 50.9% (18.4-67%) (3,4). The mechanisms for the antiepileptic effects of VNS are not fully understood but probably relate to its effects on the reticular activating system. It was demonstrated that there were afferent projections from the vagus nerve, travelling within the nucleus tractus solitarius, and synapsing in the locus coeruleus and raphe magnus nuclei, affecting the release of norepinephrine and serotonin. The vagus nerve provides an easily accessible peripheral route to modulate central nervous system function (5). VNS inhibits seizure activity and protects blood brain barrier integrity using the transcellular pathway (6). We aimed to determine the adverse effects and efficacy of VNS and show seizure outcome in this study.

MATERIAL AND METHODS

Patients

This study includes patients who had DRE and could not undergo or refused surgery, who were scheduled for invasive electroencephalography (EEG), had interictal multifocal EEG abnormalities, and thus underwent VNS device implantation at Istanbul University, Department of Neurosurgery, between 2001 and 2014. The patients' follow-up records were retrospectively reviewed. We noted the average seizure frequency per month for each patient at baseline, 3, 6, and 12 months, and each year thereafter until the latest follow-up after the implantation.

The database includes data such as sex, age, age at epilepsy onset, epilepsy duration, neurologic examinations, seizure types and frequencies, interictal EEGs, video-EEG monitoring (VEM), psychiatric evaluations, neuropsychological tests, and magnetic resonance imaging (MRI) before VNS device implantation.

We had patients with both focal and generalized seizures. All patients were treated with at least two anti-epileptic drugs (AEDs) prior to VNS. VEM showed multi-focal abnormal discharges from one or both hemispheres, which were seen independently in at least 2 or more foci interictally. Patients were classified according to possible prognostic factors:

1- Epilepsy onset age <6 to >6 years

2- Epilepsy duration before VNS <15 or >15 years

3- Etiology: lesional or non-lesional

Surgery and stimulation

Surgical implantation techniques for VNS devices have been explained previously in

the literature (7,8). The implantation operation is performed under general anesthesia. The stimulator is switched on approximately 2-3 weeks postoperatively. Long-term follow-up and VNS parameters were controlled by a team of epileptologists.

The VNS System (Cyberonics, Houston, TX, USA) was used in this study. The in vitro control device included a parameter-controlled instrument and magnet. We followed the protocol in which the initial stimulation is 0.25 mA, 30 seconds "on" followed by 5 minutes "off"; the stimulation period is 500 μs at a frequency of 30 Hz. The stimulation severity is increased progressively according to efficacy and patient tolerance.

In this study, responses were evaluated according to the McHugh classification system. We termed patients as "good responders" when seizure frequency was reduced by at least 50%, and "positive responders" when there was any reduction in seizure frequency.

Statistical analysis

Data are expressed as means ± standard deviation (SD) and minimum - maximum values. All statistical analyses were performed using SPSS version 21.0. A descriptive analysis was run to summarize patient characteristics. The Chi-square test was used to compare the effectiveness of VNS in different epilepsy onset age (<6 or >6 years) groups, epilepsy duration before VNS (<15 or >15 years), and etiology (lesional or non-lesional). A P value of < 0.05 was considered statistically significant.

RESULTS

Study population

This study consisted of 17 patients; 70.6% were male (n=12) and 29.4% were female (n=5). Follow-up durations ranged from 1 to 14 years (4.1±3.9 years). Detailed demographic data can be seen in Table 1. Fourteen patients had focal seizures (focal motor n=2 and focal seizure with impairment of consciousness n=12), one of those with focal motor seizures had startle epilepsy, the other 2 patients had generalized seizures with progressive myoclonic epilepsy, and the remainder had startle epilepsy with asymmetric tonic seizures. The good response rate in focal seizures with impairment of consciousness was 58.3% (7/12). Both patients with focal motor seizures benefited from VNS. The seizure frequency of the patient with only focal motor seizures dropped from approximately 120 seizures to 30 seizures/month with VNS. As for the other patient with startle epilepsy, seizure frequency reduction was from 30 to 4 seizures/month with VNS. In another patient with startle epilepsy with asymmetric tonic seizures, seizure frequency decreased by approximately 66%. Two patients who had generalized seizures with progressive myoclonic epilepsy did not benefit from VNS treatment.

Six patients, one with startle epilepsy, had normal MRI, whereas 2 patients had tumors, one of which was seated on the eloquent cortex. The other patient with startle epilepsy had widespread encephalomalacia; 2 patients had traumatic, 2 had encephalitic sequel, 1 had postanoxic sequel, and 3 patients had failed surgery for hippocampal sclerosis. The main reasons for accepting VNS as an alternative treatment: seven patients refused to undergo resection surgery; the seizures of one patient could not be controlled with resection surgery, and 5 patients had multifocal EEG abnormalities.

Patient 13 had undergone two operations, the first was selective amygdala hippocampectomy, followed by anterior temporal lobectomy. The patient with progressive myoclonus epilepsy (PME) had drug resistance against all AEDs marketed in Turkey. He had no alternative but VNS because he had progressive disease with severe seizures and SE.

Table 1. Demographic and clinical data for the 17 patients

Variables		Data
Sex	**Male**	12 (70.6%)
	Female	5 (29.4%)
Age (years)		31.8 (20-52) ±9.9
Age of seizure onset (years)		11.4 (0-36) ±8.5
Age at VNS implantation (years)		28.8 (16-51) ±10.5
Duration of epilepsy before VNS (years)		17.4 (5-40) ±8.5
Duration of VNS implantation (years)		4.1 (1-14) ±3.9
Median seizure frequency pre VNS (per month)		28.5 (3-120) ±37.3
Median seizure frequency post VNS (per month)		16.4 (1-90) ±24.9

Seizure outcomes and follow-up

The mean duration of follow-up was 4.1 years (range, 1-14 years). The mean age at epilepsy onset was 11.4 years, epilepsy duration before receiving VNS was 17.4 years, and seizure frequency before and after VNS were 28.5/16.4 per month. Eleven (64.7%) patients had epilepsy caused by structural or metabolic disorders (lesional) including neoplasms, infarct, trauma, mesial temporal sclerosis, and encephalitis. The good response rate (McHugh class I + II) was 63.6% (7/11) in this group. Six patients (35.2%) were in the genetic or unknown etiology group. The good response rate was 50% (3/6) in this group. The overall good response rate was 58.8% (10/17). The good response rate in focal seizures with impairment of consciousness was 58.3% (7/12). Both patients with focal motor seizures who could not be considered for surgery because their epileptogenic zones were on the motor cortex benefited from VNS. They attained near seizure-freedom with very rare episodes. The other patient who had startle epilepsy with asymmetric tonic seizures also benefited from VNS. His seizure frequency decreased by approximately 67%. Two patients who had generalized seizure with progressive myoclonic epilepsy did not benefit from VNS treatment.

The mean age at initial seizure (P = 0.29) and duration of VNS use (P = 0.39) were not associated with better response to VNS. Bilateral epileptiform abnormalities were associated with positive response (P = 0.007) (Table 2).

The overall positive response rate (McHugh class I+II+III) was 64.7% (11/17), with regard to McHugh classification Table 3. The good response rate (McHugh I-II) was 58.8% (10/17); no patients were seizure-free.

Complications and Adverse Effects

No infections, bleeding, or permanent neurologic deficits were reported during the perioperative period. The most frequent adverse effect was hoarseness (41.1%); 35.3% of the patients had no adverse effects. One patient underwent re-do surgery to change the VNS battery after 10 years. There was no decline in clinical response after changing the battery. Only one stimulator was removed because of poor response (McHugh class V). There were no serious complications with permanent neurologic deficits.

Table 2: The relationship between VNS efficacy and other variables.

Number of patients	McHugh class I+II	Others	*P*
EEG lateralization			0.007
Right	1	6	
Left	2	0	
Bilateral	7	1	
Age of epilepsy onset (mean year)	13.3 ± 9.2	8.7±7.4	0.29
Initial epilepsy			0.162
Age <6 years	1	3	
Age >6 years	9	4	
Preimplant epilepsy duration (mean years)	18.9±9.1	15.2±7.7	0.392
Preimplant epilepsy duration			0.268
<15 years	3	4	
>15 years	7	3	
Lesional	7	4	0.484
Non-lesional	3	3	
Total	10	7	

Table 3: McHugh classification of outcomes after VNS implantation in the 17-patient series as reported at the last follow-up.90

	McHugh classification	n (%)
Class I	80–100% reduction in seizure frequency	4 (23.5)
Class II	50–79% reduction in seizure frequency	6 (35.3)
Class III	<50% reduction in seizure frequency	1 (5.9)
Class IV	Magnet benefit only	0 (0)
Class V	No improvement	6 (35.3)

DISCUSSION

VNS is now an accepted treatment for patients with DRE and it seems to be effective for different types of epilepsy. It is indicated for patients who are excluded from resection surgery, but there is no consensus as to who are the best candidates for VNS or who will be "good responders." Long- term studies of VNS efficacy showed a seizure frequency reduction rate of 63.8% for adults (7,9-11). A meta analysis of VNS efficacy in epilepsy, which included 74 clinical studies with a total of 3321 patients with DRE, found that seizure frequency was reduced by an average of 45%, with a 36% reduction in seizures at 3-12 months after surgery and a 51% reduction after >1 year of therapy (12). Our study, which only included adults, showed 58.8% good response, and at least a 50% reduction in seizure frequency. On the other hand, using a classification based on seizure frequency reduction (McHugh class I+II+III), the responder rate of our series was 64.7%. It was observed that patients with focal motor seizures, one of whom had a tumor and the other no lesions, benefited from VNS more than the others. In addition, VNS proved to be more effective on 2 patients with startle epilepsy, one of whom had asymmetric tonic seizures. In the literature, 4 patients with epilepsia partialis continua and another with epilepsia partialis continua and Rasmussen"s encephalitis were reported to have benefited from VNS treatment (13). Although these numbers were low, they are significant in terms of their seizure types, supporting the effectiveness of VNS on this seizure type.

Although VNS is an effective and relatively safe adjunctive therapy in patients with DRE who are not amenable to resection, it is important to recognize that complete seizure freedom is rarely achieved using VNS.14 Literature data show a non-responder rate ranging between 25% and 65%; it could be useful to better define the selection criteria of candidates for VNS (15,16). Although more than 100,000 patients with epilepsy have undergone VNS, the predictors of outcome are still under investigation and the reported data are contradictory (15,17-

19). Our series showed no improvement in 35.3% of patients.

Several predictors of good outcome, including duration of epilepsy, age, malformation of cortical development, unilateral interictal epileptiform discharge, or multifocal epilepsy have been reported (20-22). Englot et al. suggested that patients with generalized epilepsy and children benefited significantly. Moreover, tuberous sclerosis and posttraumatic epilepsy were indicated as positive predictors of a favorable outcome (12).

Younger age and having focal or multifocal epilepsy are related to better seizure and cognitive outcomes (23,24). In our study, no correlation was found between the age of patients, age at VNS implantation, epilepsy onset age, and clinical effect. We showed that bilateral EEG abnormality was related with better response. We suggest that VNS would be more effective if EEGs have bilateral and multifocal discharges. VNS has been offered as an effective procedure in severe conditions, such as drug-refractory epilepsy partialis continua, which is regarded as a form of SE in the literature (24,25).

The limitations of this study include its retrospective design and the small size of the patient group, which makes it difficult to generalize the prognostic factors in VNS implantation.

CONCLUSION

VNS is an effective therapy for DRE. We suggest that bilateral abnormalities in ictal/interictal EEG is associated with better prognosis in VNS. VNS adverse effects are relatively more favorable than antiepileptic drugs. We think that VNS could be preferred when resection surgery is not an option, and when patients are waiting for invasive surgery. Our study contributes to the limited literature on VNS and focal motor epilepsy. Our results support greater benefits from VNS in focal motor seizures and startle epilepsy. VNS may be considered as an effective alternative treatment approach for patients with drug-resistant epilepsy and those who cannot undergo surgery owing to involvement of the eloquent cortex in the epileptic zone.

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