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Original Investigation

Vagal Nerve Stimulation Effects on Generalized-Partial Seizures and Medication in Adult Drug-Resistant Epilepsy Patients

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ABSTRACT

AIM: The aim of this study was to find out if vagal nerve stimulation (VNS) affect the generalized-partial seizure count and medical treatment in adult drug resistant epilepsy patients.

MATERIAL and METHODS: Twenty adult patients who were diagnosed with drug-resistant epilepsy were investigated retrospectively for vagal nerve stimulator implantation between 2001 and 2010 at the Neurosurgery Departments of Ufuk University and Gulhane Military Medical Academy. The effects of vagal nerve stimulation on generalized-partial seizures and medical treatment was scored and if a significant difference was found, a comparison was made by Wilcoxon Signed Ranks test and Pairwise. For all the group analyses, the statistical significant rank was accepted as a p value <0.05. Bonferroni correction was made when it was needed during pairwise comparisons.

RESULTS: VNS significantly decreased the scores of generalized-partial seizures. There was no decrease in the doses of anti-epileptic drugs and the medical treatment was resumed as before the implantation. The results were correlated with the relevant literature.

CONCLUSION: VNS is an alternative treatment option for drug resistant epilepsy for patients who are not ideal candidates for surgery or are not healed after epilepsy surgery.

KEYWORDS: Drug resistant epilepsy, Vagus nerve stimulation, Epilepsy surgery

INTRODUCTION

Epilepsy is a common neurologic disorder, characterized by abnormal electrical discharges in the brain, resulting in seizures, possibly with involuntary movements of the extremities and/or loss of consciousness (5,8,15). Approximately 1/3 of the patients cannot be cured even they try all of the medical treatments (2,6). For this reason, vagal nerve stimulation (VNS) is an alternative treatment when medical treatment and epilepsy surgery is insufficient (3,14,29,30). After animal studies, the first human implantation for treating epilepsy occurred in 1988, which was followed by U.S. Food and Drug Administration (FDA) approval in 1997 for the adjunctive use in treatment resistant focal epilepsies (4,7,31,32,38,39).

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In our study, the first implantation of VNS was made in 2001. The aim of this study was to find out if VNS affects the generalized-partial seizure count and medical treatment in adult drug-resistant epilepsy patients (27).

MATERIAL and METHODS

Twenty adult patients, who were diagnosed drug-resistant epilepsy between 2001 and 2010, and who underwent VNS implantation based on the decision of the Epilepsy Surgery Council, were analyzed retrospectively. The data of the patients were gathered from the hospital databases of Ufuk University Faculty of Medicine and Gulhane Military Medical Academy.

The Council chose the patients in 3 phases. After a detailed anamnesis, non-invasive tests like electroencephalography (EEG), video-EEG, magnetic resonance imaging (MRI), positron emission tomography (PET) and neuropsychiatric tests were performed. If more detailed tests were needed, we performed invasive EEG with deep or strip electrodes. The last phase was to discuss the type of surgery through hemispherectomy, callosotomy, temporal lobectomy, hippocampectomy, amygdalectomy or palliative surgeries like VNS. All surgeries were performed by the senior neurosurgeon (EE).

The demographics of the patients were presented by descriptive statistics. Generalized and partial seizure frequencies were recorded in 5 discrete periods, and these were compared by Friedman non-parametric analysis of variances. When a significant result was found by the Friedman test, the Wilcoxon Signed Ranks test was then used for pairwise comparisons between groups. Differences in measurements were visually presented with box-plot graphics. An alpha error level of 5% was considered as a Type 1 error limit for statistical significance, and the Bonferroni correction was calculated for determining statistically significant p values in pairwise comparisons.

RESULTS

This study included 20 patients (12 men, 8 women). The mean age was 29.9±10.96 (range 19 to 65) years. When frequencies of generalized seizures were compared between pre-operative and post-operative 2^{nd}, 6^{th}, 12^{th}, and 24^{th} months, a statistically significant difference was noted ($p=0.038$), (Table I).

The reduction rates of frequencies in generalized seizures after VNS implantation were 60.4% reduction in 2^{nd} month, 70.6% reduction in 6^{th} month, and 84.9% reduction in 12^{th} month.

Only 11 of the patients were followed-up for over 2 years, and these patients showed a 89.3% reduction when compared with the first group (Table II). There was a statistically significant difference between partial seizure frequencies at the preoperative and postoperative 2^{nd}, 6^{th}, 12^{th}, and 24^{th} months ($p<0.001$, Table III). Partial seizures were decreased 57.8% at 2^{nd} month, 59.2% at 6^{th} month, 54.9% at 12^{th} month after VNS implantation. Only 11 patients were followed up for 2 years, and these patients had a reduction of 75.9% in partial seizures (Table IV). Analyses of medical treatment between the preoperative and postoperative period revealed that there were no changes in medications. Patients neither changed nor decreased their antiepileptic drug doses.

Briefly, VNS implantation significantly decreased the frequencies of generalized and partial seizures. Additionally, medical treatment did not change after VNS implantation.

DISCUSSION

The mechanism of VNS therapy is complicated. Henry (18) and Nemeroff et al.(26) tried to find out the mechanism and they saw that VNS causes increased synaptic activity in the thalamus and thalamo-cortical projection pathways as a result of increased arousal and a decreased synchrony of synaptic activities at cortical regions. VNS leads to intermittently increased synaptic activities in the components of the central autonomic system, such as the insula and the hypothalamus (3). There is decreased synaptic activity in components of the limbic system. Finally, VNS therapy results in intermittently increased release of norepinephrine and serotonin over widespread cerebral regions. (18,25,26,28).

We have some limitations in our study. First this is a retrospective study and we could reach a limited number of patients for the long-term follow up period. In addition, we cannot compare our results with the placebo surgery trials where one must deactivate the VNS, because of the ethical problems. The same limitations can be seen in other studies in the literature as well. The earlier studies reported that the decrease rate of seizures with the use of VNS changes from 40% to 90% in the literature. Our results are between the rates of 54.9% and 89.3% which are similar to the previously reported rates. Amar et al. (1) compared the reduction in seizure burden following VNS insertion of 3822 patients without a prior history of epilepsy surgery with that of 921 patients with persistent seizures following cranial surgery. In patients without prior epilepsy surgery, 62% had ≥ 50% reduction in seizures and 27% had ≥ 90% reduction in seizure burden. Patients who failed epilepsy surgery had a poorer response to VNS therapy as 55% of patients had ≥50% and 17% had ≥90% reduction in seizure frequency (1). Similarly, Labar et al. examined 1407 patients and reported no difference in VNS efficacy between patients who remained on a stable antiepileptic drug regimen and those who required more medications or changed medications (20).

DeGiorgio et al. investigated 195 patients with generalized and partial TRE and showed a median reduction in seizure burden of 40% at a follow-up duration of 12 months (9). Vonck et al. analyzed the efficiency of VNS in 118 adults and pediatric patients with TRE who received VNS therapy at least 6 months. At a mean follow-up duration of 33 months, they reported a mean reduction of 55% in seizures of the patients. The results were similar in adolescents and children who were under 13 years (36). Elliot et al. analyzed 436 patients and inspected that seizure control ≥90% was achieved in 90 patients (22.5%), ≥75% seizure control in 162 patients (40.5%), ≥50% improvement in 255 patients (63.75%), and 50% improvement in 145 patients (36.25%) (12,13). Probably

Table I: Frequencies of Generalized Seizures in the Preoperative and Postoperative Periods

Period	Mean	SD	Median	Minimum	Maximum	Range	p
Preop	25.5	33.11	8.5	2	94	92	
VNS 2nd Month	10.1	15.13	3.5	1	61	60	
VNS 6th Month	7.5	14.35	1.5	0	60	60	0.038
VNS 12th Month	3.83	4.23	1.5	0	15	15	
VNS 24th Month	2.73	2.49	2	0	8	8	

Table II: Changes in Frequencies of Generalized Seizures Between the Preoperative Period and Postoperative 2nd, 6th, 12th, and 24th Months

Before VNS – 2 months after VNS (% change)	Before VNS – 6 months after VNS (% change)	Before VNS – 1 years after VNS (% change)	Before VNS – 2 years after VNS (% change)
60.4	70.6	84.9	89.3

Table III: Frequencies of Partial Seizures at the Preoperative and Postoperative Periods

Period	Mean	SD	Median	Minimum	Maximum	Range	p
Preop	128.35	70.34	124.5	4	250	246	
VNS 2nd Month	54.05	45.21	31	4	151	147	
VNS 6th Month	52.4	42.87	31	1	150	149	<0.001
VNS 12th Month	57.78	53.14	31	0	180	180	
VNS 24th Month	30.91	25.87	30	0	90	90	

Table IV: Changes in Frequencies of Partial Seizures Between Preoperative Period and Postoperative 2nd, 6th, 12th, and 24th Months

Before VNS – 2 months after VNS (% change)	Before VNS – 6 months after VNS (% change)	Before VNS – 1 years after VNS (% change)	Before VNS – 2 years after VNS (% change)
57.8	59.2	54.9	75.9

the highest reduction in seizure count was reported by Spanaki et al. This study also included only patients with follow up longer than 5 years. They reported an overall seizure reduction of 72% (34). At 5 years of follow-up after beginning the stimulation, Kuba et al. reported 64.4% of patients were responders whose 15.5% experienced 90% seizure reduction, and 5.5% were seizure-free (19). Tatum et al. showed that seizure duration and postictal recovery improved in 15 of 21 patients after VNS implantation (35). Similarly, McHugh et al. reported improvement in ictal and/or postictal severity in 19 of 48 patients (24). Moreover, Tatum et al. reported a reduction in the number and dosage of antiepileptic drugs after VNS (35). Wheeler et al. used Engel Classification in their study of 189 patients. Six percent of patients had a class I outcome which means seizure-free, 13% a class II outcome (almost seizure-free), 49% a class III outcome (worth while improvement) and 32% had a class IV outcome (no improvement) (37). Similar to our study, De Herdt et al. reported no changes in medical treatment after VNS implantation (10). There are many studies made for usage of VNS from different modalities. In addition to a reduction in seizure frequency, Tatum et al. and McHugh et al. found that seizure duration and postictal recovery improved as a result of VNS implantation (24,35).

Several studies reported the efficacy of VNS in different disorders except epilepsy such as Lennox–Gastaut syndrome, migraine, depression, Alzheimer disease, multiple sclerosis for postural cerebellar tremor and dysphagia, eating disorders like bulimia nervosa and Tourette syndrome (11,16,17,21,22,23,33). It seems VNS will be a treatment modality for many diseases in the future.

■ CONCLUSION

Implantation of VNS decreases the scores of generalized-partial seizures. Our results were correlated with the relevant literature. VNS implantation is a featured alternative treatment option for epilepsy drug resistant patients who cannot accept surgery or are not healed after epilepsy surgery.

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