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Efficacy of Neuromodulation Therapy with Vagus Nerve Stimulator in Patients with Drug-Resistant Epilepsy on Unchanged Antiepileptic Medication Regimen for 24 Months Following the Implant

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Abstract

To establish efficacy of vagus nerve stimulation (VNS) therapy in the treatment of intractable epilepsy, we compared outcome data from the baseline period to the maintenance period (7 to 24 months post-implant) by calculating the mean seizure frequency at 6-month intervals (7 to 12 months - first study period, 13 to 18 months - second study period, and 19 to 24 months - third study period), in 39 consecutive patients on unchanged anti-epilepsy drug (AED) regimen for 24 months following the VNS implant. Of the 39 patients24 (61.5%) at first study period, 25 (64.1 %) at second study period and 25 (64.1 %) at third study period were responders (≥50% reduction in seizures). Twenty one (53.9 %) patients were responders in all three study periods. Incremental seizure control was seen in 15 of these 21 patients. Although 3 (7.7%), 4 (10.3 %) and 8 (20.5%) patients had a total (100%) seizure control at first, second and third study periods respectively, no patient remained seizure-free through all 3 study periods. Seven (17.9%) patients were partial responders (≥ 50% seizure reduction in two or less study periods). Eleven patients (28.2%) were non-responders (< 50% seizure reduction in all 3 study periods). Twenty three patients (59%) had partial epilepsy with and without secondarily generalization and 16 patients (41%) had primary generalized epilepsy. Eleven (47.8%) of the 23 patients with partial epilepsy and 10 (62.5%) of the 16 patients with generalized epilepsy were responders in all three study periods. We conclude that: 1) More than 60 % of patients on unchanged AED regimen continued to be responders at 24 months following the VNS implant. 2) A trend towards increasing responder rate with increasing duration of VNS therapy was observed.3) No major complications or side effects requiring discontinuation of VNS therapy were noted.

Keywords: Drug resistant epilepsy; Vagus nerve stimulation

Introduction

Vagus nerve stimulation (VNS) therapy is an effective adjunctive neuromodulation treatment for medically refractory epilepsy [1-5]. Several studies that demonstrated VNS efficacy have reported ≥ 50% seizure reduction in 23.4%-39% patients with follow up duration of 3-3.5 months [5-8],35% - 61.8% with follow up duration of 6-12 months [9-12] and 39% - 63.8% with follow up duration of 1-10 years [13-25]. However, as antiepileptic drug (AED) regimens during the study period were adjusted as needed, these studies do not truly reflect the role of VNS in incremental seizure frequency reduction seen with longer duration of VNS therapy. So far only two studies (with follow-up for 12 months and 18 months respectively) have demonstrated the continued efficacy of VNS with stable AED regimens [18,26]. We present the results of a retrospective analysis study of prospectively collected data showing the efficacy and safety of VNS therapy in a group of patients with intractable epilepsy in whom the AED regimen remained unchanged(due to either non-availability of next generation AEDs or patients' refusal to change AED regimen) for a period of 24 months following VNS implant.

Methods

All the patients who undergo treatment at our Comprehensive Epilepsy Center maintain a seizure diary which is entered in the data base during follow up visits on an ongoing basis. We conducted a retrospective analysis of this prospectively collected clinical data of 160 consecutive patients with drug resistant epilepsy (failed adequate trial of at least 3 appropriate AEDs)who underwent vagus nerve stimulator (VNS) implantation surgery at Kaiser Permanente Medical Centers in Anaheim and Los Angeles in California, U.S.A. from September 1998 to December 2011. A total of 39 patients were identified in whom AED regimen had remained unchanged for a period of 24 months following VNS implant. The patients were on high therapeutic doses of AEDs, which remained unchanged either due to non-availability of next generation AEDs or patients' refusal to change AED regimen.

All patients underwent pre-operative evaluation which included long term video EEG monitoring, MRI brain examination and approval by Kaiser multidisciplinary epilepsy surgery case conference. Patients were admitted for surgical implantation of VNS device from Cyberonics by our neurosurgeons, who had received required training.

To allow wound healing, the VNS system was not activated for 1 week postoperatively. With starting current being 0.25 mA, output current was gradually increased in 0.25 mA increments once per week for six weeks and subsequently during biweekly visits up to maximum of 3.5 mA if needed. Output current was adjusted on the basis of

patients' tolerance to the electrical stimulation and impact on seizure control. The VNS stimulation parameters were either standard cycle or rapid cycle per preference of the treating epileptologist. For standard cycling, the signal-on time was >30 seconds and signal-off time ranged from 3 minutes to 5 minutes. For rapid cycling, signal-on time was < 21 seconds and signal-off time ranged from 0.2 minutes to 1.8 minutes. Duty cycle was maintained at <50% in most cases.

The first 6 months after VNS implant was the titration period and the period from 6 months to 24 months was the study period. Efficacy of VNS therapy was analyzed by calculating mean change in seizure frequency from baseline (seizures frequency in the last 6 months before patients received VNS implant) to mean seizure frequency for 6-month intervals for the three study periods (7 to 12 months - first study period, 13 to 18 months - second study period, and 19 to 24 months - third study period). We determined the VNS therapy success rate by calculating reduction of seizure frequency in different types of epilepsies during the three study periods. Those with ≥ 50% reduction of seizure frequency in all three study periods with respect to the pre-implant seizure frequency were defined as total responders; those with ≥50% reduction of seizure frequency in less than three study periods were categorized as partial responders; and those with < 50% reduction of seizure frequency in all three study periods as non-responders.

We also assessed postoperative adverse events, side effects, and tolerability of the implantation procedure and of the VNS device, and impact on alertness, mood and behavior.

Results

There were 20 females and19 males with age ranging from 5 years to 70 years. The mean age at onset of epilepsy was 8.8 ± 11.9 years and mean age at VNS implantation was 21.3 ± 14.6 years. Mean number of AEDs at baseline was 2.02. Clinical characteristics of the patients at base line are summarized in Table 1.

Etiology	**Number of Patients**
Lennox Gastaut syndrome	6
Encephalitis	4
Tuberous sclerosis	3
Tumor	3
Head injury	2
Porencephaly	1
Prenatal encephalopathy	1
Unknown	19
Antiepileptic drugs	
1 drug	8
2 drugs	23
3 drugs	7
4 drugs	1
Epilepsy Type	
Simple partial	2
Complex partial	13
Complex partial with secondary generalization	8
Generalized tonic-clonic	3
Atypical absence	4
Tonic	2
Mixed generalized	7

Table 1: Clinical characteristics of the patients at base line

In 24 month period, 34 patients were treated with the standard cycle of VNS. Four patients who initially were on standard cycling were later switched to rapid cycling. One patient was treated with only rapid cycling. The output current used ranged from 0.5 mA to 3.5 mA with median setting of 2.5 ± 0.7 mA at 6 months, 2.8 ± 0.7 mA at 12 months, and 2.8 ± 0.7 mA at 24 months.

Responder rates during the three study periodsare shown in Table 2. Twenty one patients (53.9%) had ≥ 50% reduction in seizure frequency in all three study periods, 15 of which showed incremental response. Although 3 (7.7%), 4 (10.3%) and 8 (20.5%) patients had a total (100%) seizure control at first, second and third study periods respectively, no patient remained seizure-free through all 3 study periods. Partial response was seen in 7 (17.9%) patients. Eleven patients (28.2%) were non-responders or had worsening of seizure frequency.

Of the 39 patients, ≥ 50% reduction in seizure frequency was seen in 15 patients (38.5%) during the titration period, in 24 patients (61.5%) during the first study period (7 to 12 months), in 25 patients (64.1%) during the second period (13to 18 months) and in 25 patients (64.1%) during the third period (19 to 24 months) (Figure 1).

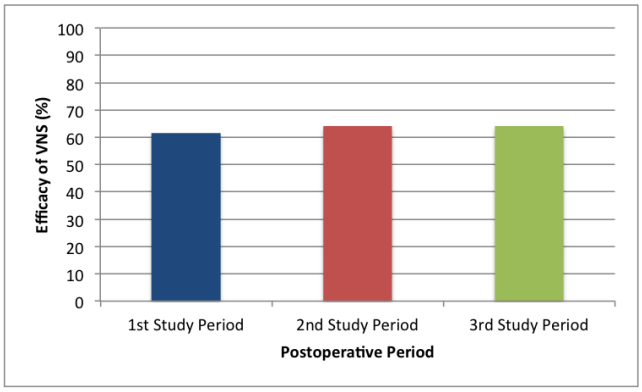

Figure 1: Efficacy of VNS (≥50% reduction in seizure frequency) in all 3 Study periods

We also analyzed the efficacy of VNS according to the type of epilepsy. Out of 39 patients, 23 (59 %) had partial epilepsy with and without secondary generalization, and 16 (41%) had primary generalized epilepsy. Eleven (47.8%) of the 23 patients with partial epilepsy and 10 (62.5%) of the 16 patients with generalized epilepsy showed ≥ 50% reduction of seizure frequency.

Twenty three patients (59%) were reported being more alert over the 24 months study period. Twenty two (56.4%) patients experienced intermittent hoarseness, cough and/or throat irritation when signal was "on". These side effects subsided after the output current parameters were lowered and therefore did not necessitate discontinuation of the VNS treatment in any patient.

Vital signs and electrocardiographic data analysis showed no clinically significant change while on VNS therapy.

Discussion

VNS therapy has been established as an effective therapy for drug-resistant epilepsy [1-5]. No particular AED has been identified as having additive anti-seizure effect with VNS therapy. If the net effectiveness of VNS therapy is to be established, it is imperative to maintain the doses of concomitant AEDs constant. Many studies on VNS therapy have reported the incremental increase in responder rate with increasing duration of treatment. However, the success rate reported in most of these long term studies does not adequately reflect the effectiveness of VNS therapy as AEDs were not kept constant during the study period. Frequent follow up visits required during early VNS ramp-up stage, which facilitate careful adjustment of AED regimen, and the potential for addition of newer generation AEDs permitted during the study period, may have contributed to the reported reduction in seizure frequency [12-25]. On the other hand, the patients' and the treating neurologists' desire to achieve decreased dose and reduced number of AEDs after VNS implantation may have resulted in the reported impact of VNS therapy being suboptimal.

A 2002 study involving 1407 patients who were treated with VNS therapy for at least 12 months reported no difference in VNS efficacy between patients on stable regimen and those with AED adjustment [12]. This result probably indicates either ability to optimize and thus achieve better efficiency of VNS therapy due to stable AED pharmacodynamics and/or lack of improved efficacy due to maximum response to AEDs already attained. Interestingly, the same study also showed that 40% to 50% of patients on VNS therapy were able to reduce the dose of concomitant AEDs without adversely affecting seizure control and at the same time achieving improved quality of life [12]. As no specific protocol was followed while adjusting AED regimen, the results of this study should be reviewed with caution.

To date, only two studies where AED regimen was kept constant (with follow-up for 12 months and 18 months respectively) have demonstrated continued efficacy of VNS therapy [18,26]. The first study (n = 269) demonstrated ≥ 50% reduction of seizure frequency in 57% of the patients after 12 month of therapy following VNS implant [18]. A more recent study(n = 43) demonstrated that 62.8% patients had ≥ 50% reduction in seizure frequency at 18 months follow-up [26]. In our study (n=39), the efficacy of VNS is analyzed by calculating the mean seizure frequency at 6-month intervals from the baseline to 24-month period. The response of VNS therapy is demonstrated throughout the 24-month period. Results of our study and 2 other similar studies where AED regimens were kept constant following VNS implant fall within the higher range of the VNS efficacy (35% to 61.8%) reported by other long term follow up (1-10 years) studies where modification of concomitant AEDs was permitted [9-12], thereby proving the efficacy of VNS therapy.

We also demonstrate a trend towards increasing responder rate with increasing duration of VNS therapy (Table 2).

Study Period	Number of patients
Total Responders	21
Partial Responders	
Period from 7 months to 12 months	1
Period from 7 months to 18 months	2
Period from 13 months to 24 months	4
Non- responders	11
Total Responders: ≥ 50% reduction of seizure frequency in all three study periods; Partial Responders: ≥ 50% reduction of seizure frequency in < three study periods; Non-responders: < 50% reduction of seizure frequency in all three study periods.	

Table 2: Responder rate (≥50% reduction of seizure) at 3 study periods

In our study, VNS appears to have the antiepileptic effects on both partial and primary generalized epilepsies with responder rates of 47.8% and 62.5% respectively. Our previous study [11] also demonstrated that patients with primary generalized epilepsy had better responder rate than patients with partial epilepsy with and without generalized epilepsy. However, small study size may precludedelineating statistical significance of these numbers.

Cough and pharyngeal pain commonly occur during initial application of current or when incremental increases of output current are too large. These adverse events can be minimized by increasing the current at 0.25 mA increments or setting the pulse width to the lower value. Voice alteration such as hoarseness which occurs in many patients during the stimulation resolves over time and therefore may not require any lowering of output current setting. No major complications or side effects requiring discontinuation of VNS therapy were noted in our study.

Conclusion

We conclude that:

1) More than 60% of patients on unchanged AED regimen continued to be responders at 24 months following the VNS implant.

2) A trend towards increasing responder rate with increasing duration of VNS therapy was observed.

3) No major complications or side effects requiring discontinuation of VNS therapy were noted.

We realize the limitations of the small size of our retrospective data analysis study but still consider it to be an important study as 1) due to ethical issues it is not possible to design a prospective double blind large research study to further characterize the findings of this study; and 2) due to availability of third-generation AEDS, in the near future similar retrospective data analysis study will not be available.

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