Seizure (2004) **13**, 587–590

SEIZURE

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Vagus nerve stimulation therapy: 5-year or greater outcome at a university-based epilepsy center

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KEYWORDS
Epilepsy;
Pharmacoresistant;
Refractory;
Vagus nerve stimulation;
VNS;
Outcome

Summary *Objective*: This retrospective study documented long-term outcome of patients receiving vagus nerve stimulation (VNS) therapy for pharmacoresistant epilepsy. *Methods*: Medical charts of 28 patients implanted for 5 years or longer were reviewed for changes in seizure frequency after 1 year of VNS therapy and at follow up, which ranged from 5 to 7 years. Numbers of antiepileptic drugs (AEDs) taken by the patients were also computed at 1 year and follow up. One patient had died and one had discontinued VNS therapy; data were available for 26 patients. *Results*: The median percent change in seizure frequency from baseline increased from −28% ($P = 0.0053$, Wilcoxon signed-rank test) at 12 months to −72% ($P < 0.0001$) at follow up. Some patients whose seizure frequency was not reduced during the initial 12 months of VNS therapy did experience reductions in seizure frequency during the follow-up period. *Conclusion*: In this retrospective study, the effectiveness of VNS therapy increased over time. Physicians should be aware that response to VNS therapy may be delayed for some patients.

Introduction

Clinicians who treat patients with vagus nerve stimulation (VNS) therapy for epilepsy are acquainted with the technique of adjusting stimulation parameters to optimize effectiveness for the individual patient. Several studies have shown that the effectiveness of VNS therapy increases with time[1] and have suggested a cumulative effect of VNS therapy in reducing the frequency of seizures.[2–4] Although some attention has been devoted to tailoring VNS therapy to achieve maximum effectiveness,[5] little discussion has focused on the length of time that clinicians should continue VNS therapy before determining that it is ineffective for a particular patient. Schachter[6] cautions against premature cessation of VNS therapy and encourages the clinician to continue the treatment for up to 2 years before discontinuing it on the basis of inefficacy.

Numerous studies have described the safety and effectiveness of VNS therapy.[6] In addition to reducing the frequency of seizures, other reported

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doi:10.1016/j.seizure.2004.01.009

benefits have included reductions in the severity of seizures[7] as well as improvements in quality of life.[6] Reports of improved alertness, memory, and mood have prompted the manufacturer of the VNS therapy system (Cyberonics, Inc., Houston, TX, USA) to undertake clinical trials among patients with intractable depression.[8] In this university-based epilepsy center, we are aware of patients who continued VNS therapy, even though they had not experienced any reduction in the frequency of seizures after 12 months of treatment. We therefore undertook a retrospective record review to identify benefits other than seizure reduction and evaluate whether these patients attained some reduction in seizure frequency after the initial 12 months of VNS therapy. At the same time, we investigated whether patients whose seizure frequency decreased during the first year subsequently experienced greater reductions.

Methods

We conducted a retrospective review of records of patients receiving VNS therapy for 5 years or more at this university-based epilepsy center. Of the 28 records reviewed, 26 provided usable data. One of the 28 patients had died of SUDEP and a second had discontinued VNS therapy because benefits did not outweigh side effects. Several of the patients had participated in the clinical trials conducted before FDA approval[9] of VNS therapy for commercial use in 1997, thereby accounting for some follow-up periods that exceeded 5 years.

The records review collected data regarding the number of years the patients had received VNS therapy; epilepsy syndromes; types of seizures reported at baseline and follow up; number of antiepileptic drugs (AEDs) prescribed at baseline, after 1 year of VNS therapy, and at follow up; seizure frequency at baseline; percent reduction of seizure frequency from baseline at 1 year and follow up; and the percentage of seizure frequency reduction between 1 year and follow up.

Maximum increase and decrease in seizure frequency was bounded at −100 and +100%. The statistical significance of changes in seizure frequency was measured with the Wilcoxon signed-rank test. Results were considered statistically significant when $P \leq 0.05$.

Results

The follow-up period for the 26 patients, 14 males and 12 females, ranged from 5 to 7 years. Records were available for 5 years for 17 patients, 6 years for 3, and for 7 years for 6. Median age at the onset of seizures was 8 years (range, 0—44), and median age at implantation was 35 years (range, 18—55). Epilepsy syndromes were partial (24 patients), atypical absence (1 patient), and generalized (1 patient). Six of the patients had previously undergone unsuccessful epilepsy surgery. Two patients with left mesial temporal sclerosis had declined epilepsy surgery. One patient had inoperable left neocortical temporal epilepsy in which the seizure focus was co-localized with language; surgery would have resulted in major language deficits. Five patients had widespread seizure onset in one hemisphere and were not considered to be good candidates for surgery. Five patients had severe neonatal insult; four had idiopathic epilepsy, which may have been multifocal, and the remaining three had severe head injury.

Fig. 1 shows the number of patients taking zero to four AEDs at each time point. At baseline and 1 year, the median number of AEDs was two (range, 1—4).

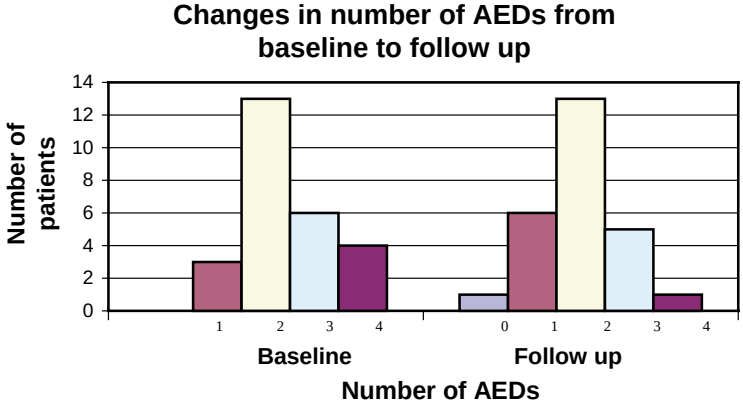

Figure 1 At follow up, the median number of antiepileptic drugs (AEDs) was unchanged from baseline, but the number of patients taking three or four AEDs decreased and one patient discontinued AED therapy.

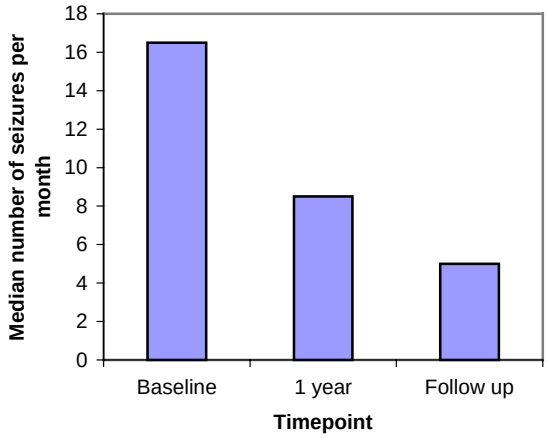

Figure 2 The median number of seizures per month was decreased after the initial 12 months of VNS therapy and was further decreased by follow up.

At follow up, the median number of AEDs remained at two, but the range had increased from zero to four.

Reductions in seizure frequency across time are shown in Fig. 2. Median seizure frequency at baseline was 16.5 seizures per month (range, 2—2800). After 1 year of VNS therapy, the median percent change in seizure frequency was −28% (range, −100 to +100), the median number of seizures per month was 8.5 (range, 0—1400; $P = 0.0053$), and seizure frequency and type remained unchanged for six patients. At follow up, the median percent change in seizure frequency was −72% (range, −100 to +100), and the median number of seizures per month was 5 (range, 0—36.5; $P < 0.0001$). Between 1 year and follow up, the median percent change in seizure frequency was an additional −33% (range, −100—100; $P < 0.0001$). During this interval, seizure frequency did not change for 8 of the 26 patients and decreased for 18 patients; 8 patients had reductions <50% and 10 patients had reductions ≥50%. By follow up, seizure frequency had decreased for four of the six patients whose seizure frequency and type had not changed during the initial 12 months of VNS therapy.

Discussion

In this retrospective review, the median percent reductions in seizure frequency were statistically significant not only during the first year of VNS therapy, but also between 1 year and follow up, which ranged from 5 to 7 years. The patients with the longest follow up were selected for the VNS therapy clinical trials because all other treatment modalities had been exhausted. Given the established intractability of this group, the favorable outcome and long-term retention (only one patient discontinued) is remarkable.

Of the six patients whose seizure frequency and type had not changed after 12 months of VNS therapy, four experienced reductions in seizure frequency by follow up. These six patients were continued on VNS therapy beyond the initial 12 months because they experienced other benefits, including shorter seizures, reduced postictal confusion, and interrupted seizures or diminished seizure severity, with magnet activation of VNS therapy. Interestingly, five of these six patients had undergone unsuccessful epilepsy surgery before they were implanted with the VNS therapy device.

An early investigation of VNS therapy suggested that patient response during the first 3 months of treatment could foretell subsequent effectiveness,[10] but the analysis lacked the lengthy follow-up period of this study. This study has some limitations: data were gathered retrospectively and the number of patients was small. However, the additional reductions in seizure frequency of the patients in this study support the premise that the effectiveness of VNS therapy can increase after the initial 12 months.

Conclusion

In this retrospective study, the effectiveness of VNS therapy increased over time. Some patients have a delayed response and eventually benefit from VNS therapy. A clinician evaluating a patient whose seizure frequency has not decreased should not rush the decision to discontinue VNS therapy.

Acknowledgements

The authors thank Marcella M. Johnson, MS, for preparing the statistical analyses and Susan E. Siefert, ELS, CBC, of Cyberonics, Inc., for assistance in preparing the manuscript. This work was supported by an unrestricted grant from Cyberonics, Inc.

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