Original Article

Vagus Nerve Stimulation Therapy in Pediatric Patients With Refractory Epilepsy: Retrospective Study

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ABSTRACT

This six-center, retrospective study evaluated the effectiveness, tolerability, and safety of vagus nerve stimulation in children. Data were available for 125 patients at baseline, 95 patients at 3 months, 56 patients at 6 months, and 12 patients at 12 months. The typical patient, aged 12 years, had onset of seizures at age 2 years and had tried nine anticonvulsants before implantation. Collected data included preimplant history, seizures, implant, device settings, quality of life, and adverse events. Average seizure reduction was 36.1% at 3 months and 44.7% at 6 months. Common adverse events included voice alteration and coughing during stimulation. Rare adverse events, unique to this age group, included increased drooling and increased hyperactivity. Quality of life improved in alertness, verbal communication, school performance, clustering of seizures, and postictal periods. We concluded that vagus nerve stimulation is an effective treatment for medically refractory epilepsy in children. (*J Child Neurol* 2001;16:843–848).

In July 1997, the US Food and Drug Administration approved the NeuroCybernetic Prosthesis® System (Cyberonics, Houston, Texas) to deliver vagus nerve stimulation for adjunctive therapy in patients aged 12 years and older with refractory partial seizures. Clinical studies showed average reductions of 25% in seizure frequency over the first 3 months of vagus nerve stimulation therapy and 40 to 50% reductions through the first year to 18 months. These results are comparable with the efficacy of the newer anticonvulsants.[1,2]

Since the US Food and Drug Administration approved the NeuroCybernetic Prosthesis, more than 11,000 patients have been implanted. Nevertheless, very little information is available regarding patients aged 18 years or younger.[3–7] The combined, preapproval clinical studies (EO1-EO5) included 60 patients aged 18 years or younger, 16 of them younger than age 12 years. Registration cards, supplied with all implanted devices and filled out by the implanting physician, indicated that approximately 14% of the 11,000 patients implanted since July 1997 were younger than age 12 years (data on file at Cyberonics).

This multicenter, retrospective study was undertaken to gather and provide more information on the effectiveness and safety of vagus nerve stimulation therapy in children.

METHODS

Inclusion Criteria

Six centers (Children's Hospital-Boston, University of Texas Medical School-Houston, Minnesota Epilepsy Group, The Children's Hospital-Denver, Children's National Medical Center, and Louisiana State University Comprehensive Epilepsy Center) collaborated on this

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Data for this analysis were collected at the institutions listed above.

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study during late 1998. Two centers (Boston and Houston) had been involved in the preapproval clinical studies of vagus nerve stimulation therapy, and the other four centers had postapproval experience only. Informed consent and approval by the Institutional Review Board were obtained at those centers where such approval was required for retrospective studies.

All patients from the six centers who were aged 18 years or younger at implantation and had medically refractory epilepsy were included in the analysis. Approval from the US Food and Drug Administration includes use of the NeuroCybernetic Prosthesis System in patients aged 12 years or older with partial-onset seizures that are refractory to antiepileptic medications. Therefore, in cases of patients younger than 12 years or with seizure types other than partial onset, the patient and parent or guardian were informed of the limitations of the US Food and Drug Administration approval. All patients and parents or guardians elected to proceed with the implant.

Implantation

Implantation of the vagus nerve stimulator in children was performed using a technique similar to that used in adults and previously described by Madsen and Helmers[5] and Amar et al.[2] In many of the children, the device was activated immediately after implantation.

Data Collection

Data collection forms were designed for retrospective collection of data on all patients implanted before December 31, 1998, and included follow-up data through March 31, 1999. Data were captured from existing patient records and then documented on a uniform data collection form. During the 2-month period before implantation, caregivers had collected information on each patient's preimplant history and had maintained an accurate seizure diary. Typically, patients kept seizure calendars that were reviewed by the investigators. Seizure frequency was entered into patient records. Investigators consulted patient records to obtain monthly seizure rates and recorded them on the data collection forms for the study. Seizure counts from the 2 months before implantation were averaged to determine baseline seizure frequency. Information on seizures, implant, device settings, and adverse events was collected after implantation (Table 1). In some instances, investigators interviewed patients to obtain data that were missing from patient records.

Given the retrospective nature of the study, seizure frequencies were obtained by reviewing patient charts for exact seizure counts over specific dates; monthly averages for the previous 3 months; or daily, weekly, or monthly ranges. Seizure-frequency data were gathered as available for each patient at baseline and 3, 6, and 12 months after implantation. Data were collected by type of seizure as had been reported by the patient or parent and then combined to calculate each patient's average rate. To verify the correct interpretation of seizure counts, investigators carefully reviewed seizure records across all visits.

In addition to examining changes in seizure frequency, this analysis examined other, more subjective data. Parents or caregivers reported changes in the patient's quality of life at 3, 6, and 12 months. Changes were documented on a simple, unvalidated, 5-point scale that featured ratings of much worse, worse, same, better, and much better.

Table 1. Data Collection Forms

Preimplant Data	*Implant Data*	*Postimplant Data*
Age at seizure onset	Implant date	Device settings
Gender	Weight	Interval seizure frequency (3, 6, and 12 mo)
Institutionalized	Current antiepileptic drug treatment	Magnet use/effect
Previous antiepileptic drug treatment		Quality of life (3, 6, and 12 mo)
Ketogenic diet	Device settings	Adverse events
Magnetic resonance imaging		Antiepileptic drugs
Etiology of epilepsy		
Syndrome classification		
Baseline seizure type/ frequency		

Informed consent was obtained from the patients' parents or guardians in compliance with rules governing the individual institutions participating in the study. After data entry and verification, data were first analyzed with Microsoft Excel (Microsoft Corporation, Redmond, WA) and then confirmed with SAS© (SAS Institute, Cary, NC). Paired *t*-tests were used to analyze percent changes from baseline. Student's *t*-tests were used for analysis of within-group comparisons. *P* values of $< .01$ were considered statistically significant.

RESULTS

Demographics

As of December 31, 1998, 125 patients meeting inclusion criteria had been implanted with the NeuroCybernetic Prosthesis System. Because some patients were implanted toward the end of the data collection period, follow-up data were not available for every patient at every time point. Follow-up data were available for 96 patients at 3 months, 56 patients at 6 months, and 12 patients at 12 months. The average age at implant was 11.8 years (median age 12 years, range 3–18 years), with 41 patients younger than age 12 years at implant. The average age at onset of seizures was 3.1 years (median 2, range 0–12.5). More males were implanted—79 (63%) versus 46 females (37%). Only 3 (2.4%) patients were institutionalized, but a notable number, 49 (39%), were mentally retarded (IQ less than 70, on the basis of an investigator's judgment). Forty-six patients (37%) had previously tried the ketogenic diet, although only 3 (2.4%) were on the diet at the time of implantation.

Among this group of patients with resistant epilepsies, the most common seizure types were partial (59 patients, 47%) and generalized seizures (23 patients, 18.5%). Lennox-Gastaut syndrome was noted in 43 patients (34.5%). Patients with Lennox-Gastaut syndrome were characterized as having mixed-seizure disorder with drop, atypical absence, and complex partial seizures. Some patients had associated diagnoses of tuberous sclerosis complex and mitochondrial disorders. Of 33 patients who had previously undergone

Table 2. Patient Characteristics at Baseline and After 3 Months of Vagus Nerve Stimulation Therapy

Characteristic	*Baseline Average (Range)*	*3-Month Follow-up Average (Range)*
Number of patients	125 (79 males, 46 females)	95 (60 males, 35 females)
Age at implant (yr)	11.8 (3–18)	12.0 (3.0–18.0)
Age at seizure onset (yr)	3.1 (0–12.5)	2.0 (0.0–12.5)
Previous AEDs	8.8 (2–17)	9.0 (2.0–17.0)
Most common AEDs	Topiramate (32.8%), lamotrigine (32.8%), valproate (31.2%), carbamazepine (17.6%)	Lamotrigine (32.9%), valproate (32.9%), topiramate (25.9%)

AED = antiepileptic drug.

epilepsy surgery, 13 had previous lobectomy, 18 had previous callosotomy, and 2 had previously undergone both procedures. Seizure types reported for patients who had previously undergone callosotomy included drop, absence, atypical absence, simple and complex partial, secondary generalized, and generalized tonic clonic.

Effectiveness

Data describing outcomes at 3 months after implantation were available for 95 of the 125 implanted patients. The remaining patients were not lost to follow-up but had been implanted more recently and did not have the opportunity to complete 3 months of stimulation before the data collection cutoff point. These 95 patients were demographically similar to the entire group (Table 2).

Three months after implantation, the average reduction in seizure frequency was 36.1% ($P < .0001$), with a median reduction of 51.5% (range, −100% to +312%). Of the 95 patients, 27 (28.4%) had decreases in seizure frequency exceeding 75%, and 50 (52.6%) patients had decreases exceeding 50%. Two patients (2.1%) reported no seizures. Seizure frequency increased by more than 50% in six patients (Figure 1). The reduction in seizure frequency did not differ among patients with aura or simple partial seizures and patients with other types of seizures.

Data were available for 56 patients at 6 months. The average reduction in seizure frequency improved to 44.7% ($P < .0001$), with a median reduction of 51.0% (range, −99.9% to +100.0%). Of the 56 patients, seizure frequency decreased more than 75% in 17 (30%) and more than 50% in 32 (57%). No patients reported zero seizures at 6 months. Seizure frequency increased by more than 50% in one (2%) patient.

Data were available for 12 patients after 12 months of vagus nerve stimulation therapy. The percentage of reduction in seizure frequency was similar to that in patients at 6 months.

Anticonvulsants

An average of 8.8 (median 8, range 2–17) anticonvulsants had been tried before implantation. Patients were taking an average of 2.3 (range 1–5) anticonvulsants when they were implanted with the pulse generator. At 3 months, the number of anticonvulsant medications had decreased from baseline in 10 (11%) of the 95 patients, had increased in 20 (21%) patients, and had not changed in the remaining patients (68%). There was no difference in seizure rates across the three groups (no change, increased, and decreased anticonvulsants) at 3 months. Changes in anticonvulsants at 3 months were not appreciably different from the changes at 6 months: 16% reduction, 25% increase, and 59% unchanged.

Special Populations

Among patients with Lennox-Gastaut syndrome, the average percent reduction in seizure frequency was 26.6% at 3 months and 47.11% at 6 months. The average reduction in seizure frequency among patients with atypical absence, symptomatic, and idiopathic generalized seizures was 25.32% and 47.25% at 3 and 6 months, respectively.

Of the 35 patients who had undergone epilepsy surgery, the 15 patients with previous lobectomy did not respond as well as the group as a whole. Median reduction in seizure frequency was 32% at 3 months: reductions exceeded 50% in 7 patients, and 1 patient reported no seizures. The 20 patients who had previous callosotomy responded well, with a median reduction in seizure frequency of 79% at 3 months. Seizures decreased by more than 50% in 13 patients and by more than 75% in 10 patients (Table 3). The two patients with both previous lobectomy and previous callosotomy were included in each analysis.

Patients younger than age 12 years ($n = 41$) responded similarly to the group as a whole. After 3 months of vagus nerve stimulation therapy, average seizure frequency had decreased by 18% (median 27%). At 6 months, data were available for 20 patients and showed an average reduction of 46% (median 51%). The responses of patients younger than 6 years were similar to the responses of the entire group: an average reduction in seizure frequency of 16% (median

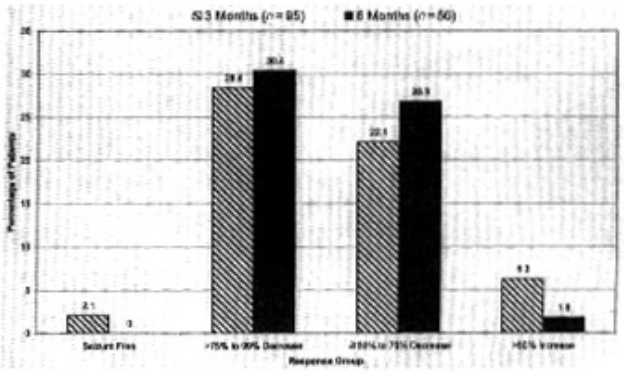

Figure 1. Changes in seizure frequency after 3 and 6 months of vagus nerve stimulation therapy.

Table 3. Effectiveness of Vagus Nerve Stimulation Therapy after 3 and 12 Months Among Patients Who Failed Epilepsy Surgery

	N	*Median (%)*	*Range (%)*
Callosotomy			
3 months	20	−79	−99 to 0
12 months	12	−43	−98.9 to +3
Lobectomy			
3 months	15	−32	−100 to +114
12 months	9	−52	−76 to 0

Table 5. Duty Cycle Settings After 3 Months of Vagus Nerve Stimulation Therapy (*N* = 95)

No. of Patients	*On (sec)*	*Off*
45	21 or 30	5 or 10 min
26	21 or 30	3 min
16	7	12 or 21 sec
6	21 or 30	1.1 or 1.8 min
1	60	3 min
1	—	—

26%) for the 12 patients at 3 months and an average reduction in seizure frequency of 42% (median 50%) in the 7 patients at 6 months.

Device Settings

Rather than observing the patient for a 2-week period between implantation and initiation of vagus nerve stimulation therapy, physicians activated vagus nerve stimulation during the hospitalization for implantation of most (91%) of the patients in this analysis. Initial settings usually started at 0.25-mA output current, 30-Hz stimulation frequency, 30 seconds on time, and 5 minutes off time. Nevertheless, 28 of the 125 implanted patients (22%, all from one site) were initially started at "rapid duty cycle" settings, typically 7 seconds on and 12 seconds off. At 3 months, the reduction in seizure frequency was no greater in patients programmed with the rapid-cycle settings than the entire group.

Table 4 lists the most common device settings after 3 months of vagus nerve stimulation therapy, and Table 5 lists duty cycles for 94 of the 95 patients. Output current was 0 mA for one patient, an indication that vagus nerve stimulation was not turned on at that time. The patient had no side effects, and vagus nerve stimulation therapy was effective, but the patient's parent had requested that the patient not receive vagus nerve stimulation during this period. Output current and duty cycle appeared to have little influence on effectiveness. Higher output currents and shorter off times were likely to be tried in patients who did not respond at typical settings. After 3 months of vagus nerve stimulation therapy, seizure frequency decreased an average of 43.6% among 50 patients with output currents of 1.25 mA and less and 31.3% among the 44 patients with settings exceeding 1.25 mA. Average output current was 1.5 mA in the 29 patients with a greater than 75% reduction in seizure frequency and 1.75 mA in 9 patients with a greater than 25% increase in seizure frequency.

Table 4. Most Common Device Settings After 3 Months of Vagus Nerve Stimulation Therapy

Output Current (mA)	*1.25*
Pulse width (μsec)	500
Stimulation frequency (Hz)	30
Time on (sec)	30
Time off (min)	3
Magnet output current (mA)	1.50
Magnet pulse width (μsec)	500
Magnet on time (sec)	60

With regard to duty cycle, seizure frequency decreased an average of 31% among patients with off times of less than 2 minutes and 46% among those with off times of 5 minutes or more.

At 3 months, 84% of patients or their family members had used the magnet to start stimulation at the onset of a seizure. Only 6% of the patients reported using the magnet themselves. Success in aborting some or all of the seizures was reported by 42% of patients or caregivers. Use of the magnet to shorten seizures was reported by 44% of the patients and caregivers. Reports of magnet use at 6 months were similar: 39% aborted some or all seizures and 39% shortened seizures. At 12 months, half of the group reported aborting some or all of their seizures, and 42% reported shortening the seizures.

Quality of Life

The changes in quality of life reported by parents or caregivers after 3 months of vagus nerve stimulation therapy included better or much better alertness in 46 (48.4%) of the 95 patients, better or much better seizure clustering in 34 (almost 36%), better or much better verbal communication and postictal periods in 26 (27%), better or much better school achievements and mood in 21 (22%), better memory in 13 (14%), and better or much better ambulation in 5 (just over 5%) (Figure 2). Quality of life reports were similar after 6 and 12 months of vagus nerve stimulation therapy.

A separate analysis of changes in the quality of life of the 36 nonresponders (less than 25% reduction in seizure frequency) at 3 months showed better or much better alertness in 16 (44%) patients, better or much better seizure clustering

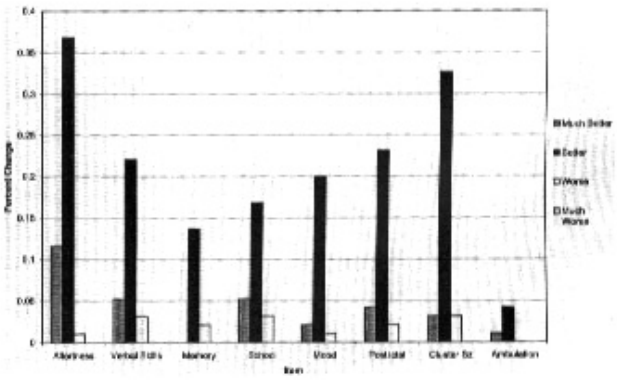

Figure 2. Changes in quality of life after 3 months of vagus nerve stimulation therapy. Sz = seizure.

in 13 (36%), better or much better verbal communication in 8 (22%), better or much better school achievements in 7 (19%), better or much better postictal periods in 6 (17%), better mood in 5 (14%), better memory in 4 (11%), and better ambulation in 2 (6%).

Adverse Events

Chart review indicated that this group of patients reported the usual pain and discomfort associated with surgery, which resolved within several days of implantation. No explants for infection were performed, and no cases of technical or device failure were reported.

Information about adverse events was obtained from patient records and recorded on a data collection form. Adverse events did not lead to discontinuation of vagus nerve stimulation therapy for any patients. Adverse events associated with vagus nerve stimulation therapy were similar to the clinical study results reported in patients aged 12 years and older. The most commonly reported adverse events were voice alteration (57.9%) and coughing (37.9%) during stimulation. A less common complaint was ear pain (1.1%) with stimulation, which resolved with changes in stimulation parameters. Increased drooling was seen in the rare patient (<1%) who had preexisting problems with drooling. This adverse event usually resolved spontaneously during the months after implantation. Unique to this age group were a few patients who had reports of increased hyperactivity associated with stimulation and fewer seizures. This adverse effect was usually manageable with institution of a behavioral program and, uncommonly, medication.

Serious adverse events and device complications were rare. One patient reported moderate-to-severe dysphonia characterized by diplophonic speech and swallowing difficulties resulting from left vocal cord paralysis associated with the surgery. Approximately 4 months after implantation, the dysphonia and swallowing difficulties had almost completely resolved. Another patient reported three emergency room visits for right-sided weakness and incoordination, which were evaluated with carotid ultrasonography and cranial computed tomography, both of which were normal. An etiology remains obscure, but the episodes resolved spontaneously and did not recur. Broken electrode leads were reported for three patients. Two broken leads were related to the implantation procedure, and all three were replaced. There were no explants, occurrences of status epilepticus, or deaths.

DISCUSSION

To our knowledge, this analysis is the largest reported group of children aged 18 years and younger who have undergone NeuroCybernetic Prosthesis Pulse Generator implantation for refractory epilepsy. The purpose of this study was to evaluate and demonstrate the effectiveness and safety of vagus nerve stimulation therapy in children.

Comparison of the current data with that gathered from pediatric patients in the clinical studies showed similar patient types with regard to the refractory nature of the epilepsy and the types of seizures.[6] Whereas the pediatric patients in the clinical trials numbered 60, with 16 patients aged younger than 12 years, the present group was much larger with 125 patients, and 41 patients were aged younger than 12 years. Reductions in seizure frequency were greater in this analysis than in the clinical trials. In the current analysis, average percent reduction in seizures was 36.1% at 3 months and 44.7% at 6 months compared with 23% and 31% reported from the clinical trials.[6] In addition, at 6 months, 17 (30%) patients in the current analysis had a greater than 75% decrease in seizure frequency that exceeded the 11% reported in the clinical trials.[2] There did not appear to be any difference in effectiveness among the various seizure types in the present analysis.

A study of 38 pediatric patients treated at the University of Alabama reported that after a median of 12 months of vagus nerve stimulation therapy, 68% of the patients achieved greater than 50% reductions in seizure frequency.[10] The Alabama study reported a greater number of patients with 50% or greater reductions than the current study, but differences in the data analyses of the two studies preclude direct comparisons.

Output current and duty cycle appeared to have little influence on effectiveness. Most patients had an output current of 1.25 mA, an on time of 30 seconds, and an off time of 3 minutes after 3 months of vagus nerve stimulation therapy. Higher output currents and changes in duty cycle were likely to be used in patients who did not respond. The strategy of adjusting device settings certainly warrants further investigation.

One might question the role of placebo effect in vagus nerve stimulation therapy. Previous studies (E03/E05) attempted to address this issue by using an active control (low versus high stimulation) because patients can perceive the stimulation. In the E03 study, the mean reduction in seizure frequency at 12 weeks was 6.1% in the low-stimulation group and 24.5% in the high-stimulation group.[11] After 3 months of therapy in the E05 study, average reductions in seizure frequency were 28% in the high vagus nerve stimulation group and 15% in the low vagus nerve stimulation group.[2] If reductions in seizure frequency were entirely attributable to placebo effect in the E03 and E05 studies, between-group differences might not have been as pronounced. In the present analysis, which had no control population, the reduction in seizure frequency remained steady or continued to decrease at 6 months. Such continued improvement argues in favor of the effectiveness of vagus nerve stimulation therapy.

Vagus nerve stimulation therapy was especially effective in two groups of patients: those with Lennox-Gastaut syndrome and those who had previously undergone epilepsy surgery. At 6 months, seizure frequency was reduced by more than 75% in more than one third of the patients with Lennox-Gastaut syndrome and by almost one half in the patients who had previously undergone epilepsy surgery. Of the postoperative patients, the previous callosotomy patients did

exceptionally well, with a 61.9% average reduction in seizure frequency. There is a suggestion that vagus nerve stimulation therapy may be effective in patients with other disorders such as tuberous sclerosis and mitochondrial disorders, but the number of patients is too small for further comment.

The surgical implantation of the stimulator was no different in children and adolescents than adults, and vagus nerve stimulation therapy was well tolerated by patients in these age groups. The number and types of adverse events were similar to those reported in adults and adolescents.[2] Adverse events unique to children and usually associated with preexisting conditions are increased drooling and hyperactivity. Both of these adverse events either resolved spontaneously or responded to routine treatments.

In addition to its effectiveness in decreasing seizure frequency, vagus nerve stimulation therapy was associated with marked improvements in various aspects of quality of life including alertness, verbal communication, and school performance. Clustering of seizures and postictal periods were also greatly improved. These improvements did not seem to depend on the degree of seizure reduction or changes in medication.

This study has several limitations. The retrospective nature of the study entailed setting a date after which no data would be collected. As a consequence, data from all time points were not available for each patient. In a prospective study, such missing data might be attributed to patient attrition. Missing data in this study are mostly due to the cutoff points, although some patient records were incomplete. Another aspect of the retrospective trial is reliance on documentation in patient records. The accuracy of some of the information for this study (eg, changes in quality of life and frequency of seizures) depended on the reports of caregivers and parents. Establishing a baseline is subject to the limitations of a retrospective study. Therefore, differences between prospective and retrospective trials should be considered in comparisons of the results of this study with the results of clinical trials.

In summary, the effectiveness, safety, and tolerability of vagus nerve stimulation therapy were evident in this study. The reduction in seizure frequency in this study exceeded reductions reported in the initial clinical trials and are comparable with reductions reported in adolescents and adults. Additionally, the quality of life greatly improved in these patients. Although further studies to evaluate optimal device settings, strategies in patient management, and quality of life issues are necessary, these data show that vagus nerve stimulation therapy is an effective treatment in children and adolescents with refractory epilepsy.

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