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Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome

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Abstract

Purpose: Vagus nerve stimulation (VNS) is approved for use for refractory partial seizures. Nevertheless, information regarding VNS therapy for special populations, including Lennox-Gastaut Syndrome (LGS) is limited. This paper discusses the effectiveness, tolerability, and safety of VNS therapy in patients with LGS.

Methods: A six-center, retrospective study evaluated the effectiveness of VNS therapy in patients with LGS at three and six months and compared pre-implant and post-implant seizure frequency. Adverse effects and quality of life (QOL) were included as secondary measures.

Results: Fifty patients, median age 13 years, with medically refractory epilepsy were implanted. Median age at onset of seizures was 1.4 years, and a median of nine anticonvulsants had been tried before implantation. Data collection forms were designed for retrospectively gathering data on each patient's pre-implant history, seizures, implants, device settings, QOL, and adverse events. Median reductions in total seizures were 42% at one month, 58.2% at three months, and 57.9% at six months. The most common adverse events reported were voice alteration and coughing during stimulation. Other uncommon adverse events included increased drooling and behavioral changes. Investigators noted that QOL had improved for some patients in the study.

Conclusions: VNS is an effective treatment for medically refractory epilepsy in LGS. This treatment is well tolerated, safe, and may improve QOL.

Introduction

Vagus nerve stimulation (VNS) was commercially introduced in 1997 as an adjunctive therapy in patients aged 12 years and older with refractory partial seizures. Clinical studies found a 25% average reduction in seizure numbers during the first three months of VNS therapy, and a 40% to 50% reduction through the first 18 months. Such results are comparable with the efficacy of the newer anticonvulsants.[1-3]

Since approval, more than 11,000 patients have been implanted with the stimulation system (NeuroCybernetic Prosthesis [NCP®], Cyberonics, Inc.). Nonetheless, only small series and anecdotal information are available on special epilepsy populations, including patients with Lennox-Gastaut syndrome (LGS).[4-7]

After assessing the risks and benefits of a number of therapies for LGS, Schmidt and Bourgeois[8] developed recommendations for treatment. If valproic acid (sodium valproate), regarded as the standard treatment, does not curtail seizures as a monotherapy, lamotrigine[9-11] or topiramate[12] may be added as adjunctive therapy. If these medications are ineffective in reducing seizures or cannot be tolerated by the patient, several third-line choices are available.[8] Vagus nerve stimulation, the subject of this paper, now falls into this category that also includes the ketogenic diet[13, 14] and a number of less frequently prescribed medications: clonazepam, phenobarbital, (phenobarbitone), ethosuximide, methsuximide, corticotropin (adrenocorticotropic hormone), corticosteroids, pyridoxine

(vitamin B_6), vigabatrin, benzodiazepine nitrazepam, and clobazam.[8,15] Felbamate in combination with valproic acid reduced drop attacks among patients with LGS,[16] but rare side effects of aplastic anemia and hepatic failure have resulted in a warning on the felbamate package insert.[17]

Despite the positive effects of medical therapy for patients with epilepsy, incidents of worsened seizures have been reported in some patients with LGS who have received barbiturates, benzodiazepines, or vigabatrin.[18] Occasionally, a medication may both improve and worsen seizures: tonic seizures associated with LGS may respond to carbamazepine, but the drug may also worsen atypical absences.[19]

Callosotomy is sometimes considered for patients with LGS who have frequent, intractable, and disabling drop attacks, but the procedure has associated risks. [8,**20,21**]

As part of a broader retrospective study of children younger than 18 years, the present study was undertaken to gather and provide more information on the effectiveness and safety of VNS therapy in patients with LGS. Six centers (Children's Hospital-Boston, University of Texas Medical School-Houston, Minnesota Epilepsy Group, The Children's Hospital-Denver, LSU Comprehensive Epilepsy Center, Children's National Medical Center) collaborated during late 1998 for this study. Two centers (Boston, Houston) were involved in the pre-approval clinical studies, and the other four centers had post-approval experience only.

Methods

Subject Inclusion

The study included all patients at the above-listed centers who had been diagnosed with LGS and implanted with the NCP system. Parents or guardians of patients younger than 12 years were informed that VNS therapy for their children was outside the usage approved by the Food and Drug Administration: adjunctive therapy in reducing the frequency of seizures in adults and adolescents older than 12 years who have partial onset seizures that are refractory to antiepileptic medications. Seizures were documented according to type. Before implantation, the patients had mixed-seizure disorder with drop seizures as one of the types, delayed development, and slow spike-wave discharges on EEG. A two-month, baseline frequency of seizures established before implantation was used for comparison with seizure frequency after implantation. Implantation technique and revision have been described elsewhere.[22, 23] In general, implantation includes both a cervical incision for implanting the electrode and a subclavicular or mid-axillary incision for implanting the stimulating unit.

Data Collection

Data collection forms were designed for retrospective data collection on all patients implanted before December 31, 1998. Data collection was allowed through March 31, 1999. Information was collected regarding each patient's pre-implant history, seizures,

implant, device settings, quality of life (QOL), and adverse events. Approval for the chart review was obtained as required at participating institutions.

Given the retrospective nature of the study, extensive chart review provided seizure rates. Rate of seizures according to type were recorded as reported by the patient or parent, and then combined to calculate each patient's average rate. After data collection, seizure records were carefully reviewed across all patient visits to verify correct interpretation of seizure counts. Patients' QOL was assessed with a simple, unvalidated, five-point rating scale, which featured ratings of much worse, worse, same, better, and much better.

Data were gathered as available at one, three, and six months after implantation for each patient. After data entry and verification, the data were analyzed by simple summary statistics and the Signed Rank test. P values <0.01 were considered statistically significant.

Results

Demographics

As of December 31,1998, 50 patients who met criteria for LGS had been implanted with the NCP system and had received at least one month of VNS therapy. Median age at implant was 13 years (range 5 to 27), with 21 patients (42%) younger than 12 years at implant. The median age at onset of seizures was 1.4 years (range 0.1 to 7.5).

More males than females were implanted (32 males and 18 females). Only four patients were institutionalized, but 30 of the 50 patients (60%) were mentally retarded (IQ less than 70) as indicated by the Investigator who relied on standardized IQ assessments or personal observations. Eighteen patients (36%) had previously tried the ketogenic diet, although only three (6%) were on the diet at the time of implantation. A median of nine (range three to seventeen) anticonvulsants had been tried before implantation, and from three to five anticonvulsants had been prescribed at the time of implantation. The most commonly prescribed anticonvulsants were valproate (44%), topiramate (36%), and lamotrigine (30%).

In this group, 33 (66%) of the patients had drop attack seizures. Six of the patients had previously undergone epilepsy surgery: callosotomy in five and lobectomy in one.

Effectiveness

After one month of VNS therapy, 46 patients had evaluable effectiveness data; chart review revealed inadequate seizure records for four patients. The median percent reduction in seizure number was 42%, (range, -98% to +63%) (P<0.0001, Signed Rank test). Seizures decreased by more than 75% in seven of the 46 (15%) patients, and seizures decreased by 50% or more in 20 (43%) patients. No patients were seizure free. Seizures increased by more than 50% in one of the 46 (2%) patients.

Data for further analysis were available for 43 patients after three months of VNS therapy and for 24 patients after six months. The declining number of patients was due to the data collection cutoff point, not to patient attrition. The median seizure reductions at three and six months were 58.2% (P<0.0001, Signed Rank test) and 57.9% (P<0.0001), respectively. After three months, seizures had decreased by more than 75% in 15 of 43 (35%) patients, and by 50% or more in 24 of 43 (56%). After six months of stimulation, data were available for 24 of the 43 patients. Seizures had decreased by more than 75% in 9 of the 24 (38%) patients, and by 50% or more in 14 (58%) patients. After three months of VNS therapy, seizures had increased more than 50% in three patients. No increases in seizures exceeding 50% were reported at six months.

Drop Attack Seizures and Other Seizure Types

Data were further analyzed by seizure type. Drop attack seizures decreased by medians of 47% after one month of VNS therapy, 55% after three months, and 88% after six months. Signed Rank tests indicated that decreases in the number of drop attack seizures were statistically significant at one month (P <0.0001), three months (P <0.0001) and at six

months ($P = 0.0002$). Atypical absence seizures decreased by 48% after one month, 73% after three months, and 81% after six months. In contrast, complex partial seizures decreased by only 20% after one month, and 23% after three months.

Seizure Surgery

Of six patients who had previously undergone therapeutic brain surgery; five had corpus callosotomy. In these five patients, seizures were reduced by 73% after three months of VNS therapy and by 69% after six months. The number of seizures did not change in the patient who had previously undergone lobectomy surgery.

Age

The 20 patients younger than 12 years responded similarly to the group as a whole with a median reduction of 37% after one month of VNS therapy. Among the 16 patients who received three months of VNS therapy, median reduction was 48%. After six months, data were available for only nine patients; median reduction was 79%.

Device Settings

The NCP Generator was activated in most (98%) of the patients during implant hospitalization. Initial settings were typically 0.25 mA output current, 30 Hz stimulation frequency, 30 seconds ON time, and 5 minutes OFF time. However, 19 patients (38%) were started at "rapid cycle" settings, typically 7 seconds ON and 12 seconds OFF (0.2 minutes).

After three months of stimulation, typical settings were 1.25 mA output current, 30 Hz. frequency, 500-microsecond pulse width, with a magnet output current of 1.5 mA. Fifteen patients were at 30 seconds ON and 5 or 10 minutes OFF. Thirteen patients were at 30 seconds ON and 3 minutes OFF, six patients were at 7 seconds ON and 12 or 21 seconds OFF, and two patients were at 21 or 30 seconds ON and 1.8 minutes OFF. Seven patients had no device-setting data available for analysis at three-month follow-up.

Quality of Life

Figure 1 shows the percentage of patients reported as improved and unchanged in various aspects of QOL after three months of VNS therapy, and Figure 2 shows the same information after six months. To simplify the graphs, ratings of better and much better were combined. After both three and six months of VNS therapy, more patients were rated as better or much better for alertness than were reported as unchanged.

After three months of treatment, one patient (3%) was rated as worse in school achievement and one patient (3%) was rated worse in seizure clustering. All patients were rated for alertness, but QOL ratings were either unknown or not provided in verbal communication (three patients, 8%), memory (four patients, 11%), schoolwork (four patients, 11%), mood (three patients, 8%), postictal period (three patients, 8%), seizure clustering (three patients, 8%), and ambulation (four patients, 11%).

After six months of treatment, one patient (4.5%) was rated as worse in mood, two patients (9%) were rated worse in seizure clustering, and QOL ratings were not provided for one patient (4.5%).

Adverse Events

Few adverse events related to the surgical procedure were reported. Two patients (4%) reported superficial wound infections at the subclavicular incision site. These infections were successfully treated with antibiotics and resolved without surgical intervention (device removal). Five patients (10%) reported some transient pain at the incision site.

Stimulation was also well tolerated. Thirteen patients (26%) reported no adverse event of any kind. Twenty-two patients (44%) reported voice alteration or hoarseness associated with stimulation. Fifteen patients (30%) reported increased coughing with stimulation adjustments. Both of these events are expected with increased stimulation settings, and typically resolved one to two days after the stimulation adjustment. In patients for whom the event was bothersome, stimulation settings were decreased. Other expected events included paresthesia (neck tingling during stimulation; 8%), non-specific pain sensation (8%), shortness of breath during exertion (4%), decreased appetite (4%), hiccups (4%), and dyspepsia (4%). One patient (2%) reported dysphagia, insomnia, and another (2%) reported vomiting after stimulation started. These events resolved over time and with adjustments in stimulation. One patient reported both ear pain and jaw pain as stimulation settings increased; both resolved over time.

Two less-typical events possibly associated with VNS therapy in this group were also reported. Four patients (8%) reported increased salivation after stimulation started. These events either resolved or were treated with glycopyrrolate. After stimulation was started, worsened behavior or hyperactivity was reported in three patients (6%). These events were typically concurrent with the reduction in the number of seizures. A combination of reducing AED medication, adding medication, and modifying stimulation resolved the behavior changes.

After approximately six months of VNS therapy with no marked reduction in seizure frequency, stimulation was discontinued in one patient at the caregiver's request. However, after stimulation was discontinued, seizure intensity increased and language skills decreased (a benefit discounted during stimulation), so stimulation was resumed. No instances of aspiration, serious adverse events, deaths, increased status epilepticus, device complications, or device malfunctions were reported.

Discussion

Our results showed improvements in seizures among LGS patients who received VNS therapy. These results were documented for all seizure types as well as for the most debilitating seizure type seen in this group, drop attack seizures. These results compared favorably with those reported in other patient groups treated with VNS therapy.[1,2,4,5]

Device-setting changes did not appear to systematically improve patients' responses. Although increases in output current led to improved response in some patients, response worsened or did not change in other patients. This was also true of duty cycle changes (increased stimulation cycles). The most important factor in improvement appeared to be the duration of stimulation.

In this study, some seizure types responded better than others did. Partial seizures (for which the device is approved) seemed to respond at a lower rate than other seizure types. Drop attack seizures responded well to stimulation. Although no ambulatory or video EEG was performed, typical absence seizures also seemed to respond to stimulation, but conclusions regarding this difficult-to-count seizure type must be limited. Age does not seem to be an influential factor; patients younger than 12 years responded similarly to the group as a whole.

Although this study did not directly compare VNS therapy with corpus callosotomy, some comparison is warranted. Callosotomy is a standard palliative treatment for LGS patients with drop-attack seizures. Outcomes of callosotomy are reported by inconsistent methodologies, but various series report that seizures are reduced in approximately 40% to 80% of patients, with the greatest reductions in drop-attack and generalized seizures.[20,21,24,25] However, postoperative development of language disorders, neuropsychological impairment, motor dysfunction, and disconnection syndrome have been described. Reports have also included notable surgical complications and, rarely, death.[25-28] In comparison, VNS therapy is a less invasive, fully reversible surgery with far fewer serious side effects and a broader spectrum of effectiveness. Both treatments are palliative and are not usually curative. After comparing the results of VNS therapy with corpus callosotomy, we typically recommend that patients try VNS therapy before undergoing callosotomy. Patients who have previously undergone callosotomies do well with the addition of VNS therapy, so previous callosotomy does not preclude VNS therapy.

The surgical implantation of the stimulator was no different in LGS patients than other groups of patients. The surgical procedure was well tolerated, as was stimulation itself. Adverse events were similar to those observed in other populations. However, we recommend that special care be taken with patients who have swallowing difficulties, as stimulation may cause some slight dysphagia or increased salivation. This type of event is manageable and should not preclude treatment. Also, as seen with antiepileptic

medications, decreased seizure rates may cause behavior changes that must be addressed as they occur. To properly assess adverse events and verify tolerance, we suggest special care in handling non-verbal patients; a slower stimulation ramp-up process may be implemented to address this issue.

Investigators noted changes in QOL among some patients. Most notably, alertness improved in more than half the patients after both three and six months of treatment. After six months, one-fourth or more of the patients showed improvements in verbal communication, school work, postictal recovery, and seizure clustering. Improvements in memory, mood, and ambulation were noted among only a few patients. A decline was noted in the mood of one patient and the seizure clustering of two patients. These changes did not depend on the degree of seizure reduction or medication changes. Many caregivers reported that the improvements in QOL were more important or life effecting than the seizure reductions. Nevertheless, because our scales were simple, unvalidated measures, further studies of QOL are indicated.

To our knowledge, this is the largest reported group of patients with LGS who have received VNS therapy. Effectiveness, safety, and tolerability were comparable with or better than that observed in other groups. Possible improvements in QOL should be considered in the decision process to select a suitable treatment. We believe that VNS therapy is appropriate for patients with LGS.

Figure Legends

Figure 1

Quality of life reports at three months after NCP implantation

Figure 2

Quality of life reports at six months after NCP implantation

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