



Vagus Nerve Stimulation for Refractory Epilepsy

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Abstract

Context: Vagus nerve stimulation (VNS) is a relatively new treatment for epilepsy. Past studies have proposed that the antiepileptic action is related to the effect on the brainstem reticular activating system, and is mediated largely by the widespread release of two inhibitory agents (gamma aminobutyric acid [GABA] and glycine).

Objective: To confirm the safety and efficacy of vagus nerve stimulation in postmarketing clinical practice.

Design: Prospective case series.

Intervention: Implantation of a device for vagus nerve stimulation (the NeuroCybernetic Prosthesis (NCP) system) in 24 patients with refractory epilepsy and monitoring their condition for six months.

Main outcome measures: Frequency and type of postoperative seizures.

Methods: Under general anesthesia, the Neurocybernetic Prosthesis was implanted in subcutaneous tissue on the upper left side of the chest by a neurosurgeon. Antiepileptic drug dosages were stable before patients entered the study and were not changed or adjusted during the six-month study period. The patients were evaluated with the Quality of Life in Epilepsy Inventory (QOLIE-10).

Results: During the six-month study period, 14 patients had partial seizures with and without generalized seizures; 10 patients had multiple types of generalized seizures. Of the 24 patients, 15 (62.5%) had > 50% reduction in seizure frequency after NCP implantation; eight of those 15 patients had > 90% reduction in seizure frequency. Nine (37.5%) of the original 24 patients showed no clinically significant benefit. The seizure types that responded best to VNS were atonic, tonic, and generalized tonic-clonic. Partial seizure showed moderate response. Partial complex seizure showed the least response to VNS. No patients were completely without seizures at the six-month follow-up period. In general, the patients were more alert, in a better mood, and better able to concentrate. Two patients had vocal cord paralysis during NCP implantation but gradually recovered vocal function within a few months.

Conclusion: This study in a large HMO, with an integrated delivery system, supports the safety and demonstrates significant efficacy of vagus nerve stimulation for treatment of medically refractory epilepsy.

Introduction

Although vagus nerve stimulation (VNS) is a relatively new therapy for epilepsy, the effects of VNS on brain activity have been studied since the 1930s. More than 80% of cervical vagus nerve fibers are afferent, and these afferent fibers terminate in diffuse areas of the central nervous system after traversing the nucleus of the solitary tract. These afferent fibers project to the cerebellum, hypothalamus, amygdala, hippocampus, medial reticular formation, dorsal raphe, locus ceruleus, nucleus ambiguus, thalamus, insular cortex and other areas of the brain.¹⁻³ Many studies in the biomedical literature²⁻⁶ have proposed that the antiepileptic action of VNS is related to effects on the brainstem reticular activating system, which extends to numerous forebrain structures; most studies suggest that the antiepileptic action of VNS is mediated largely by the widespread release

of two inhibitory agents, gamma aminobutyric acid (GABA) and glycine, throughout the brainstem and cerebral cortex.

The antiepileptic effect of VNS has been confirmed in multiple animal models of epilepsy. VNS terminates strychnine-induced seizures in dogs^{5,6} and inhibits pentylentetrazole-induced seizures in rats.^{3,4,7} The observation that VNS used with alumina gel foci reduces frequency of recurrent spontaneous seizures in monkeys⁸ led to development of a device called the Neurocybernetic Prosthesis (NCP) system, which, in 1988, was first used for clinical trials in humans.⁹ Since that time, clinical trials in the United States and Europe have studied placement of the NCP system in humans. On July 16, 1997, the US Food and Drug Administration (FDA) approved use of VNS as adjunctive therapy for refractory partial-onset seizures in adults and in adolescents aged 12 years and older.

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Epileptic patients were selected for implantation of the NCP system on the basis of four criteria ...

The Department of Clinical Analysis and the Comprehensive Epilepsy Program of the Southern California Permanente Medical Group have set selection criteria for using VNS to treat refractory epilepsy. In this article, we report our initial postmarketing observations of the safety and efficacy of VNS in a selected group of epileptic patients.

Methods

Epileptic patients were selected for implantation of the NCP system on the basis of four criteria: 1) refractory response to antiepileptic drugs given alone or in various combinations. Patients or family must have recorded at least six seizures per month (four weeks considered as 28 days) in a diary or on a calendar at the time of seizure; diaries are distrib-

uted to all patients in the practice at routine neurology visits; diaries for the study patients were reviewed during the six-month postoperative study period; 2) unsuitability as a candidate for epilepsy surgery; 3) no evidence of nonepileptic seizures; and 4) no previous left cervical vagotomy.

Patients who met these selection criteria received routine laboratory tests: complete blood count; levels of serum electrolytes, blood urea creatinine, glucose, blood urea nitrogen, and antiepileptic drugs; prothrombin time; partial thromboplastin time; electrocardiography; and chest x-ray examination. Patients were admitted to the hospital on the morning of the operation. NCP implantation was completed in less than two hours with the patient under general anesthesia.

The NCP system was implanted by our neurosur-

Table 1. Clinical data for 24 patients treated with vagus nerve stimulation at Kaiser Permanente Orange County and Los Angeles Medical Centers

| Patient no. | Sex | Age at device implantation (years) | Age at onset of Epilepsy | Etiology/Syndrome | Type of seizure | Medications |
|-------------|-----|------------------------------------|--------------------------|-------------------------|--------------------|---------------|
| 1 | F | 43 | 8 years | encephalitis | PS, PCS, GS | CBZ, PRM |
| 2* | M | 24 | 6 months | Lennox-Gastaut syndrome | AB, AS, GS, MS, TS | CBZ, VPA |
| 3* | M | 11 | 2 months | Lennox-Gastaut syndrome | AB, AS, GS, MS, TS | VPA |
| 4 | M | 22 | 2 years | oligodendroglioma | PS, PCS, GS | CBZ, PRM |
| 5 | M | 54 | 12 years | unknown | PS, PCS, GS | CBZ, PRM |
| 6 | M | 18 | 12 years | head injury | PS, PCS, GS | CBZ, TGB |
| 7 | F | 45 | 5 years | unknown | PS, PCS | CBZ, TPM |
| 8* | M | 16 | 2 months | meningoencephalitis | PS, GS | CBZ, VPA |
| 9 | F | 70 | 17 years | unknown | PCS, GS | PHT, TGB |
| 10* | M | 9 | 8 years | encephalitis | PS, GS | VPA |
| 11* | F | 10 | 2 years | tuberous sclerosis | AB, AS, GS, MS, TS | PHT, VPA |
| 12 | F | 23 | 18 years | head injury | PS, PCS, S | ETT, LTG |
| 13* | F | 12 | 1 day | tuberous sclerosis | AB, AS, GS, MS, TS | PRM, TPM, TGB |
| 14 | M | 41 | 7 years | unknown | AB, GS | VPA |
| 15 | F | 45 | 31 years | epidermoid tumor | PS, PCS | CBZ |
| 16 | M | 32 | 15 years | cavernous angioma | PS, PCS, GS | CBZ, TPM |
| 17* | M | 13 | 11 months | Lennox-Gastaut syndrome | AB, AS, GS, MS, TS | CBZ, VPA |
| 18* | M | 27 | 3 months | Lennox-Gastaut syndrome | AB, AS, GS, TS | PB, VPA |
| 19 | F | 46 | 27 years | unknown | PCS, GS | CNZ, GBP |
| 20* | M | 14 | 11 months | Lennox-Gastaut syndrome | TS, GS | VPA, TPM |
| 21 | M | 43 | 1 day | porencephaly | PS, GS | PRM, LTG, TGB |
| 22* | M | 6 | 2 years | Lennox-Gastaut syndrome | AG, AS, GS, MS, TS | LEV |
| 23 | F | 15 | 6 months | prenatal encephalopathy | PS, GS | PHT, TPM, LEV |
| 24* | F | 12 | 2 months | tuberous sclerosis | AB, GS | CBZ, VPA |

*mentally retarded

AB = absence; AS = atonic seizure; GS = generalized tonic-clonic seizures; MS = myoclonic seizure; PS = partial seizure; PCS = partial complex seizure; TS = tonic seizure; CBZ = carbamazepine; CNZ = clonazepam; ETT = ethosuximide; GBP = gabapentin; LEV = levetiracetam; LTG = lamotrigine; PB = phenobarbital; PHT = phenytoin; PRM = primidone; TGB = tiagabine; TPM = topiramate; VPA = valproate.



geon, who is specially trained in the required surgical technique and procedure. The NCP system consisted of a programmable pulse generator (Cyberonics' Model 100 NCP Pulse Generator), which was implanted in subcutaneous tissue on the upper left side of the chest. The signal from the generator was conducted via a unified lead to a bifurcated stimulating coil electrode (Cyberonics' Model 300 NCP Bipolar Lead); this electrode was applied to the cervical trunk of the left vagus nerve. The generator was tested during the procedure by using a magnetic field induced by a programming wand connected to an IBM-compatible microcomputer. Additional electrodiagnostic examination was also done to measure impedance, to appraise the coupling of all connections, and to verify the overall integrity of the system.

After the operation, patients were monitored in the hospital overnight for any sign of vocal cord dysfunction, dysphagia, respiratory compromise, or seizures. Administration of prophylactic antibiotics began preoperatively and was continued for 24 hours postoperatively. Cervical and chest x-ray films were obtained to confirm proper placement of the device and electrodes before patients were discharged from the hospital.

To allow wound healing, the NCP system was not activated until one week postoperatively. Output current was gradually increased in 0.25 mA increments once per week at six weekly visits to the epilepsy clinic at the medical centers, at six subsequent biweekly visits to the clinic, and then at each of three monthly visits to the clinic. Output current was adjusted on the basis of patients' subjective sensation and tolerance to the electrical stimulation. Maximum output current applied was 3.5 mA. All other VNS parameters were kept constant during the six-month study period. Antiepileptic drug dosages were stable before patients entered the study and were not changed or adjusted during the six-month study period.

Efficacy of VNS was analyzed by calculating mean change in seizure frequency during the last two months (eight weeks considered as 56 days) of the six-month study period and by comparing this mean number with the baseline mean number of seizures in the month (four weeks considered as 28 days) before patients received VNS. We also examined postoperative adverse events, side effects, and tolerability of both the surgical implantation procedure and the NCP device.

The patients who had no mental retardation as part

of their clinical syndrome were evaluated with a quality-of-life questionnaire preoperatively and during the postoperative period. We used the standard Quality of Life in Epilepsy Inventory (QOLIE-10)¹⁰ to evaluate overall disposition, physical energy, mental concentration, and school work performance. The parents of the patients with mental retardation were asked similar questions about alertness, mood, and behavior of those patients.

Results

Between September 1998 and December 1999, 24 patients (14 male, 10 female) met the selection criteria and received NCP implantation. Ages of patients ranged from 6 years to 70 years (mean age, 27 years). Clinical data for the patients are summarized (Table 1).

Electrical current settings, treatment duration, and effects of VNS on seizure frequency for each patient are summarized (Table 2). The current used for treatment ranged from 1.75 mA to 3.5 mA (median setting, 2.77 mA); duration of activation, 30 seconds; interval between activation sessions, five minutes; duration of pulse, 500 milliseconds; pulse frequency, 30 Hz. In seven patients, VNS began to be effective at the low output current, 0.5 mA. Seven patients had seizure aura; for four (57%) of these patients (patients 4, 5, 12, and 15) activation of NCP by handheld magnet passing over the implanted generator could abort the seizures at the outset of aura. Fifteen (62.5%) of the 24 patients had more than 50% reduction in seizure frequency; eight of those 15 patients had more than 90% reduction. Nine (37.5%) patients showed no clinically significant benefit.

Among those 24 patients, 14 patients had partial seizures with and without secondarily generalized seizures, and 10 patients had multiple types of generalized seizures. Eight (57.1%) of those 14 patients with partial seizures showed more than 50% reduction of seizure frequency. Seven (70.0%) of those ten patients with multiple type of generalized seizures showed more than 50% reduction of seizure frequency. No patients were completely without seizures at the six-month follow-up period.

We also analyzed six patients who were 12 years old and under; three patients had tuberous sclerosis, two Lennox-Gastaut syndrome, and one encephalitis. Five patients (three tuberous sclerosis and two Lennox-Gastaut syndrome) or 83.3% showed more than 50% reduction of seizure frequency.

All side effects were well tolerated and did not precipitate discontinuation of the treatment. Hoarseness

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developed in two (8.3%) of the 24 patients (patients 4 and 7) because of left vocal cord paralysis. Both patients regained normal voice within three months. Twelve (50%) of the 24 patients had intermittent hoarseness which developed during VNS; other transient events during VNS included paresthesia in the

left side of the neck. Vital signs and electrocardiographic findings showed no clinically significant change after VNS.

Among the 13 patients who had no mental retardation, nine patients (patients 1, 4, 5, 7, 9, 14, 15; 16; 23; 69.2%) reported being more alert and better able

Table 2. Efficacy of vagus nerve stimulation in 24 epileptic patients

| Patient no. | Current settings (mA) | Type and baseline no. of seizures per month | Mean no. of seizures at six-month follow-up | % Decrease in frequency of seizures |
|-------------|-----------------------|---|---|-------------------------------------|
| 1 | 2.75 | PCS 127 | PCS 122 | 3.9 |
| 2 | 2.25 | GS 24 TS 12 | GS 12 TS 2 | 50.0 83.3 |
| 3 | 2.50 | AS 241 GS 74 | AS 4 GS 7 | 98.3 90.5 |
| 4 | 2.00 | PS 34 GS 6 | PS 3 GS 1 | 91.2 83.3 |
| 5 | 2.50 | PCS 18 PS 10 | PCS 7 PS 5 | 61.1 50.0 |
| 6 | 3.00 | PCS 6 | PCS 4 | 33.3 |
| 7 | 1.75 | PCS 31 | PCS 12 | 61.3 |
| 8 | 2.75 | PS/GS 63 | PS/GS 4 | 93.7 |
| 9 | 2.75 | PCS 6 | PCS 4 | 33.3 |
| 10 | 3.5 | PS/GS 30 | PS/GS 25 | 16.7 |
| 11 | 2.5 | AS 1072 GS 231 | AS 78 GS 41 | 92.7 82.3 |
| 12 | 2.0 | CPS 10 GS 2 | PCS 4 GS 0 | 60.0 100.0 |
| 13 | 3.25 | AS 1204 GS 56 | AS 84 GS 4 | 93.0 89.3 |
| 14 | 3.25 | AB 136 GS 14 | AB 66 GS 0 | 51.5 100.0 |
| 15 | 2.0 | PS 11 PCS 8 | PS 1 PCS 0 | 90.9 100.0 |
| 16 | 3.25 | PCS 28 | PCS 25 | 10.7 |
| 17 | 3.25 | MS 60 GS 74 | MS 56 GS 60 | 6.7 19.0 |
| 18 | 3.5 | AB 30 GS 12 | AB 15 GS 11 | 50.0 8.3 |
| 19 | 2.75 | PCS 84 | PCS 15 | 82.1 |
| 20 | 3.0 | TS 126 | TS 98 | 22.2 |
| 21 | 3.0 | PS 75 GS 43 | PS 95 GS 57 | -32.6 -26.7 |
| 22 | 2.5 | TS 168 | TS 32 | 81.0 |
| 23 | 3.25 | PCS 5 GS 6 | PCS 2 GS 2 | 60.0 66.7 |
| 24 | 3.25 | AB 71 | AB 5 | 93.0 |

AB = absence; AS = atonic seizure; GS = generalized tonic-clonic seizure; MS = myoclonic seizure
PS = partial seizure; PCS = partial complex seizure; TS = tonic seizure.



to concentrate at six-month follow-up; two patients (patients 1 and 5; 15.4%) reported having better mood; and one patient (patient 4; 7.7%) reported having better memory and work performance. The families of nine mentally retarded patients (patients 2, 3, 8, 11, 13, 17, 18, 22, 24) reported that the patients were more mentally alert. Two mentally retarded patients (patients 3 and 8) were reported to have occasional nocturnal wakefulness and required sedation to relieve this symptom.

Discussion

Our study agrees with others¹¹⁻¹⁴ showing that intermittent VNS reduces frequency of seizures in patients with medically refractory epilepsy. Some patients started to show the effect of VNS at the low output current of 0.5 mA. High-output current (2.5 mA to 3.5 mA) was associated with greater degree of seizure reduction. In our limited experience, VNS appears to have a broad spectrum of antiepileptic effects on both generalized seizures and partial seizures. The seizure types that respond best to VNS are atonic seizures and complex absence seizures. Generalized tonic-clonic seizures and partial seizures show moderate response to VNS. Separately analyzing patients who are 12 years old and under yields even greater seizure reduction. The reason is that patients in this age group present with multiple types of generalized seizures, particularly atonic seizures and complex absence seizures. Atonic seizures and complex absence seizures are common seizure types in patients with Lennox-Gastaut syndrome and tuberous sclerosis. We agree with previous studies¹⁴⁻¹⁶ that children with Lennox-Gastaut syndrome demonstrated the best response to VNS. This factor may have contributed to better results in our study.

Our study results do not completely support the contention of other studies,^{17,18} which found that higher baseline frequency of seizures predicts a more favorable response to VNS.

Adverse events can occur during NCP implantation and during VNS therapy. One obvious surgical complication of NCP implantation is dysphonia caused by left vocal cord paralysis. The dysphonia gradually disappears in a few months. Direct manipulation of the vagus nerve must be avoided as much as possible to minimize incidence of surgical complications during VNS therapy. Cough and pharyngeal paresthesia commonly occur during initial application of current or when incremental increases of current are too large.

Practice Tips

- Consider vagus nerve stimulation in patients with medically refractory epilepsy with significant impact of their quality of life.
- In general, the patients were more alert, in a better mood, and better able to concentrate.
- The Quality of Life in Epilepsy Inventory (QOLIE-10) is useful to evaluate adult and adolescent patients overall disposition, physical energy, mental concentration and school work performance.

These adverse events can be minimized by postponing VNS therapy until one week after surgery, when the surgical wounds are completely dry. The stimulation should be increased at 0.25 mA increments to avoid adverse effects. Voice alteration occurs in most patients during the stimulation but does not require any lowering of current setting.

VNS appears to be safe and effective as adjunctive treatment for epilepsy. In our comprehensive epilepsy program, we recommend that VNS be limited to patients with epilepsy intractable to most commercially available medications, who are not candidates for epilepsy surgery, and whose epilepsy impacts on their quality of life to such an extent that the risks and the expense of the VNS are justifiable. ❖

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Pleasure

To learn

And from time to time

To apply what one has learned—

Isn't that a pleasure?

Confucius, 551-479 BC, Chinese philosopher