Vagus Nerve Stimulation Therapy for Drug-resistant Epilepsy

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Abstract-

Context: Vagus nerve stimulation is a relatively new treatment for epilepsy.

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

Design: Prospective case series.

Setting: Comprehensive Epilepsy Program of the Southern California Permanente Medical Group.

Patients: Thirty four patients with drug-resistant epilepsy.

Intervention: We implanted a device for vagus nerve stimulation (the NeuroCybernetic Prosthesis (NCP) system) in all 34 patients and monitored their condition for six months.

Main outcome measures: Frequency and type of postoperative seizures.

Results: During the six-month study period, 22 patients had partial seizures or and without generalized seizures; 12 patients had multiple types of generalized seizures. Of the 34 patients, 21 (61.8%) had >50% reduction in seizure frequency after NCP implantation; ten of those 21 patients had >90% reduction in seizure frequency. Thirteen (38.2%) of the original 34 patients showed no clinically significant benefit. Three patients (8.8%) had vocal cord paralysis during NCP implantation but gradually recovered vocal function within a few months. Seventeen patients (50.0%) had mild hoarseness or voice changes during vagus nerve stimulation. Transient throat pain and coughing sometimes occurred at the beginning of vagus nerve stimulation at each current setting. No substantial effects on vital signs or any clinically significant cardiovascular or gastrointestinal side effects were observed or reported during vagus nerve stimulation. Nineteen patients (55.9%) were more alert after vagus nerve stimulation.

Conclusion: Our experience with this small series of patients supports the efficacy and safety of vagus nerve stimulation for treatment of epilepsy.

Key Words: Epilepsy, Intractable epilepsy, Vagus nerve stimulation, Epilepsy treatment

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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

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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].

The antiepileptic effect of VNS has been confirmed in multiple animal models of epilepsy. VNS terminates acute symptomatic seizures induced by the systematic proconvulsants pentylenetetrazol and strychnine in rats, dogs and monkeys[3-6]. The VNS studies in these acute epilepsy models also demonstrated that antiseizure effects of VNS outlast the period during which the nerve is stimulated. A chronic model of neocortical epilepsy provided further evidence of the antiseizure effects of VNS in that VNS abolished or reduced seizures due to topical instillation of cobalt on neocortex in primates[7]. More recently, a study of VNS in a chronic model of temporal lobe epilepsy also showed antiseizure effects of VNS[8] in that amygdala kindling in cats was markedly reduced by pretreatment with VNS. The observation that VNS reduced frequency of recurrent spontaneous seizures in monkeys with alumina gel foci[9] led to development of a device called the NeuroCybernetic Prosthesis (NCP) system, which in 1988 was first used for clinical trials in humans[10]. Since that time, clinical trials in the United States and Europe have studied placement of the NCP system in humans. The desired antiepileptic action of VNS in human epilepsies may be mediated (a) through increased synaptic activities in the thalamus and thalamocortical projection pathways bilaterally by effecting on the brainstem reticular activating system, leading to increased arousal and possibly to decreased synchrony of synaptic activities between and within cortical regions; (b) through intermittently increased synaptic activity in the insula, hypothalamus, and other components of the central autonomic system; (c) through transiently decreased synaptic activities in the amygdala, hippocampus, and other components of the limbic system; or (d) through intermittently increased released of norepinephrine (and perhaps also of serotonin) over widespread cerebral regions[11].

On July 16, 1997, the U.S. Food and Drug Administration (FDA) approved VNS as adjunctive therapy for refractory partial-onset seizures in adults and in adolescents aged 12 years and older. 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 post-marketing 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 (4 weeks considered as 28 days) in a diary or on a calendar at the time of seizure; diaries are distributed 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 2 hours with the patient under general anesthesia.

The NCP system was implanted by our neurosurgeons, who are specially trained in the required surgical technique and procedure. The NCP system consisted of a programmable pulse generator (Model 100, 101 or 102 NCP Pulse Generator, Cyberonics, Houston, Texas), 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 or 302 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 (8 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 (4 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, and 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)[12] 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 May 2003, 34 patients (20 males, 14 females) met the selection criteria and received NCP implantation. Ages of patients ranged from 5 years to 70 years (mean age, 27.6 years). Clinical data for the patients are summarized in Table 1.

Electrical current settings, treatment duration, and effects of VNS on seizure frequency for each patient are summarized in Table 2. The current used for treatment ranged from 0.5 mA to 3.5 mA (median setting, 2.69 mA); duration of activation, 30 seconds; interval between activation sessions, 5 minutes; duration of pulse, 500 ms; pulse frequency, 30 Hz. In eight patients, VNS began to be effective at the low output current, 0.5 mA. Twelve patients had seizure aura; for eight (66.7%) of these patients (patients 4, 5, 12, 15, 28, 29, 30 and 34) activation of NCP by hand-held magnet passing over the implanted generator could abort the seizures at the outset of aura. Twenty one (61.8%) of the 34 patients had more than 50% reduction in seizure frequency; Ten of those 21 patients had more than 90% reduction. Thirteen (38.2%) patients showed no clinically significant benefit. No patients were completely without seizures at the six-month follow-up period.

We analyzed the efficacy of VNS in different types of seizures in Table 3. Among those 34 patients, 22 patients had partial seizures with and without secondarily generalized seizures, and 12 patients had multiple types of generalized seizures. Twelve (54.5%) of those 22 patients with partial seizures showed more than 50% reduction of seizure frequency. Nine (75.0%) of those 12 patients with multiple type of generalized seizures showed more than 50% reduction of seizure frequency.

We also analyzed nine patients who were 12 years old and under; four patients had Lennox-Gastaut syndrome, three tuberous sclerosis, and two encephalitis. Seven patients (4 Lennox-Gastaut syndrome and 3 tuberous sclerosis) or 77.8% showed more than 50% reduction of seizure frequency.

Table 1. *Clinical data of 34 patients treated with vagus nerve stimulation*

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, PS/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, PS/GS	CBZ, PRM
5	M	54	12 years	Unknown	PS, PCS, PS/GS	CBZ, PRM
6	M	18	12 years	Head injury	PS, PCS, PS/GS	CBZ, TGB
7	F	45	5 years	Unknown	PS, PCS	CBZ, TPM
8*	M	16	2 months	Meningoencephalitis	PS, PS/GS	CBZ, VPA
9	F	70	17 years	Unknown	PCS, PCS/GS	PHT, TGB
10*	M	9	8 years	Encephalitis	PS, 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, PS/GS	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, PS/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, PCS/GS	CNZ,GBP
20*	M	14	11 months	Lennox-Gastaut	Syndrome	TS,GS,VPA,TPM
21	M	43	1 day	Porencephaly	PS, PS/GS	PRM,LTG,TG
22*	M	6	2 years	Lennox-Gastaut	Syndrome	AG,AS,GS,MS,TS LEV
23	F	15	6 months	Prenatal Encephalopathy	PS, PS/GS	PHT,TPM,LEV
24*	F	12	2 months	Tuberous sclerosis	AB,GS	CBZ,VPA
25	F	37	16 years	Temporal sclerosis	PCS	TGB,VPA,ZNA
26	F	48	27 years	Head injury	PCS	PB,CNZ
27*	F	13	2 months	Cortical dysplasia	PS, PS/GS	CNZ,VPA
28	M	9	6 years	Encephalitis	PS, PS/GS	GBP,LEV,ZNS
29	M	27	7 years	Unknown	PCS, PS/GS	LTB,TOB
30*	M	5	6 months	Lennox-Gastaut syndrome	AB, GS, MS	CBZ,VPA
31	M	55	21 years	Unknown	PS, PCS	FBM,GBP,LEV
32*	M	7	10 Days	Lennox-Gastaut syndrome	AB, GS, MS, TS	LTG,TPM,VPA
33	F	55	39 years	Fibrous dysplasia	PS, PCS	LEV
34	M	33	4 years	Meningoencephalitis	PS, PS/GS	CBZ,PRM

*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: ethotoin; GBP: gabapentin; LEV: levetiracetam; LTG: lamotrigine; PB: phenobarbital; PHT: phenytoin; PRM: primidone; TGB: tiagabine; TPM: topiramate; VPA: valproate.

All side effects were well tolerated and did not precipitate discontinuation of the treatment. Hoarseness developed in three (8.8%) of the 34 patients (patients 4, 7 and 34) because of left vocal cord paralysis. All patients regained normal voice within three months. Seventeen (50%) of the 34 patients had intermittent hoarseness which developed during VNS; other transient events during VNS included intermittent coughing and paresthesia in the left side of the neck. Vital signs and electrocardiographic findings showed no clinically significant change after VNS.

Nineteen patients or 55.9% were reported being more alert at six-month follow-up. Eight patients with no mental retardation (patients 1, 4, 5, 7, 9, 14, 15, 29)

Table 2. *Efficacy of vagus nerve stimulation in 34 epileptic patients*

Patient no.	Current settings (mA)	Type and baseline no. of seizures per month	Mean no. of seizures at 6-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 PS/GS 6	PS 3 PS/GS 1	91.2 83.3
5	2.50	PS 10 PCS 18	PS 5 PCS 7	50.0 61.1
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	PCS 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 PS/GS 43	PS 95 PS/GS 57	-32.6 -26.7
22	2.5	TS 168	TS 32	81.0
23	3.25	PCS 5 PS/GS 6	PCS 2 PS/GS 2	60.0 66.7
24	3.25	AB 71	AB 5	93.0
25	1.75	PCS 9	PCS 2	77.8
26	3.0	PCS 90	PCS 28	68.9
27	3.5	PS/GS 52	PS/GS 43	17.3
28	3.5	PS 30 PS/GS 12	PS 25 PS/GS 11	16.7 8.3
29	3.0	GS 9	GS 8	11.1
30	2.5	GS 28	GS 10	64.3
31	1.75	PS 84	PS 10	88.1
32	2,5	GS 8 MS 56	GS 2 MS 0	75.0 100.0
33	0.5	PS 6	PS 1	83.3
34	3.0	PS/GS 8	PS/GS 8	0.0

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

reported being more alert and better able to concentrate; three patients (patients 1, 5 and 29) reported having better mood; and one patient (patient 4) reported having better memory and work performance. The families of eleven mentally retarded patients (patients 2, 3, 11, 13, 17, 18, 21, 22, 24, 30, and 32) reported that the patients were more mentally alert. Two mentally retarded patients (patients 3 and 8) were reported to have occasional noc-

Table 3. *The efficacy of VNS to different types of seizures*

Seizure type	> 50 % Reduction of seizure	
	Number of responders	Percent of responders
Partial simple seizure (7)	5	71.4
Partial complex seizure (12)	8	66.7
Partial with secondary Generalized seizure (10)	4	40.0
Generalized seizure (9)	7	77.8
Absence seizure (3)	3	100.0
Atonic seizure (3)	3	100.0
Tonic seizure (3)	2	66.7
Myoclonic seizure (2)	1	50.0

The number in parenthesis is the number of patients.

turnal wakefulness and required sedation to relieve this symptom.

DISCUSSION

Our study agrees with others[13-16] 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 experience, VNS appears to have a broad spectrum of antiepileptic effects on both generalized seizures and partial seizures (Table 3). 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. Partial seizure with secondary generalized seizure did not respond well to VNS. Separately analyzing patients who were 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 studies[15,16,17] 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[18,19] 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. These adverse events can be minimized by increasing the current at 0.25 mA increments or setting the pulse width in the low range. 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 the six-month study period. Recent studies have shown that efficacy increases robustly after one year of VNS therapy[20]. Patients receiving VNS therapy earlier in their treatment course were three times more likely to report no seizures after 3 months of treatment[21]. Further improvement of the efficacy of VNS may depend on the role of each device parameter-output current, pulse duration, frequency, and duty cycle. These parameters may provide an algorithm for their adjustment to achieve seizure control. In our comprehensive epilepsy program, we recommend that VNS should 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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