Experience with Vagus Nerve Stimulation for Intractable Epilepsy: Some Questions and Answers

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Abstract

Vagus nerve stimulation (VNS) is gaining increasing popularity and credibility as a treatment option for patients with intractable epilepsy. VNS is a relatively recent innovation, however, and like many other incipient developments, it has engendered a number of unresolved controversies and perplexities. Limitations in our current understanding of how VNS works lie at the crux of these uncertainties. In this article, we present our clinical experience with VNS and review the fundamental issues which remain unsettled, such as the mechanism of VNS action, the factors underlying variability in patient outcome, and the selection of ideal candidates for VNS therapy. Although many enigmas persist, VNS has proven to be a safe, feasible, and potentially effective method of reducing seizures in select patient populations. It offers several advantages over extant treatments and, as a result, holds much promise for future therapy of medically refractory epilepsy.

Key words: epilepsy, epilepsy surgery, vagus nerve, vagus nerve stimulation

Introduction

Vagus nerve stimulation (VNS) with the Neurocybernetic Prosthesis (NCP) system (Cyberonics, Webster, Tex., U.S.A.) is emerging as a novel adjunct in the management of patients with intractable seizures. This device delivers intermittent electrical stimulation to the cervical vagus nerve trunk, which secondarily transmits rostral impulses to exert widespread effects on neuronal excitability throughout the central nervous system (Fig. 1). We have comprehensively reviewed the theoretical background and practical application of VNS in a previous publication. In this article, we present the outcome of our clinical experience with the method and examine some of the intriguing questions raised by our results.

Clinical Experience

To date, we have treated over 50 patients with the NCP device. Seventeen of them participated in the E05 study, a multicenter, double-blinded, randomized, active control trial of high- versus low-stimulation parameters conducted between 1995 and 1996. Eligible subjects in this study had med-

Fig. 1 Schematic representation of vagus nerve stimulation. A pulse generator placed in the subcutaneous tissue of the chest delivers intermittent electrical stimulation to the vagus nerve trunk in the neck via a bifurcated helical electrode. The nerve then transmits rostral impulses to the brain to suppress seizure activity. Reprinted with permission from Cyberonics.
ically refractory epilepsy with at least six partial onset seizures involving alteration of consciousness (complex partial and/or secondarily generalized convulsions) per month and no more than 21 days between ictal events. Patients were excluded for progressive systemic or neurological disease, cardiac arrhythmia, active pulmonary or peptic ulcer disease, insulin-dependent diabetes, pregnancy, or history of prior left cervical vagotomy.

The mean patient age was 38.5 years (range 21 to 65 years), and the mean duration of epilepsy 31.8 years. The mean baseline seizure frequency was approximately one per day, despite an average of 2.6 concomitant antiepileptic medications. Thus, all patients had longstanding, medically refractory seizures resulting in severe incapacitation.

Patients with both structural and idiopathic origin were included in the study. Three patients with mesial temporal sclerosis and epileptic spikes arising from the ipsilateral temporal lobe were deemed good candidates for temporal lobectomy but elected to undergo VNS instead. Other patients had imaging or electroencephalographic findings that were contraindications to resective cerebral surgery, such as the presence of porencephalic cysts, Sturge-Weber syndrome, hemiatrophy, frontal lobe epilepsy, Lennox-Gastaut syndrome, bitemporal epilepsy, or ictal onset confined to Wernicke's area in the dominant hemisphere. Ineligibility for other surgical procedures was not a prerequisite for enrollment in this study, however, and not all patients received complete presurgical evaluation.

After a 3 month baseline to document seizure frequency, each patient underwent placement of an NCP pulse generator in the chest connected to helical leads applied to the left cervical vagus nerve trunk (Fig. 1). The surgical protocol has been described elsewhere. Typically, the procedure is conducted under general anesthesia and lasts less than 2 hours. While it can be performed as an outpatient procedure, it may be desirable to observe patients overnight for vocal cord dysfunction, dysphagia, respiratory compromise, or seizures induced by the anesthetic, although these complications are infrequent.

All surgeries in our study were successful, uneventful, and without adverse sequelae. Postoperatively, patients were observed for 2 weeks to allow for wound healing, resolution of local edema, and proper electrode fixation to the nerve. Patients were subsequently randomized to receive either high or low parameters of stimulation (Table 1). All programming was performed transcutaneously, using radiofrequency signals emitted from a programming wand attached to a personal computer.

Stimulus parameters were titrated empirically during serial office visits according to the tolerance and efficacy of VNS in individual patients.

The two groups were compared during a 3-month double-blinded treatment phase. During this time, patients were maintained on stable regimens of the antiepileptic medications they had been taking preoperatively. At the conclusion of this period, subjects who were initially randomized to low stimulation settings were converted to the higher stimulation protocol during a 15-month partial-crossover extension trial. Thus, during the latter phase, all participants received high stimulation settings. Medication changes were made in 12 patients in the course of this phase.

Seizure frequency was the primary outcome variable, but quality of life indices were also measured. Numerous safety assessments, including physical examination and vital signs, serum chemistries, pulmonary function tests, and Holter recordings were monitored at regular intervals.

Seven patients were randomized to receive the high stimulation protocol. After 3 months of follow-up, the change in seizure frequency for this group ranged from −100% to +22%, with a mean of −71% (Fig. 2). At the end of the extension trial (after 18 months of stimulation), the range was −100% to −18% and the mean −81% (Fig. 3). Five (71%) of these patients experienced a greater than 75% reduction in seizure frequency at 18 months, and one (14%) has remained seizure free after more than 3 years of follow-up. These results compare favorably with the multicenter E05 study as a whole, which observed a 28% mean reduction in seizure frequency among patients in the high group after 3 months, with some centers actually reporting an increase in seizure frequency compared with baseline.

For the 10 patients randomized to low stimulation, the change in seizure frequency after 3 months of follow-up ranged from −75% to +108%, with a mean of −6% (Fig. 2). The difference in mean seizure reduction between the two treatment groups was statistically significant (p = 0.004). When these patients were subsequently converted to higher stimulation settings, the range was −98% to +35%, with a mean of −34% (Fig. 3). Thus, a disparity

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persists between the two treatment groups after 18 months of stimulation, despite the fact that all patients received high stimulus parameters throughout the extension trial.

No substantial changes were noted in pulmonary function, cardiac rhythm, blood pressure, pulse, serum gastrin levels, and other safety variables. The most common adverse events, including hoarseness or cough during simulation, were generally transient and mild. Formal swallow evaluations with x-ray video fluoroscopy were performed in 10 patients and revealed no evidence of dysphagia or aspiration except in one patient, whose symptoms resolved after reducing the stimulating current by 0.25 mA.8

**Discussion**

As with many other anticonvulsant therapies, information about the neural mechanisms underlying VNS lags behind the appreciation of its clinical efficacy.16 Our experience with VNS raises a number of important questions, including the following:

1. What factors account for the variable results reported from institution to institution?
2. What factors underlie the variable patient outcomes within one center?
3. What factors predict a favorable response?
4. Why do patients initially treated with low stimulation settings fare worse than those originally assigned to the high group, even after converting to the high stimulation protocol?
5. What are the optimal stimulation parameters?
6. Who is the ideal candidate to receive VNS?

Because many of these queries could be answered by understanding precisely how VNS produces its antiepileptic effects, it is appropriate to preface the discussion of these dilemmas by considering what is presently known about the mechanism of VNS action.

I. How does VNS work?

The exact mechanism by which VNS modulates seizure activity and its locus of action have been reviewed elsewhere but remain uncertain.16,20,21 Although the vagus nerve is generally regarded as an efferent projection that innervates the larynx and
provides parasympathetic control of the heart, lungs, and gastrointestinal tract, the majority of its fibers are sensory. While it was initially proposed that VNS works by recruiting afferent C-fibers and A-delta fibers within the nerve, this contention has been recently challenged by observations that VNS retains its antiepileptic effects despite selective destruction of these small unmyelinated fibers by treatment with capsaicin.

Vagal afferent fibers originate from receptors in the viscera and terminate in diffuse areas of the central nervous system, many of which are potential sites of epileptogenesis. These include the cerebellum, diencephalon, amygdala, hippocampus, insular cortex, and multiple brainstem centers. Some of these projections relay through the nucleus tractus solitarius, while others form direct, monosynaptic connections with their targets. Although it remains unclear which of these pathways underlie the mechanism of VNS action, the locus ceruleus and raphe nucleus appear to be key intermediaries, since bilateral chemical lesions of these centers abolish the seizure-suppressing effects of VNS therapy in animal models.

These results imply that norepinephrine and serotonin, which are diffusely released by the locus ceruleus and raphe nucleus, respectively, may mediate the anticonvulsant actions of VNS. Indeed, these two neurotransmitters are known to modulate seizure threshold in some parts of the brain by inducing interneurons to release gamma-amino butyric acid (GABA), leading to widespread inhibition of neuronal excitability throughout the brain.

However, the levels of GABA and serotonin metabolites in the cerebrospinal fluid of patients undergoing VNS appears to be inversely correlated with the efficacy of treatment, and the neurotransmitter systems that mediate the antiepileptic actions of VNS remain uncertain.

Recently, some animal studies have suggested that the mechanism of VNS action derives from cardiac rate and conduction changes leading to transient cerebral ischemia, rather than direct effects on neurotransmitter release or neuronal membrane conductance. However, such experiments conflict with the majority of human studies, which report no significant effects on cardiac performance in response to VNS therapy. Although studies of cerebral blood flow using positron emission tomography (PET) have delineated some regions of decreased perfusion, such changes are presumed to reflect altered synaptic activities rather than global impairments of systemic hemodynamics. These PET studies have revealed inconsistent findings in response to VNS and suffer from many methodological variations that may confound their results; however, they may help elucidate the mechanism of VNS action and eventually even predict the likelihood of a favorable outcome.

II. What accounts for variable responsiveness to VNS?

A recent meta-analysis of 454 patients enrolled in one of five controlled clinical trials suggests that the response of individual patients to VNS varies greatly. While a few subjects enjoy complete seizure cessation, others derive no benefit, and the remainder experience intermediate results. Because such variability is inherent to trials of many anticonvulsant therapies, a standard measure of efficacy has been the 50% responder rate (the proportion of subjects who experience a 50% reduction of baseline seizure frequency). In the meta-analysis of VNS, the 50% response rate was approximately 40% after 3 years of follow-up. While this figure is similar to the initial results of many new drug trials, it remains unclear why some patients respond to VNS and others do not.

Some of this variation may reflect deviations in clinical practice from center to center, since the efficacy of VNS reported by individual institutions ranges widely. For instance, some centers have documented up to a 40% seizure-free response rate, whereas fewer than 1% of patients in the multicenter E05 trial became completely seizure-free. Similarly, in our cohort, the mean reduction in seizure frequency among patients in the high group was 71% after 3 months of stimulation, compared with only 28% in the E05 trial as a whole. Although these results may represent the statistical variation of small sample sizes, it is possible that differences in surgical technique, stimulation protocols, or other clinical practices may account for such discrepancies. Clearly other factors are also important, since patient outcomes range widely even within a single institution.

Recently, a multiple regression analysis was performed in an effort to identify the patient characteristics associated with a favorable response to VNS. Of the several factors that were examined, baseline seizure rate was found to account for 50% of the variance in patient responsiveness, with higher rates predictive of better outcomes. This finding may explain the disparity we observed in our study between the two treatment groups at the end of the extension trial, since the patients originally randomized to receive high stimulation parameters had slightly higher baseline seizure rates than those who were randomized to the low group and subsequently crossed over. However, as dis-
cussed later, other explanations for this observation are also possible.

III. What are the optimal stimulation parameters?

Early experiments in animals revealed that intermittent stimulation of the vagus nerve could suppress the onset of new seizures, in addition to shortening seizure duration and halting seizure progression. VNS is thus both a preventative (antiepileptic) and an abortive (anticonvulsant) form of therapy, with the period of seizure suppression outlasting the stimulus duration.\(^1^)\) The sustained antiepileptic effects have been confirmed by PET scans, serial electroencephalograms, and markers of neuronal gene transcription.\(^1^,12^)\)

These observations form the basis of the stimulation parameters currently utilized in clinical practice. In the E05 trial, for instance, the settings in the high group were derived from pilot data and animal studies which suggested a high likelihood of efficacy, while those in the low group were intended to be perceptible as a tingling sensation in the neck (to maintain patient blinding), but less effective (Table 1). Thus, this study employed an active control, rather than a true placebo.

The rationale underlying these stimulation protocols has recently been challenged.\(^2^8^)\) In addition to its anticonvulsive effects, VNS also inhibits the nociceptive reflex (NR) in anesthetized rats, elicited by delivering a strong stimulus to the tail or hind paw. By titrating the parameters of VNS to the endpoint of NR inhibition, new stimulation settings have been proposed, based on the premise that maximal activation of afferent C fibers mediates both the anticonvulsive and antinociceptive effects of VNS.\(^2^8^)\)

Currently, the selection of stimulation parameters in particular subjects remains empiric. Typically, patients receive 30 second trains of 30 Hz, 500 microsecond pulses separated by 5 minute intervals between stimulation, with current adjustments according to individual tolerance and efficacy. However, it is possible that the full potential of VNS has not yet been realized, secondary to our relative ignorance about the ideal dosing parameters. Thus, further experimentation with alternative stimulation paradigms is needed to optimize the therapeutic outcome of VNS.\(^2^8^)\)

The timing of stimulus adjustment may also be an important factor in determining outcome. As mentioned, the disparity between our two treatment groups at the end of the extension trial could be explained by differences in baseline seizure frequency between the two cohorts. Alternatively, patients might be conditioned by their initial stimulation parameters and, unless their current settings are ramped up quickly, may become relatively refractory to further increases in stimulation. Indeed, for the multicenter E05 trial as a whole, patients in the low group only sustained a 34% reduction in seizure frequency after converting to high settings, while those initially randomized to the high group experienced a 46% reduction after 6 months of stimulation.\(^4^)\)

IV. Who should receive VNS?

In the United States, VNS is only approved as an adjunctive treatment for intractable seizures of partial onset in patients over the age of 12. However, multiple studies confirm the safety, tolerance, and efficacy in children as young as 3 years old.\(^10^,11^)\) Patients with Lennox-Gastaut\(^5^,17^)\) and other types of primary generalized epilepsies have also derived significant benefit from VNS, although preliminary experience with infantile spasms has been disappointing.\(^2^9^)\) Of note, VNS has been used successfully in patients who have failed to respond to other surgical procedures such as lobectomies, topectomies, corpus callosotomies, multiple subpial transections, and functional hemispherectomy,\(^6^)\) confirming the potential efficacy of VNS in highly refractory patient populations.

At present, we consider VNS therapy to suffer from two principal limitations. The first is the inability to predict which patients are likely to respond, and the second is the low likelihood of complete seizure cessation. For these reasons, we generally reserve VNS for patients in whom resective surgery is not indicated. These include patients whose seizure focus is bilateral, not associated with a structural abnormality, or cannot be completely resected due to overlap with functional cortex.\(^6^)\) As our understanding of the mechanism of VNS action improves, however, these indications are likely to expand.

Conclusions

VNS offers several theoretical advantages over pharmacotherapy and other surgical modalities.\(^1^)\) These include the lack of significant toxicity or neuropsychological deficits, the potential for reversibility, the potential for guaranteed treatment compliance, the sustained efficacy over time, and the absence of adverse drug interactions. VNS improves cognitive function independent of its ability to reduce antiepileptic medication requirements or seizure frequency,\(^3^9^)\) and leads to dramatic improvements in overall quality of life.\(^1^)\)
Although many enigmas about VNS persist, these advantages over other extant treatments argue for continued application and study of the method. VNS has proven to be a safe, feasible, and potentially effective means of reducing seizures in select patient population and holds much promise for future therapy of medically refractory epilepsy.

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