Vagus nerve stimulation: current concepts

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Vagus nerve stimulation (VNS) has become an accepted treatment option for pharmacologically resistant epilepsy. Although initially approved for adults, it increasingly has gained acceptance in children. In this article the author reviews the current state of knowledge of VNS therapy and discusses its potential utility. (DOI: 10.3171/FOC/2008/25/9/E9)

KEY WORDS • children • epilepsy • vagus nerve stimulation

Vagus nerve stimulation was first approved by the US FDA in July 1997 “for use as an adjunctive therapy” in the treatment of epilepsy “for adults and adolescents over 12 years of age.” The stimulator is manufactured and supplied by Cyberonics, Inc., and more than 50,000 have been implanted over the past decade. Although there has been a push to expand the indications for implantation—for example, depression, anxiety disorder, and obesity—this review is limited to VNS’s use in the management of medically refractory epilepsy. As our understanding of the definition of medically refractory epilepsy has become more refined and with the realization that most intractable cases are identified earlier in the disease process, one is left with an ~ 40% incidence of pharmacologically intractable epilepsy. In this article an estimate of ~ 3 million people in the US with epilepsy (or ~ 1% of the population) has been accepted.

Mechanism of Action of VNS

There is as yet no consensus regarding the mechanism of action of VNS, but it likely acts at multiple sites. It was initially hypothesized that VNS works by desynchronizing electroencephalography activity, and this hypothesis as well as VNS’s antiseizure effects has been proven in animal models. Electroencephalography studies in humans have suggested that chronic VNS therapy causes a clustering of epileptiform activity followed by increased periods of spike-free intervals. However, this pattern does not seem to correlate with improved control of clinical seizures, and neither does it address the ability of acute VNS to prevent or shorten seizures. Cerebral blood flow studies using PET have demonstrated increased blood flow in the dorsocentralostral medulla, the site of the dorsal medullary vagal complex. Other areas that showed increased blood flow were the hypothalamus and insular cortices. There were decreases in the blood flow of the amygdala, hippocampus, and cingulate gyrus. Interestingly, the increased blood flow observed bilaterally in the thalami seemed to be related to a diminution in seizures following VNS therapy. In studies in which the authors assessed more chronic VNS, blood flow changes persisted in the deeper structures but returned to baseline in cortical areas. Although this is an interesting set of observations, it does not as yet provide a mechanistic understanding.

Indications for VNS

Due in part to a lack of understanding with respect to the mechanism of action, indications for the placement of a vagus nerve stimulator remain fluid, primarily because one cannot predict which patients will benefit and which will not. Currently, VNS is not regarded as a front-line therapy but instead is considered only after medical therapy has failed and a patient has been deemed an unsuitable candidate for resection or is unwilling to accept the risks of surgery. Vagus nerve stimulation is reserved for those who have drug-resistant epilepsy, and the FDA limits its use to patients older than 12 years of age. Note, however, that there is an increasing use of VNS in children younger than 12 years old, in part because of the recognition that earlier control of seizures generally results in improved long-term outcomes. Drug-resistant epilepsy, defined as a failure to attain adequate seizure control after 3 treatment attempts, is a significant problem affecting 35–40% of people with epilepsy. Interestingly, the majority of treatment failures

Abbreviations used in this paper: FDA = Food and Drug Administration; VNS = vagus nerve stimulation.
seem to be caused by an inability of the patient to tolerate the adverse effects of the medication. Such effects further compound the disabling symptoms of epilepsy. Treatment failure due to poorly controlled epilepsy or the intolerable side effects of medication has a deleterious effect on a patient’s quality of life.

The Operation and Its Complications

Implantation of a vagus nerve stimulator generally has been well described elsewhere. Briefly, perioperative antibiotics are administered. An incision is made on the left side of the neck to expose the vagus nerve. The approach is similar to that in anterior cervical discectomy or carotid artery endarterectomy. The platysma is opened and the plane medial to the sternocleidomastoid muscle is developed, exposing the carotid sheath. The sheath is opened, the jugular vein is retracted laterally, and the vagus nerve is usually apparent in the groove between the jugular vein and carotid artery, although it can be deep and lateral to the carotid artery. The nerve is then exposed for a length of ~3–4 cm. An incision is made below the clavicle, and a pocket for the pulse generator is developed just above the fascia of the pectoralis muscle. In very obese patients one must ensure that the pocket is not placed so deep as to preclude palpation and possibly testing of the device. An electrode lead is passed from the neck to the chest incision. Electrodes are then placed around the vagus nerve, the lead is attached to the pulse generator, and the construct is tested. At this point, the anesthesia team should be notified given that bradycardia, complete atrioventricular block, and asystole have been reported. If the device is functioning properly, the pulse generator is placed in the subcutaneous pocket and tacked down with a nonresorbable suture. Any excess lead should be placed in the chest pocket in such a way that when the pulse generator is exposed at a later date for exchange, inadvertent damage will be avoided. A protective loop of wire is placed in the neck incision and tacked down, usually to the underside of the sternocleidomastoid muscle, by using the radiopaque silicone tiedown provided and a nonresorbable suture. Usually I use the lead immediately distal to the electrodes, which has a slightly different appearance from the rest of the leads, as the relief loop. The construct is tested and turned to the off position. The wound is closed in the usual fashion. (Further information from Cyberonics on implantation can be found at http://www.vnsthetherapy.com/epilepsy/hcp/manuals/default.aspx Part V Implantation Procedure.) Most patients are ready for discharge within 24 hours and often earlier than that. Although the stimulator is generally implanted on the left side, there have been reports on the successful use of the right vagus nerve in patients whose left nerve is unavailable. The concern with right-sided placement is the increased number of cardiac efferent branches in the right vagus nerve. Placement of a stimulator is generally safe, with few complications or side effects. The most common and vexing problem is infection, which occurs in up to 5–7% of patients. This complication usually leads to an explantation, making reimplantation even riskier. If reimplantation is required, it may be helpful to locate the nerve above or below the initial implantation site. Having a standby surgeon with experience in repeated carotid artery surgery or neck dissections can be very comforting. Generally, if a different portion of the nerve must be exposed, it will be more accessible superior to the original implant. Inferior to the implant, one often must follow the nerve into the chest to get enough exposure. Each case must be considered individually based on prior surgery. Recent reports concerning other types of implanted generators have suggested using a low-dose antibiotic solution such as Bacitracin in the subcutaneous pocket. These reports have demonstrated an improvement in the infection rate, although the sample sizes were small. The most common neurological problem following implantation is vocal cord paralysis, occurring in ~1% of patients. Patients have also reported a significant number of transient effects, which do not usually require ceasing therapy. These symptoms include hoarseness, cough, dyspnea, nausea, and obstructive sleep apnea. Should the device require explantation, especially after prolonged use, one should exercise care in removing the coils around the vagus nerve, although it is possible to leave these coils in place.

Seizure Control

The majority of long-term reports on VNS efficacy have featured patients older than 12 years of age and probably have represented a patient population with uncontrolled epilepsy for many years. Improvements in our understanding of the mechanism of VNS action and refinements in pulse parameters as well as the institution of VNS treatment elsewhere the course of the disease should lead to improved outcomes. That said, one must take care when evaluating the efficacy of implantation devices to control epilepsy. Most devices currently under consideration either modulate abnormal cortical activity (the presumed mechanism for VNS) or directly affect the epileptic focus, that is, the ictal onset zone (currently resection or radiosurgery are the only therapies directed to the epileptic focus). There are differences in the way one evaluates a device as opposed to a drug. Primarily, it is difficult to have a control arm without surgery. In surgical trials, this control effect can sometimes be attained by not activating the device, although one cannot be certain that the act of implantation does not somehow alter the neural networks. Acceptable baseline improvement with drugs is also usually lower than that with implantable devices given the risks of surgery, although experience with VNS suggests that it is a relatively safe surgery. Finally, appropriate end points are difficult to choose, for example, fewer seizures, fewer falls, shorter hospital stays, and so on. In virtually all studies published since the advent of VNS, 35–45% of patients have demonstrated a decreased frequency of seizures exceeding 50% of their baseline level and ~2% have become seizure free. There appears to be no subset of epilepsy for which the results are substantially different. Much has also been made of the fact that further improvement is seen in seizure reduction 1 year after VNS. This claim must be viewed with caution given that adjustments to seizure medications were permitted in that timeframe. A handful of studies have shown that 40–50% of patients can reduce their drug therapy by either lowering the dose or taking less of a drug without adversely affect-
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Longer-term follow-ups (> 5 years) have indicated that there is a 60–70% median reduction in seizure frequency. This rate begs the question of whether it represents extensive improvement in a few patients or general improvement in most patients. Other long-term studies have demonstrated a 50% seizure reduction in ~ 40% of patients, thus implying that some patients benefit a fair bit and others less so. A number of authors have shown that, after VNS, quality of life measurements track the diminution of seizures and a reduction in pharmacological therapy. In addition, once the first 6 months of VNS therapy have passed, there seems to be a reasonable reduction in the utilization of healthcare services and the time spent on epilepsy-related tasks. Authors of these studies generally assumed that the stimulator battery would last 4 years, and the improved results were modest. It has been reported that as the battery reaches the end of its life, one can see increased seizures and changes in mood and attentiveness even if testing is unremarkable.

Vagus Nerve Stimulation in Children

As mentioned previously, the FDA's 1997 approval for the use of VNS for pharmacologically resistant epilepsy did not include children younger than 12 years of age, and thus long-term experience in this age group is not as robust as that in adolescents. Concomitantly, there has been a paradigm shift toward an earlier identification of pharmacologically resistant epilepsy and of patients who would benefit from surgical intervention. This change has been driven by the realization that many nonseizure parameters (for example, behavior, school performance, and mood) are more improved with earlier seizure control and the minimization of adverse drug effects. Further motivators have included a better understanding of epilepsy in childhood as well as technological and epidemiological advances such as 3-T MR imaging and magnetoencephalography. This evolving conceptualization of epilepsy treatment in children has led to an increase in the use of VNS in children younger than 12 years of age. Initial concerns were raised because of an early report on the multiple adverse effects in a small series of children. However, most of these problems were related to lead or pulse generator problems, which appear to have been rectified. Currently used leads and pulse generators are much smaller and more suitable for implantation in children. Multiple studies have shown an equivalent to slightly higher response rate in children as compared with adults (~ 45–55% of patients with a > 50% reduction in seizure frequency). A few long-term studies have shown a 50% decrease in seizure frequency in ~ 60% of patients and a 75% decrease in 40% of patients. Furthermore, there is a suggestion that these patients also showed significant improvement in quality of life measures, which cannot be explained solely by seizure control. Attempts to combine the ketogenic diet and VNS in children have suggested synergistic results; some patients stopped the diet because of a lack of response rather than the restrictiveness of the diet. Except for initial problems with leads and pulse generators, recent studies have shown no difference in complications or adverse effects in children as compared with adults, and the main-tenance of VNS therapy over time seems to be higher in children than adults. These results have proven to be durable, although peripheral or central nervous system complications in children undergoing chronic VNS therapy have yet to be defined.

Conclusions

Vagus nerve stimulation is a well-tolerated and effective therapeutic alternative in the management of pharmacologically resistant epilepsy, even when compared with newer drug therapies. There appears to be no difference in the response rates between adults and children, and these results seem durable. Improvement is seen in nonseizure measures such as quality of life scales, mood, attentiveness, and learning. Although we do not yet know the mechanism of action or the ideal combination of device parameters, drugs, and diet, VNS certainly appears to have a positive effect in a subset of patients with epilepsy. Currently, Cyberonics is putting into production a much smaller pulse generator that will be especially useful in children. They also have developed a new lead that reportedly is stronger and less likely to result in lead fracture, especially the microfracture type. As epileptologists further refine medication and treatment parameters and the manufacturer improves the durability and ease of use of the implant, we can expect to see improvements in our ability to treat pharmacologically resistant epilepsy.

Disclaimer

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References


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