ABSTRACT

The number of pediatric patients receiving vagus nerve stimulation (VNS) therapy in the United States continues to grow despite the fact that no controlled clinical trials have been conducted regarding VNS in this population. In addition, there are currently no well-defined guidelines for selecting appropriate candidates for VNS therapy. Prospective and retrospective analyses of VNS in pediatric patients with age-related or specialized syndromes indicate that this treatment is safe and effective across a broad range of seizure types and syndromes, independent of age. VNS can reduce seizure frequency and is not associated with the cognitive or developmental impairment that may result from pharmacologic interventions for epilepsy. The efficacy, safety profile, and lack of adverse events usually associated with antiepileptic drugs (AEDs) suggest that VNS has a role as an adjunctive therapeutic option for patients with refractory epilepsy who have not responded to other therapies (eg, AEDs, ketogenic diet, or surgery) or are not surgical candidates. The fact that no compliance issues are associated with this intervention makes it an attractive option in the pediatric population. In addition, there is the suggestion that implementing this intervention early in the course of epilepsy may increase the therapeutic response rate and reduce the potential for sequelae associated with long-term epilepsy.


Vagos nerve stimulation (VNS) therapy may be a useful option for patients with refractory epilepsy, as it has been shown to reduce seizure frequency and is not associated with cognitive or developmental impairment that may result from pharmacologic intervention.1 However, patients must undergo careful evaluation in advance of this intervention to achieve accurate diagnosis and appropriately discuss treatment options for their refractory epilepsy. Other alternatives to conventional therapy with antiepileptic drugs (AEDs) include ketogenic diet, new drug therapies, epilepsy surgery, and experimental therapies. Physicians treating refractory epilepsy have the challenge of matching patients to the most appropriate therapy and to create a logical sequential plan for potential future treatments.

Approximately 33% of all VNS devices are currently placed in patients younger than 20 years. VNS is approved in the United States for indications of epilepsy and depression. Most children treated with VNS have developmental delays, fixed neurologic deficits, behavioral problems, cerebral palsy, autism, and other severe neurologic problems. These children represent the most challenging groups of patients and those most at risk for refractory epilepsy. As no randomized, controlled clinical trials have been performed as yet regarding VNS in the treatment of childhood epilepsy, most clinical evidence existing on this subject is based on expert opinion, case series, and studies with historical controls.

A few adolescent patients were included in early randomized trials involving adults, but these numbers are too small to lead to any meaningful conclusions. However, 2 multicenter randomized trials involving adolescent patients are scheduled to begin soon. One trial will evaluate VNS versus medical therapy in the treatment of children and adolescents with early onset epilepsy, and the other trial will compare treatment...
with VNS versus best medical therapy in adolescents who are not candidates for surgical intervention.

**Identifying Appropriate Candidates for Vagus Nerve Stimulation**

An appropriate treatment sequence leading to VNS is emerging. Eligible patients are those who have previously undergone an appropriate evaluation and have not achieved seizure control with adequate medical therapy, usually indicated by a trial of 2 or 3 appropriate AEDs. Likely candidates for epilepsy surgery include children whose lesions do not involve functional cortex and children with temporal lobe epilepsy. Children who do not meet those parameters may be considered for VNS as an alternative to traditional surgical intervention, and children who do not improve after epilepsy surgery should certainly be re-evaluated for possible VNS treatment versus an additional surgical procedure. One of the primary groups of potential candidates for VNS is children with nonlesional frontal lobe epilepsy and normal magnetic resonance imaging, positron emission tomography, and interictal electroencephalograph results.

**Effect of Vagus Nerve Stimulation in Selected Patient Populations**

**Autism**

There were initially many concerns regarding the use of VNS in children with epilepsy and autism, including whether these children would tolerate the device. However, overall, outcomes in children with autism have been quite encouraging. A recent retrospective analysis of data from 59 patients in the VNS registry revealed that 58% of children with autism experienced a greater than 50% reduction in seizure episodes after 12 months of treatment, with consequent improvements in the quality of life and alertness.²

**Younger Children**

Another question regarding the use of VNS is whether it works as effectively in young children as it does in adolescents and adults. Although limited, available clinical data on VNS effectiveness by patient age suggest that VNS efficacy is comparable in all age groups (Figure).³

**Refractory Epilepsy**

Vagus nerve stimulation efficacy was recently evaluated in 125 patients with refractory epilepsy of various etiologies.⁴ In this study, average age at seizure onset was 3 years, and patients had had epilepsy for an average of 8 years. Seizure syndromes included partial seizures, symptomatic epilepsies, and Lennox-Gastaut syndrome. In addition, many patients had significant cognitive impairment or had failed the ketogenic diet. This subject group had all the clinical characteristics of children whose epilepsy is usually resistant to standard epilepsy therapy. Overall, these patients achieved an average decrease in seizure incidence of 50% after 6 months of treatment with VNS. Approximately 5% of patients conversely experienced an increase in seizures, although investigators thought this increase was because of the natural course of the patients’ epilepsy. As was expected, patients who had previously failed surgical intervention for seizure control did not respond to VNS treatment as well as those patients with no history of failed epilepsy surgery. However, an interesting exception occurred among patients with prior callosotomy, as this subgroup experienced a 79% decrease in seizures after 3 months of VNS treatment.

**Figure. Effectiveness of Vagus Nerve Stimulation by Age Group**

Data as of April 2003

<table>
<thead>
<tr>
<th>Age group, y</th>
<th>3 months (n = 1525)</th>
<th>12 months (n = 1525)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>50%</td>
<td>54%</td>
</tr>
<tr>
<td>7–12</td>
<td>57%</td>
<td>57%</td>
</tr>
<tr>
<td>13–19</td>
<td>62%</td>
<td>62%</td>
</tr>
<tr>
<td>20–39</td>
<td>58%</td>
<td>57%</td>
</tr>
<tr>
<td>40–59</td>
<td>53%</td>
<td>54%</td>
</tr>
<tr>
<td>&gt;59</td>
<td>58%</td>
<td>42%</td>
</tr>
</tbody>
</table>

Data from Cyberonics.⁵
Vagus nerve stimulation has been useful clinically in patients with astatic episodes. Because of this observation, a retrospective, multicenter trial of VNS involved 50 children with Lennox-Gastaut syndrome. Patients in this group had been refractory to treatment, as they had on average been previously treated with 9 different AEDs. In addition, 33% of the group had failed treatment with the ketogenic diet, and 10% had previously undergone callosotomy. This group exhibited a favorable response to treatment, exhibiting a 60% decrease in astatic episodes after 3 months of VNS treatment and a 90% decrease in astatic episodes after 6 months.

In a related experience at the University of Texas Medical Center in Houston, we have begun over recent years to consider the combined palliative use of VNS and callosotomy in selected patients with Lennox-Gastaut syndrome to optimize the quality of life in this group of children who are difficult to treat. This combined approach of palliative treatments to alleviate astatic events in children with Lennox-Gastaut syndrome was also evaluated in a recent study of 20 patients in Minnesota. In this study, therapeutic response was defined as a 50% reduction in seizure incidence after VNS or an 80% reduction in seizure rate after callosotomy. More than 50% of the patients who did not benefit from VNS improved after callosotomy and, interestingly, the reverse was also true—more than 50% of the patients who did not respond to callosotomy improved after VNS therapy. Clearly, there is a role for both of these palliative procedures in treatment of patients with Lennox-Gastaut syndrome. Typically in these cases, VNS therapy is begun with a progression to callosotomy, if needed. However, a caveat exists regarding older children experiencing many astatic episodes; in some cases, up to 30 or 40 episodes daily. These children are at such an increased risk for injury that callosotomy may be implemented first because the therapeutic effect can be realized more quickly than with VNS therapy.

The Future Role of Vagus Nerve Stimulation in Pediatric Epilepsy Treatment

Vagus nerve stimulation is currently approved by the US Food and Drug Administration for the treatment of partial-onset epilepsy in patients older than 12 years. As discussed earlier in this article, VNS has a broad-spectrum antiepileptic effect and has proven effective in pediatric patients with symptomatic, generalized epilepsy and in those patients with astatic episodes. VNS also has been effective in patients with hypothalamic hamartomas and tuberous sclerosis.

Advantages of VNS over other treatment modalities include the absence of allergies and other systemic side effects. There are no negative cognitive side effects associated with VNS; because VNS acts by a mechanism different from AEDs, it may offer synergistic treatment without increased medication side effects. Compliance is not a problem, as VNS inherently involves complete involuntary compliance to therapy. Also, and importantly, VNS provides many families a heightened sense of control over epilepsy.

Disadvantages of VNS certainly exist. Its implementation requires insurance approval and careful scheduling with the patients and their family, and these steps take additional time. Also, ideal candidates are not identified easily, and time is required for the therapeutic effect of VNS to become apparent. Furthermore, physicians must be comfortable with device therapy if patients are to benefit from VNS and the increasing number of available device-based interventions. With continued optimization of computer and microchip technology, more device-based interventions undoubtedly will be seen in the future. Eventually, the question will not be whether to use a drug or a device, but how to use them synergistically to achieve the best possible outcomes for the patients with the most challenging cases of epilepsy.

REFERENCES

2. Park YD. The effects of vagus nerve stimulation therapy on patients with intractable seizures and Landau-Kleffner syndrome or autism. Epilepsy Behav. 2003;4:286-290.