Complications of chronic vagus nerve stimulation for epilepsy in children

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Object. The aim of this study was to define better the incidence of surgical complications and untoward side effects of chronic vagus nerve stimulation (VNS) in a population of children with medically refractory epilepsy.

Methods. The authors retrospectively reviewed the cases of 74 consecutive patients (41 male and 33 female) 18 years of age or younger (mean age 8.8 years, range 11 months–18 years) who had undergone implantation of a vagal stimulator between 1998 and 2001 with a minimum follow up of 1 year (mean 2.2 years). Of the 74 patients treated, seven (9.4%) had a complication ultimately resulting in removal of the stimulator. The rate of deep infections necessitating device removal was 3.5% (three of 74 patients who had undergone 85 implantation and/or revision procedures). An additional three superficial infections occurred in patients in whom the stimulators were not removed: one was treated with superficial operative debridement and antibiotic agents and the other two with oral antibiotics only. Another four stimulators (5.4%) were removed because of the absence of clinical benefit and device intolerance. Two devices were revised because of lead fracture (2.7%). Among the cohort, 11 battery changes have been performed thus far, although none less than 33 months after initial implantation. Several patients experienced stimulation-induced symptoms (hoarseness, cough, drooling, outbursts of laughter, shoulder abduction, dysphagia, or urinary retention) that did not require device removal. Ipsilateral vocal cord paralysis was identified in one patient. One patient died of aspiration pneumonia more than 30 days after device implantation.

Conclusions. Vagus nerve stimulation remains a viable option for improving seizure control in difficult to treat pediatric patients with epilepsy. Surgical complications such as hardware failure (2.7%) or deep infection (3.5%) occurred, resulting in device removal or revision. Occasional stimulation-induced symptoms such as hoarseness, dysphagia, or torticollis may be expected (5.4%).

KEY WORDS • vagus nerve stimulation • complication • epilepsy • seizure surgery • children

In 1938 Bailey and Bremer described the cortical representation of the vagus nerve and reported alterations in the brain wave activity in cats after VNS. The effects of the stimulation on electroencephalographic synchronization persisted even when reflex changes in systemic blood pressure and oxygenation were prevented by spinal cord transection at C-1, but were abolished if a tight ligature was placed on the proximal end of the vagal trunk. Subsequent reports appeared between the 1950s and 1970s in which authors demonstrated additional changes in electroencephalographic activation induced by VNS in animals. Because highly synchronized patterns are characteristic of seizures on electroencephalography, such studies of brain wave rhythmicity form the neuroanatomical and neurophysiological basis for the hypothesis that appropriately timed stimulation of the vagus nerve blunts paroxysmal epileptiform activity.

With data from the aforementioned studies providing a framework for the initiation of trials of chronic vagal stimulation in humans, VNS has emerged during the past decade as a viable surgical option for treating medically refractory epilepsy. Although there are many published series in which researchers address the efficacy of VNS, relatively few data have been published regarding surgical complications of this procedure in children. The aim of this study was to define better the incidence of surgical complications and untoward side effects of chronic VNS in a population of children with medically refractory epilepsy.

Clinical Material and Methods

Patient Population

This retrospective study consisted of 74 consecutive patients (41 male and 33 female) 18 years of age or younger (range 11 months–18 years, mean age 8.8 years) who had undergone implantation of a left vagal stimulator at a single institution (Children’s Hospital of Alabama, Birmingham, Alabama) between 1998 and 2001 with a minimum follow up of 1 year (mean 2.2 years). Inclusion criteria for this study were as follows: 1) age 18 years or younger at the

Abbreviation used in this paper: VNS = vagus nerve stimulation.
Vagus nerve stimulation complications

time of initial device implantation; 2) minimum follow up of at least 12 months; and 3) medically refractory multifocal or generalized epilepsy leading to implantation of a vagal stimulator. Retrospective chart reviews were performed, including a review of clinical and operative notes to identify side effects and complications of device implantation. Charts from both neurosurgical and neurological clinics were read to identify any surgical complications, adverse events, and side effects of implantation or VNS.

The details of the operative technique used at this institution have been described in a previous report.32 Prior to surgery, cefazolin is intravenously administered (25 mg/kg) and the skin is prepared for 5 minutes with Betadine. The stimulator and battery pack (model no. 100 in 1998–1999, no. 101 in 1999–2001, and no. 102 in 2002–present; Cyberonics, Houston, TX) are placed in a subcutaneous pocket developed in the infraclavicular fossa through an incision along the lateral border of the pectoralis major muscle. The electrodes are tunneled subcutaneously to a previously created transverse left anterior cervical incision. Sharp dissection techniques are used to expose the vagus nerve through the cervical incision, where it typically is found deep with respect to the common carotid artery and internal jugular vein. Careful isolation of 3 to 4 cm of the nerve is necessary to enable wrapping of the two electrodes and anchoring coil. A tension-relief loop is made in the electrodes and sutured with nonabsorbable material to the sternocleidomastoid muscle, followed by a standard layer closure. The device is tested for function and the electrode impedance is checked prior to leaving the operating suite. Typically, the device is activated in the operating room following implantation, depending on the referring neurologist’s preference. Incisions are closed in 2 layers of 3-0 Vicryl (Ethicon, Piscataway, NJ) and 4-0 running chromic absorbable sutures. Typical initial stimulation parameters are listed in Table 1.

Results

Of the 74 patients treated, seven (9.4%) had a complication ultimately necessitating device removal. The overall infection rate was 7.1% (six of 74 patients undergoing 85 implantation and/or revision procedures). Among the six patients with infections, the use of stimulators in two patients was salvaged with antibiotic agents alone (oral cephalaxin for 10 days) and in one patient with operative debridement and antibiotics (intravenous cefazolin followed by oral cephalaxin). Both of the former patients had superficial wound infections (erythema) with preservation of the deep layer of suture and no apparent infection related to the device. The patient who was successfully treated with debridement and antibiotics had demonstrated pronounced improvement in seizure control following stimulator implantation, but presented 3 weeks postimplantation with superficial wound breakdown at the stimulator site. Prior to implantation, this patient had been very difficult to treat medically. Debridement and antibiotic administration were successfully undertaken in an effort to prevent explantation of the stimulator. The remaining three patients had infections requiring device removal (3.5% of 85 procedures). All patients with infections presented within the first 4 weeks of implantation or revision. Cultures of tissue from two erythematous incisions were not made; however, intraoperatively obtained tissue from the remaining four incisions grew methicillin-sensitive strains of Staphylococcus aureus. Each wound infection occurred at the stimulator site only.

An additional four stimulators (5.4%) were removed because of the lack of clinical benefit and device intolerance (one patient with symptomatic tachycardia, two with discomfort at the stimulator site, and one with an inactivated device complicating the workup of a fever of unknown origin). Two devices were revised because of electrode fracture (2.7%). The lead fracture in both devices occurred later than 4 months postimplantation. One child presented with worsening seizure control 4 years after initial implantation, and high impedance was demonstrated when the device was tested with the Cyberonics computer at the same time the battery had begun to fail. In this case, the leads together with the battery pack were replaced and a small defect in the insulation around one of the leads was identified. The other child began pulling at the neck and chest incisions when the device was activated and manually rotated the stimulator within the subclavicular pocket. This child’s developmental delay precluded clear communication, but a workup 4 months postimplantation revealed a partially fractured lead pulled away from the vagus nerve, with worn insulation and elevated impedance. We postulate that the child’s grabbing of the neck resulted from noxious stimulus of intermittent electrical stimulation. Among the cohort, 11 battery changes have been performed thus far, none before 33 months after initial implantation. The mean battery life at reimplantation is 40.5 months. The majority of battery replacements thus far have occurred in children with typical stimulation parameters (Table 1).

Four patients (5.4%) had stimulation-induced symptoms that did not require device removal, including in one patient each brief outbursts of inappropriate laughter, intermittent dysphagia, and intermittent stimulation-induced shoulder abduction. An additional patient had significant intermittent dysphagia and cough, which were resolved with an adjustment of stimulation parameters. Interestingly, another patient experienced intermittent torticollis, drooling, and urinary retention, which required turning the output and magnet current to 0 mA for 1 week and then reinitiating stimulation at a lower setting. All of the above stimulation-induced side effects were reversible with adjustments in stimulation parameters, but the physiological mechanism causing the symptoms is unclear. A possible ipsilateral vocal cord paralysis was identified following stimulator implantation in one patient who underwent laryngoscopy for another indication. (This was not confirmed, however, because it was not clear whether the vocal cords were examined during a stimulation-off or a stimulation-on cycle,

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>output current</td>
<td>0.25 mA</td>
</tr>
<tr>
<td>output frequency</td>
<td>20 Hz</td>
</tr>
<tr>
<td>pulse width</td>
<td>250 msecs</td>
</tr>
<tr>
<td>on time</td>
<td>30 secs</td>
</tr>
<tr>
<td>off time</td>
<td>5 mins</td>
</tr>
<tr>
<td>magnet current</td>
<td>0.25 mA</td>
</tr>
<tr>
<td>magnet on time</td>
<td>60 secs</td>
</tr>
<tr>
<td>magnet pulse width</td>
<td>250 msecs</td>
</tr>
</tbody>
</table>

T A B L E  1

Initial VNS settings in 74 consecutive patients with epilepsy
TABLE 2
Surgical complications during 85 procedures (includes revisions for battery pack replacement)

<table>
<thead>
<tr>
<th>Complication</th>
<th>% Incidence (no. of patients)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>deep infection (erythema &amp; purulence, all grew methicillin-sensitive Staphylococcus aureus)</td>
<td>3.6 (3)</td>
<td>device removal</td>
</tr>
<tr>
<td>superficial infection (erythema, not cultured)</td>
<td>2.4 (2)</td>
<td>oral antibiotics alone, device retained</td>
</tr>
<tr>
<td>superficial infection (methicillin-sensitive S. aureus)</td>
<td>1.2 (1)</td>
<td></td>
</tr>
<tr>
<td>electrode fracture</td>
<td>2.7 (2)</td>
<td>lead replacement</td>
</tr>
<tr>
<td>device intolerance</td>
<td>5.5 (4)</td>
<td>device removal</td>
</tr>
<tr>
<td>ipsilateral vocal cord paralysis</td>
<td>1.4 (1)</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 3
Side effects of VNS*

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>% Incidence (no. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hoarseness/voice changes†</td>
<td>1.4 (1)</td>
</tr>
<tr>
<td>cough†</td>
<td>1.4 (1)</td>
</tr>
<tr>
<td>involuntary arm movement</td>
<td>1.4 (1)</td>
</tr>
<tr>
<td>inappropriate laughter</td>
<td>1.4 (1)</td>
</tr>
<tr>
<td>drooling†</td>
<td>1.4 (1)</td>
</tr>
<tr>
<td>torticollis†</td>
<td>1.4 (1)</td>
</tr>
<tr>
<td>drooling†</td>
<td>1.4 (1)</td>
</tr>
<tr>
<td>urinary retention†</td>
<td>1.4 (1)</td>
</tr>
</tbody>
</table>

* All of the listed side effects were reversible.
† All occurred in the same patient.

which may have mimicked vocal cord paralysis.) One patient in this series died of aspiration during a nocturnal generalized tonic–clonic seizure. Details of this case were reported previously after postmortem examination of the vagus nerve demonstrated severe demyelination and inflammation at the electrode site.78,79 Surgical complications and side effects of stimulation are summarized in Tables 2 and 3.

Discussion

The vagus nerve provides motor control for the pharynx, larynx, and thoracic and abdominal viscera, although more than 90% of its axons are afferent.8,9,20,26,35 Most of the afferent fibers originate from sensory receptors in the viscera and terminate in the nucleus tractus solitarius, from which they potentially exert widespread effects on neuronal excitability throughout the brain.8,9,15,26,35,38

The precise mechanism by which VNS modulates seizure activity and its locus of action remains the subject of much conjecture. Vagus nerve stimulation induces a significant prolongation of somatosensory evoked potentials, but does not alter visual, auditory, or cognitive evoked potentials.13,30 Much interest has been centered on its effects at the level of the brainstem, both as a site of epileptogenesis and as a regulator of seizure propagation.30 Vagal stimulation evokes responses in regions as widespread as the cerebral cortex, hippocampus, brainstem, thalamus, and cerebellum;13,14,21,25,26,35 it’s antiepileptic actions may relate to effects on these areas via the brainstem reticular activating system.2,26,35,39,40 Overall, VNS appears directly or indirectly to activate a wide array of neuroanatomical structures.31

Transient side effects of VNS often occur frequently and include hoarseness or voice changes (20–66%), cough (7–45%), dyspnea (6–25%), headache (14–24%), nausea (7–15%), and a tingling sensation in the throat or neck spasms (11%).7,12,15,17,18,31,35 These complications are usually dose-dependent and occur during stimulus delivery.25,33 Occasionally, VNS results in significant adverse neurological effects including vocal cord paralysis and facial muscle paresis. These effects occur in approximately 1% of all patients.15,19 Electrode breakage and device infection are relatively common surgical complications, with published rates being similar to those of other chronically implanted devices such as baclofen pumps1,5 and deep brain stimulators.16,22

One of the challenges that occurs in treating children with stimulator implantation is the tendency of some children to manipulate manually the device or the associated incision. Many children with medically intractable multifocal epilepsy have suffered severe brain insults and have significant developmental delay. Often such children are incapable of vocalizing concerns or complaints and will instead tend to pull at the device or incision. This can prove to be troublesome for families and health care providers alike. One of the patients in this series became fixated on the device and manually rotated it within the subcutaneous pocket enough times that the leads became detached from the vagus nerve. Two of the infected children fixated on the wound and repeatedly manipulated it with their fingers, which in at least one case contributed to a deep infection necessitating device removal. We found the use of bulky, layered dressings that were meticulously secured to be of some use in these patients. Other groups have recently advocated the implantation of the pulse generator in an inaccessible area such as the interscapular region.34

Conclusions

Vagus nerve stimulation remains a viable option for improving seizure control in difficult to treat pediatric patients with epilepsy. Surgical complications such as lead fracture (2.7%) or deep infection (3.5%), resulting in device removal or revision, occurred in this series. Occasional stimulation-induced symptoms (hoarseness, cough, or dysphagia) may be expected (5.4%), but are generally tolerated by those patients who benefit clinically from chronic VNS. Rates of stimulation-induced symptoms in this series of children were lower than those reported in adults.

Disclosure

None of the authors of or contributors to this study has any conflicting financial interest in the use of the vagal stimulator discussed in this manuscript.

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