Vagus nerve stimulation for complex partial seizures: surgical technique, safety, and efficacy

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Electrical stimulation of the vagus nerve has shown efficacy in controlling seizures in experimental models, and early clinical trials have suggested possible benefit in humans. Eleven patients with complex partial seizures were subjected to implantation of vagus nerve stimulators. Electrode contacts embedded in silicone rubber spirals were placed on the left vagus nerve in the low cervical area. A transcutaneously programmable stimulator module was placed in an infracavicular subcutaneous pocket and connected to the electrode. One patient required replacement of the system due to electrode fracture. Another patient developed delayed ipsilateral vocal-cord paralysis; the technique was then modified to allow more tolerance for postoperative nerve edema. A third patient showed asymptomatic vocal-cord paresis on immediate postoperative laryngoscopy. Vagus nerve stimulation produces transient vocal-cord dysfunction while the current is on. Nine patients were randomly assigned to receive either high- or low-current stimulation, and seizure frequency was recorded. The high-current stimulation group showed a median reduction in seizure frequency of 27.7% compared to the preimplantation baseline, while the low-current stimulation group showed a median increase of 6.3%. This difference approached statistical significance. The entire population then received maximally tolerable stimulation. The high-current stimulation group showed a further 14.3% reduction, while the low-current stimulation group showed a 25.4% reduction compared to the blinded period. The efficacy of vagus nerve stimulation seemed to depend on stimulus parameters, and a cumulative effect was evident. These results are encouraging, and further study of this modality as an adjunct treatment for epilepsy is warranted.

KEY WORDS • complex partial seizure • electrical stimulation • seizure • vagus nerve

The complex partial seizure is a common form of epilepsy, and many patients afflicted with this disorder are not well controlled by medications. Some patients have epileptogenic foci that may be identified and resected; however, many patients remain who have medically resistant seizures not amenable to resective surgery. Stimulation of the vagus nerve has been shown to reduce or abort seizures in experimental models. Early clinical trials have suggested that vagus nerve stimulation may be beneficial in complex partial seizures in humans. The neuroanatomical and neurophysiological basis for trials of vagus nerve stimulation has been previously reviewed in detail. Afferent fibers from the vagus nerve lead to the reticular formation, nucleus solitarius, nucleus cuneatus, and cerebellum. In the cat, 65% to 80% of the vagus nerve is afferent. Projections from the nucleus solitarius and the reticular formation reach the hypothalamus, amygdala, nucleus ambiguous, dorsal motor nucleus of the vagus, parabrachial area, and the thalamus. Evoked potentials have been recorded in the hippocampus, thalamus, and cerebral cortex after vagal stimulation in experimental animals. In the cat, vagal stimulation produces electroencephalographic (EEG) desynchronization and disrupts sleep spindle occurrence.

Vagal stimulation has been shown to block interictal spikes caused by strychnine administration in cats and abort pentyleneetrazol-induced seizures in dogs. In rats, vagal stimulation was found to reduce or prevent chemically induced seizures; the effect was considered to be related to stimulation of C fibers.

Intermittent vagal stimulation in patients with intractable seizures has been reported to show promising results, although the number of patients treated thus far is small, and only a brief follow-up period has been reported. One version of the surgical technique has previously been summarized. This report describes the surgical techniques used at this center and reviews problems that have been encountered in the
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first group of patients. The effect of variation of stimulation parameters on seizure frequency was examined with both double-blind and unblinded regimens.

Clinical Material and Methods

Patient Population

Twelve implantation operations were performed in 11 patients, aged 22 to 55 years. Four patients were women and seven were men. All patients had long medical histories of poorly controlled complex partial seizures resistant to pharmacological treatment; full radiological and EEG evaluations had been performed.

No patient had other concurrent significant medical problems. One patient had undergone two craniotomies for temporal and frontal cortical resections at another center without achieving seizure control. Three other patients had had implantation of intracranial electrodes at this center without identification of resectable foci. Only one patient was thought currently to be a reasonable candidate for intracranial electrode study, but he and his family refused such surgery. One patient had a large nonresectable dominant hemisphere arteriovenous malformation that had previously been treated with radiotherapy; this patient was the only one in the series with a substantial structural lesion. Patients were receiving between one and three antiepileptic drugs. Preoperatively, all patients had 24-hour electrocardiographic recordings. The last nine patients receiving implants were treated with the stimulation protocol described below.

The project was approved by the University of Miami Committee for the Protection of Human Subjects, and all patients signed informed-consent forms prior to entering the study.

Hardware

The vagus nerve stimulation system employed in this study consists of an electrode, a stimulator module, and programming hardware and software. The electrode has a bifurcation near its end that gives off two leads containing platinum contacts, each centered in a separate silicone rubber spiral. Suture tails extending out of each end of each spiral are used for manipulation of the ends of the spirals. Proximally, the electrode branches into two separate plugs that attach to the output of the stimulator module.

The stimulator is contained in a titanium module similar in size and appearance to a cardiac pacemaker. The epoxy header accepts the plugs of the electrode. The device is transcutaneously programmed by a magnetic field generated by a box-like programming wand controlled by an IBM-compatible computer. The software is menu-directed and allows user control of stimulation parameters such as current level, signal frequency, and on-off periods. The device is usually programmed to deliver a burst of current pulses for 30 to 60 seconds every 5 to 60 minutes. Output current pulses are programmable in the range of 0 to 12 mA at frequencies of 1 to 143 Hz. The stimulation may also be triggered on demand by placing a magnet over the device. In this mode, the patient or a companion may stimulate the device at the onset of an aura or a seizure.

Surgical Technique

The stimulator module is implanted in an infraclavicular subcutaneous pocket, and the electrode is tunneled to the inferior cervical vagus nerve.

Fig. 1. The stimulator module is placed in an infraclavicular subcutaneous pocket, and the electrode is tunneled to the inferior cervical vagus nerve.
of the electrode are covered with bacitracin-soaked sponges. Attention is then returned to the cervical exposure.

The platysma is opened vertically, parallel with its fibers, and dissection is carried down, medial to the sternocleidomastoid muscle, to the carotid sheath. Hand-held Cloward retractors and self-retaining Caspar retractors with blunt blades are useful during the exposure. The carotid sheath is opened, and the vagus nerve is exposed between the jugular vein and the carotid artery. At this level, the nerve tends to lie toward the posterior aspect of the carotid sheath. The nerve should be exposed for a length of approximately 3 cm (the nerve is about 3 mm in diameter). A rubber vessel loop is passed behind the nerve to aid in manipulation; traction should be gentle and minimized.

The electrode spirals are then wrapped around the nerve. The contact on the shorter lead is first placed inferiorly; the contact on the longer lead is placed superiorly (Fig. 2). The body of the electrode will then extend inferiorly. The shorter lead and its corresponding plug are marked with stripes; this lead connects to the positive terminal of the stimulator. The center of each spiral, where the actual contact is located, is placed on the nerve first. The ends of the spiral are then wrapped around the nerve. The suture tails extending from the spirals are used to aid in manipulation. In the first two patients, the suture tails extending from the two ends of each individual spiral were tied together to help prevent dislodgement of the spiral. In the second patient, a delayed vocal-cord palsy occurred, possibly due to inadequate space for postoperative edema. In subsequent procedures, the suture tails have not been tied together, and the spirals have provided adequate stability. The large vessels surrounding the nerve help to stabilize the spirals. A cylindrical cuff is included on the electrode in the bifurcated region. A suture of 4-0 polypropylene is placed through the tissue of the carotid sheath and tied around the cuff.

The device is supplied with an extra spiral separate from the electrode; silicone rubber sutures extend from the center of this extra spiral. The extra spiral may be placed on the nerve below the contacts with the sutures tied around the electrode leads to offer an extra measure of stability. In this series, the extra spiral has been used only once; it does not seem to add significantly to stability but increases trauma to the nerve. Tying the cylindrical cuff to the carotid sheath affords the same degree of immobilization as using the extra spiral. The electrode is then looped medially and superiorly and then back inferiorly to create a strain relief loop. Two small silicone rubber suture tabs are wrapped around the lead at intervals and sutured to the cervical fascia.

Sterile cables that extend off the field are then connected to the plugs of the electrode, and the impedance is measured. A programming wand in a sterile plastic drape is placed over the stimulator module, and the stimulator output is connected to the computer by another set of cables. The output of the device is tested. The stimulator is then connected to the electrode, and the set screws are tightened on the plugs. Sterile mineral oil is necessary to lubricate the passage of the silicone electrode plugs into the receptacles on the stimulator. Also, the small hex screwdriver for the set screws is placed through the silicone apertures over the set screws to allow decompression of the air in the receptacle space. Without these simple maneuvers, the plugs cannot be securely attached. The device is again interrogated by the programmer and left turned off. The stimulator module and slack portion of the electrode are placed in the pocket, and interrupted subcutaneous sutures of 3-0 Vicryl are placed. The platysma is closed with interrupted 3-0 Vicryl sutures with the electrode exiting at the inferior extent of the platysma incision. The skin of both incisions is closed with running subcuticular 4-0 Vicryl suture and sealed with tincture of benzoin and skin tapes. The patient is given preoperative prophylactic antibiotics which are continued for 48 hours after surgery.

Stimulation Protocol

In order to determine whether variation of stimulation parameters is significant for seizure control, patients were randomly assigned to receive either a high- or a low-current stimulation regimen. During baseline periods of 9 to 17 weeks prior to implantation of the stimulator, seizure frequency was recorded. After 2 weeks of postoperative recovery, patients were separated into groups and stimulation was begun. Over the next 5 days, the stimulation was gradually increased to the maximum tolerated in the high stimulation range for the high-current stimulation group and to the minimum level sufficient to produce a sensation or voice change in the low-current stimulation group. The stimulation parameters are listed in Table 1. Patients were
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| TABLE 1 |
| Parameters of high- and low-current stimulation |
| Parameter | High Stimulation | Low Stimulation |
| frequency | 20–50 Hz | 1–2 Hz |
| pulse amplitude | 0.5–3.0 mA | 0.5–3.0 mA |
| (maximum tolerable) | (minimum response) |
| pulse width | 300–900 µsec | 130 µsec |
| time on stimulation | 30–90 sec | 30 sec |
| time off stimulation | 5–10 min | 60–180 min |
| magnet response | same as above | none |

allowed to attempt to abort seizures with the magnet but, in the low-current stimulation group, the device was programmed to deliver no current in response to magnet application.

With initiation of stimulation, tabulation of frequency of seizures was begun and continued for a minimum of 12 weeks. Patients were not informed regarding their stimulation parameters, and the investigator interviewing the patients for seizure frequency was also blinded regarding the stimulation regimen. Another member of the team performed the actual device programming. After completion of the blinded stimulation period, the current parameters were adjusted in an unblinded fashion to the maximum tolerated stimulus, and seizure frequency was recorded over an additional follow-up period of at least 6 weeks.

The last nine patients receiving implants participated in this stimulation protocol. Antiepileptic drug doses were held stable during the protocol.

Statistical Analysis

The seizure frequency recorded during the baseline period was compared to the seizure frequency during the blinded and open (unblinded) periods. The percentage changes in seizures of the high- and low-current stimulation groups during the blinded period were compared using a Wilcoxon rank sum analysis. The seizure frequency of the entire population (high- and low-current stimulation groups combined) at the end of the unblinded stimulation period was compared to baseline seizure frequency by a Wilcoxon sign rank test. Two-tailed probability levels were used in both analyses. Because of the small sample sizes, tables of exact probability levels were used. 14

Results

Surgical Difficulties and Complications

A common problem with the first devices implanted in the initial centers was fracture of the electrode. This was found by the manufacturer to be related to fatigue at the junction between contact and lead wire. 18 The electrode was redesigned with substitution of a quadrifilar wire. This greatly improved the fatigue tolerance and seems to have solved the practical problem of electrode fracture related to repetitive neck motion. The first patient in this series had fracture of the electrode approximately 3 months after surgery and underwent removal and replacement of the whole system 17 months after initial implantation. This procedure was believed to carry more risk of nerve injury than the initial surgery due to the need to dissect the contacts from the scar encasing the electrode and nerve. However, the dissection was not severely difficult, and was accomplished without incurring any evident nerve injury. The second patient in the series was also implanted with the original electrode design; the remaining patients received the improved electrode.

The second patient developed a delayed neurological deficit. Five days after implantation, the patient noted abrupt onset of hoarseness. The deficit did not become known to the investigators until 3 days later, and examination disclosed severe hoarseness and a left vocalcord palsy visualized by laryngoscopy. The device was removed; the nerve appeared edematous with impressions on its surface from the spirals. This patient had implantation of the additional stabilizing spiral, and the suture tails on the spirals had been tied together, as in the first patient. Within 7 days of explantation, the patient's voice had normalized, but this was found by laryngoscopy to be due to compensation by the contralateral vocal cord. Follow-up laryngoscopy 9 months later showed recovery of normal left vocal-cord function.

The last seven patients in the series have undergone laryngoscopy 1 to 2 days after implantation. One patient was found to have postoperative ipsilateral vocal-cord paresis that was not manifest by any definite voice change. This paresis was found to have recovered on later study. The remaining patients had no postoperative abnormality on laryngoscopy. During periods of stimulation, many of the patients have a breathy and slightly hoarse voice. A slight cough may occur at the onset of each stimulation, most prominently after the intensity has been increased. Tolerance quickly develops, and coughing usually abates after the first few stimulations. The patient may perceive a tingling sensation in the neck during stimulation. These transient abnormalities have not been found by the patients to be distressing.

One patient underwent videostrobolaryngoscopy during stimulation at different current parameters. With pulse amplitudes of 1 to 4 mA, 20-Hz stimulation produced ipsilateral vocal-cord paralysis. Stimulation of 40 Hz produced a predominance of cord abduction; stimulation above 40 Hz increased strength of adduction of the cord.

Postoperative electrocardiograms were performed; no patient developed evidence of cardiac arrhythmia with ongoing vagus nerve stimulation. One patient had a preoperative asymptomatic intermittent bradycardia that was unchanged postoperatively by vagus nerve stimulation. One patient complained of moderate intermittent epigastric pain which was treated with ranitidine and antacids; the symptoms resolved after 2 months. The patient was not subjected to radiographic or invasive gastric studies.

The implants have been in place for periods of 6 to 13 months with no further delayed complications.
TABLE 2
Percentage changes in seizure frequency *

<table>
<thead>
<tr>
<th>Comparison</th>
<th>High Stimulation</th>
<th>Low Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline to blinded</td>
<td>−23.31 ± 18.65</td>
<td>+12.77 ± 31.88</td>
</tr>
<tr>
<td></td>
<td>(−27.73)†</td>
<td>(+6.30)†</td>
</tr>
<tr>
<td>baseline to open</td>
<td>−36.44 ± 11.58</td>
<td>−23.44 ± 47.75</td>
</tr>
<tr>
<td></td>
<td>(−36.24)‡</td>
<td>(−16.32)‡</td>
</tr>
<tr>
<td>blinded to open</td>
<td>−16.09 ± 8.26</td>
<td>−35.59 ± 38.25</td>
</tr>
<tr>
<td></td>
<td>(−14.33)</td>
<td>(−25.43)</td>
</tr>
</tbody>
</table>

* Values expressed are means ± standard deviation, with the median in parentheses. Significance of difference: † = 0.05 < p < 0.10 for high stimulation vs. low stimulation; ‡ = p < 0.02 for all patients, comparing open to baseline.

**Efficacy of the Technique**

Five patients were randomly assigned to the high-current stimulation regimen and four patients to the low-current stimulation group. No significant difference was found in baseline seizure frequency between the two groups. During the blinded period, seizure frequency data were collected for 12 to 17 weeks. The high-current stimulation group had a median reduction in weekly seizure frequency of 27.73%, while the low-current stimulation group showed a median increase of 6.30% compared to the baseline period. This difference approached statistical significance (0.05 < p < 0.10).

During the unblinded stimulation period, the length of follow-up review was extended by 6 to 26 weeks. The group of patients initially treated with high stimulation were found to have a median reduction in weekly seizure frequency of 36.24% compared to baseline and a median reduction of 14.33% compared to the blinded period. The patients initially assigned to the low-current stimulation group had a median reduction of 16.32% compared to baseline and a median reduction of 25.43% compared to the blinded period. Combining the entire population and comparing the unblinded period to baseline, there was significant reduction in seizure frequency (p < 0.02). The data are summarized in Table 2.

At the conclusion of the open period, five of the nine patients reported that their seizures were consistently shorter in duration. Five of the nine patients consistently experienced termination of seizures upon magnet application by a family member. Three of the nine patients reported both shorter seizures and results from magnet activation.

**Discussion**

**Surgical Technique and Safety**

Early problems with electrode fracture seem to have been corrected by the redesign of the electrode with quadrifilar wire. Stability of the electrode on the nerve seems good with the spiral design of the contact carriers. The extra tethering spiral that is provided by the manufacturer does not seem necessary, and its use has been avoided in this group to minimize trauma to the vagus nerve. The addition of a third spiral that is not secured by suture does not seem likely to add more security than the spirals with the contacts when they are not secured by sutures.

The use of sutures to complete the circumferential envelopment of the nerve does seem to add to the risk of nerve injury as evidenced by the second patient in the series. The vocal-cord palsy may well have been due to inadequate room for postoperative nerve edema with the suture tails tied. These tails are no longer tied as part of the procedure; in fact, in the current version of the device, the suture tails have been shortened and are too short to tie together. In the subsequent patients, stability of the electrodes has been adequate without the extra spiral and without tying the suture tails.

The major concern with respect to vagus nerve injury is loss of function of the recurrent laryngeal branch. This may cause symptomatic difficulty with the voice. As the technique is currently performed, the level of risk of direct surgical injury to the nerve seems low. Prolonged implantation and stimulation thus far have not been found to be detrimental to laryngeal function. The electrical parameters employed are within ranges likely to be safe for chronic neural stimulation. Effects of stimulation on vocal-cord function may be monitored directly with laryngoscopy; further detailed studies using videostroboscopic techniques on more patients are underway.

The vagus nerve has widespread visceral efferent projections. In patients implanted thus far, no significant systemic effects have been noted. Only one patient had gastric complaints; the symptoms were easily managed and were not severe enough to warrant extensive investigation. No adverse cardiovascular reactions were encountered.

Intermittent vagal stimulation has been relatively safe and well tolerated during the follow-up period available in this group of patients. The minimal side effects of tingling sensations and brief voice abnormalities have not been distressing.

**Efficacy of the Procedure**

The results of the randomized double-blind comparison of high- and low-current stimulation regimens show that efficacy is dependent on stimulation parameters. Animal studies have suggested that the antiseizure effects result from C-fiber activation. The high-current stimulation parameters were selected to accomplish this goal. Comparison of data from the high- and low-current stimulation groups showed a trend toward improvement with high stimulation, whereas the low-current stimulation regimen produced no benefit; the difference between the two groups reached a marginal level of statistical significance. When patients with low-current stimulation were switched to receive a high level of stimulation, seizure frequency was improved to a degree similar to that seen in the patients initially treated with high-current stimulation.

During the open stimulation period, the patients in the high-current stimulation group showed further improvement in seizure frequency. This suggests a cu-
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The cumulative beneficial effect of protracted vagus nerve stimulation. Given the small number of patients involved, the results are particularly suggestive of the potential efficacy of the high-current stimulation regimen. Anatomical and electrophysiological studies provide a theoretical justification for investigation of vagus nerve stimulation for treatment of epilepsy. These clinical results suggest benefit in terms of reduction of seizure frequency; however, further study is necessary prior to drawing firm conclusions on the efficacy of the procedure. Cerebellar stimulation has been attempted in the past as a treatment for epilepsy, but objective evaluation found no benefit. Although the procedure seems promising, critical assessment of additional efficacy data will be necessary prior to concluding that vagus nerve stimulation is an effective adjunct in the treatment of epilepsy.

Disclosure

The authors have no financial interest in the hardware discussed in this report.

References


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