Implantation of a responsive neurostimulator device in patients with refractory epilepsy

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Object. The authors summarize one center’s experience with a novel device, the Responsive Neurostimulation (RNS) system, which is used to treat seizures, and they provide technical details regarding the implantation procedure.

Methods. The authors reviewed seizure detection, cortical stimulation, and clinical data obtained in 7 patients in whom the RNS system was implanted. Data pertaining to seizure alteration are provided for the first 4 implant-treated patients. The implantation procedure in the case of one patient with occipital lobe heterotopia is included.

Results. Based on patients’ seizure diaries, the implanted devices functioned at a high sensitivity for clinical seizure detection. Reductions in seizure frequency, based on their diaries and on clinic follow-up notes, ranged from 50 to 75%. No adverse stimulation-induced side effects were noted, and no hardware malfunctions requiring explantation occurred. Generator replacements for battery depletion were required at 11, 17, and 20 months in 3 patients. The implantation procedure was well tolerated, and postoperative hospital stays were short. A revision cranioplasty for a skull defect was performed in the index patient, whose case will be discussed in the most detail.

Conclusions. The results obtained in this small preliminary series demonstrate a safe implantation method for the responsive neurostimulation device. (DOI: 10.3171/FOC/2008/25/9/E12)

KEY WORDS • cortical stimulation • refractory epilepsy • Responsive Neurostimulation system

Abbreviations used in this paper: ECoG = electrocorticography; RNS = Responsive Neurostimulation; VNS = vagal nerve stimulation.
onset of a seizure as well as attempt to stop it, all in a closed-loop format.

Efforts toward creating an implantable device have been further spurred by studies of patients in whom subdural strips are in place. These have involved the use of external closed-loop detection and stimulation systems that are connected to the externalized leads of the subdural strips placed close to seizure foci. Kossoff and colleagues have described in detail an open multicenter trial of such an external closed-loop system in 27 individuals. In 41% of their patients, seizure frequency was suppressed and the time evolution of the remaining seizures was altered. There were no major side effects related to the stimulation protocols.

In the present article we describe our initial experience with 7 patients involved in ongoing multicenter Food and Drug Administration-approved clinical trials that are investigating the safety and efficacy of a novel implantable form of this Responsive Neurostimulation system (NeuroPace, Inc.) for the treatment of medically intractable seizures. We describe the clinical histories, surgical procedures, and early outcomes obtained in the first 4 patients from the safety arm of the trial at our center, as well as the specific operative procedure used for 1 of the implants. Clinical information is also presented on 3 of the subsequently treated patients participating in the trial. Efficacy data on the safety arm of the multicenter trial have been presented in abstract form.

Responsive Neurostimulation Device and Implantation

Device Description

The implantable RNS system is a programmable, responsive system designed to treat patients with refractory epilepsy. Subdural strip electrodes and depth electrodes can be connected to the unit, which has 2 active ports both of which can sense or stimulate. The device can be applied percutaneously across the scalp, and both real-time and stored ECoG readouts can be obtained. Programming of the device is performed percutaneously with a telemetry wand; both stored and real-time ECoG data can be downloaded from the device. The wand can also program the pulse generator stimulation parameters.

Steps involved in the proprietary seizure detection process include bandwidth filtering and analog-to-digital conversion of the incoming signal. The digitized signal is then processed using up to 3 different algorithms to maximize the chance of seizure detection. This can be performed concurrently on the 2 input channels. The device carries a 32-minute-duration memory buffer for the recorded ECoG, which can be parsed into several stored ECoG segments. These are overwritten as detected events continue.

The detection calculations have been given the names half-wave, line length, and area determination. In a simplified view, the half-wave calculation acts as a pattern-recognition routine or as a means of detecting a specific onset frequency. It calculates the amplitude and duration of half-waves, which are defined as the signal segments between preset maximal and minimal values. The line length determination calculates a line-length measure over a small recent time window and compares this with the line length or depth electrodes, and the wireless communication system. This generator fits into a holder frame (ferrule), which has a curvature appropriate for the skull surface. A partial- or full-thickness craniectomy is fashioned during the implantation procedure to hold the device and reduce the profile under the scalp.

The subdural strip electrodes are quadripolar in format and consist of 3.175-mm-diameter circular electrodes with interelectrode spacings of 10 mm. The depth electrodes come in a quadripolar cylindrical format, with 3.5- and 10-mm interelectrode spacings available. Programming of the device is performed percutaneously with a telemetry wand; both stored and real-time ECoG data can be downloaded from the device. The device itself is approximately 4 cm wide, 6 cm long, and 7 mm thick (Fig. 1). It houses the seizure detection electronics, a battery, the connection ports for either subdural electrodes

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derived from an ongoing summed value. The area determination calculation similarly compares a windowed value of the area under the detection signal with a long-term trend area measure. Both the line length and area determination calculations try to pull out the seizure onset signal from the underlying background activity. Any combination of these tools can be used to optimize seizure detection for a given patient.

The stimulation pulse format, which can be applied to either of the attached electrodes, consists of biphasic square waves with widths ranging from 40 to 1000 µsec. Pulse frequency can range from 1 to 333 Hz, and the current intensity can range from 0.5 to 12 mA. The electrodes or generator housing can be operated as either the anode or cathode. The stimulation is limited by an electrode charge density limit to avoid damage to the brain parenchyma. A limit of 5 therapies can be applied per detection episode, and each therapy can consist of up to 2 bursts. These bursts can have different stimulation characteristics, such as frequency, pulse width, burst duration, and montage.

**Surgical Technique**

For device placement, general endotracheal anesthesia is induced, and the patient is placed in a Mayfield skull clamp. Frequently, these patients have had prior craniotomies for resection or invasive monitoring, and this variable often dictates skin incision placement. For patients who have not had prior neurosurgical procedures, a partial-thickness craniectomy can be fashioned using a high-speed drill to match the holding ferrule thickness, which is then bolted to the skull with microscrews for fixation. The subdural electrodes or depth electrode enter the brain via bur holes or by taking advantage of previous craniotomy/craniectomy sites (Fig. 2). A frameless stereotactic system (BrainLab AG) is used if a depth electrode will be passed into the presumed seizure focus, and the patients undergo preoperative MR imaging of the brain for registration and planning (Fig. 3). Postoperatively, patients are monitored in the neurointensive care unit overnight, and they are generally mobilized on Day 2. Postoperative imaging studies include skull radiographs and head CT scans. The safety profile of the NeuroPace device in an MR imaging environment is unknown, and currently MR imaging is contraindicated in patients in whom the RNS system has been implanted.

**Trial Description**

The 7 patients described in this report are all participants in multicenter randomized double-blinded, placebo-controlled trials, which have been Food and Drug Administration approved; the first 4 patients were enrolled in a feasibility study to demonstrate the safety of the NeuroPace stimulation system; the last 3 patients were enrolled in a pivotal (Phase III) study to demonstrate the safety and efficacy of the NeuroPace stimulation system. In the feasibility study, the first 4 patients at each center, including the first 4 described here, were unblinded and were used simply to test and develop the infrastructure for the implantation technique. After this set of 4 patients, all subsequent participants including all participants in the pivotal study will have the device implanted, but they are then randomized to having the device turned on or off (the sham-stimulation arm). Subsequent examining neurologists are also blinded to the status of the stimulator. Follow-up clinical assessments include seizure frequency and intensity assays, as well as neuropsychiatric evaluations. After a 3-month evaluation period, all patients enter an open-label period that continues to 2 years postimplantation. During the open-label period, the stimulation-off group is then eligible to have their stimulators turned on if they wish.

For the pivotal study, eligibility requirements include ages between 18 and 70 years, with both sexes represented. The patients must suffer from disabling complex partial seizures or motor simple partial seizures that may or may not generalize. At least 2 antiseizure medications must have previously failed, and the patients must have a minimum average of at least 3 seizures every 28 days for 3 serial 28-day intervals (an average of at least 4 seizures per 28 days for 3 consecutive 28-day periods were required for enrollment in the feasibility study). Individuals, however, must have no more than 2 clearly discernible epileptogenic foci derived from their ECoG workup. Patients in whom a VNS is already in place must have the device turned off for at least 3 months prior to enrollment in the clinical trials, and they must have the VNS generator removed before or at the time of the RNS surgery.

**Clinical Usage**

**General Patient Characteristics**

The 7 patients ranged in age from 20 to 48 years. They all had medically intractable epilepsy and met the study...
Table 1 describes the patients’ characteristics. The seizure frequency reductions for the first 4 patients underscore the range of reductions with data gathered on a monthly basis. Two of the patients (Cases 3 and 5) had previously undergone temporal lobectomies for seizure control, one 24 years before RNS implantation and the other 14 years before RNS implantation. Two of the patients (Cases 2 and 4) had nonlesional frontal lobe epilepsy and were never deemed candidates for surgery. One of the patients (Case 1) had an area of cortical dysplasia involving eloquent cortex. One patient (Case 6) suffered postpartum eclampsia with multiple generalized tonic-clonic seizures, and eventually developed left mesial temporal sclerosis but depended heavily on this lobe for memory. One patient (Case 7) had undergone a left supplementary motor area resection 3 years before RNS implantation.

Five of the patients had undergone previous monitoring with subdural electrodes, and all of the patients had undergone video-EEG monitoring. All patients underwent preoperative cognitive testing that consisted of several broad inventories including the Wide Range Achievement Test, Wechsler Adult Intelligence Scale, the Boston naming test, and several other diagnostic tools. Several of the patients had undergone Wada testing in the past associated with their previous surgeries. Imaging studies included MR imaging and ictal/interictal PET when deemed necessary.

All of the patients have been followed up every 2 weeks to once a month in clinic for at least 12 months (except for the 2 most recently implanted patients), and were brought into clinic early with any abrupt change in seizure intensity or frequency. It has been possible to record seizures in all 7 patients. There have been frequent changes in the detection and stimulation parameters to increase the efficacy of the device. In all cases the detection sensitivity is very high for clinical events based on patient seizure reporting. Subclinical epileptiform activity also frequently causes detections. The patients are also questioned about unusual sensations correlated with the stimulation periods.

Illustrative Case

Case 1

This 38-year-old woman first presented to a pediatric neurologist at the age of 5 years with the symptoms of poor visual tracking and problems with attending to external stimuli. Imaging studies at that time, which were unavailable for present review, revealed a left frontal lesion, and the patient subsequently underwent a brain biopsy with no conclusive diagnosis. She was treated for a short period with phenobarbital, but this was stopped when the final pathology was read as inconclusive. Subsequently, at age 15 years, the patient began to have complex partial seizures, 2–3 per day for 1–2 days per month. The episodes were not preceded by an aura, and typically lasted 30–60 seconds. When the patient was age of 34 years, MR imaging revealed a small left hemisphere, with possible left occipital hypoplasia, and a large region of periventricular heterotopia, which included the left lateral ventricle as well as the occipital and temporal horns. There was also a region of cortical heterotopia within the angular gyrus. Mesial temporal sclerosis was not demonstrated in these studies.

Subdural grid recordings obtained at outside institution when the patient was 37 years of age revealed the seizures to be coming from the region of the angular gyrus on the left and involved cortical speech areas, ruling out a role for resection. Multiple medications failed (11 total), and the seizures were poorly controlled just before her RNS implantation with carbamazepine 800 mg (twice daily orally) and tiagabine 16 mg every morning and 12 mg every evening. The patient’s previous left temporal parietal craniotomy was reopened for the RNS implantation, and using frameless stereotaxy, a depth electrode was placed just lateral to the region of periventricular nodularity. Two small (1 × 4) subdural grids were also placed, 1 over the temporal pole and 1 posteriorly over the angular gyrus (the region of cortical heterotopia) (Fig. 4). The patient did well postoperatively from a seizure standpoint, achieving stable RNS settings by 17 months postoperatively. Overall seizure frequency reduction was 75%. The patient’s postoperative antiepileptic dosage also stabilized (oral carbamazepine 800 mg twice daily) and tiagabine 16 mg every morning and 12 mg every evening.

The patient re-presented at approximately 1 year postoperatively complaining of chronic headaches in the region of the cranioplasty. The bone flap exhibited partial resorption resulting in a noticeable skull defect. The patient underwent cranioplasty revision at 22 months after her initial implantation. The old bone flap was removed as was the old generator, and a prefashioned polyetheretherketone cranioplasty was placed. The cranioplasty was fashioned with...
the help of computer-aided design from CT-derived data\textsuperscript{13,25} (Synthes, Inc.). This implant was also designed to work in conjunction with the RNS ferrule. A biologically stable material, polyetheretherketone is commonly used as the spacer material in anterior cervical discectomy and fusion procedures.\textsuperscript{27} This revision cranioplasty resulted in complete abolition of her headaches by the 2-month postoperative visit.

Conclusions

The results obtained in this small series have demonstrated preliminary safety and toleration data for a new implantable responsive stimulation system. Other centers have also found the procedure for fashioning the craniectomy to house the NeuroPace device to be safe and easily reproducible.\textsuperscript{11} The greatest hospital stay duration in the present series was 3 days, and no postoperative infections have been documented to date. In these patients there have been no intraparenchymal hematomas due to depth electrode placement, although this clearly remains a future risk.

Side effects from the actual stimulation have been minimal, with the patients in Case 1 and 2 reporting a transient buzzing sensation with the onset of stimulation (this was due to a component of the first-generation device that has since been disabled). Follow-up visits have been at monthly intervals and frequent device parameter changes have been made, including alterations in the blend of the 3 detection algorithms, changes to the stimulation amplitude and frequency, and montage, including, for example, reversal of the device housing polarity. Frequent changes are made over a time course of approximately 3–4 months, after which most of the patients remain fairly stable in the numbers and intensities of seizures. The device is recording clinically apparent seizures based on patient diaries with high accuracy. This parameter will be further quantified when the final results of the clinical trial are released. The patient in Case 4 had an episode involving a sudden increase in seizure frequency when the stimulator was not achieving sufficient charge; this was alleviated with a drop in stimulation frequency. Generator replacements were performed in the patients in Cases 1, 2, and 4 at 20, 17, and 11 months postoperatively, respectively, due to battery depletion.

An effort is currently under way to determine how best to optimize the cortical stimulation parameters to most effectively stop epileptic activity, which might help to reduce the time to stable seizure control with a stimulation system.\textsuperscript{12} This involves computational modeling of a large neuronal array that exhibits self-sustaining excitatory activity. The model can incorporate external stimulation and may prove useful as a guide in choosing the stimulation frequency, amplitude, and shape of the stimulation electrode. Additionally, there are no effective methods for choosing recording and stimulation sites for the varied population studied. Often placement is guided by previous invasive monitoring, and the 2 most likely ictal origins are chosen for either overlying strip placement or depth electrode placement. It might turn out that in some patients with rapid ictal spread, detection from the opposite hemisphere from ictal onset might be most effective. This is an area of active research.

The seizure reduction frequencies exhibited by the first 4 patients are promising, but no conclusions regarding efficacy can be drawn yet. Possibly the best measure of efficacy will come from the device’s ECoG recording itself. If
downloaded successively every month. ECoG recordings of several years in extent can be derived over the lifetime of the implant. Checks of ictal detection and stimulation efficacy can be accurately derived from this. More on this will be made available with the results of the ongoing multicenter trial.  

Disclosure

Dr. Kossoff received salary support from NeuroPace, Inc. The authors report that no other author maintains competing interests in NeuroPace, Inc.

References

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