Closed-Loop Stimulation in the Control of Focal Epilepsy of Insular Origin

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Key Words

Insular epilepsy · Depth electrode localization · Responsive neurostimulator

Abstract

Background: Previous studies have shown that closed-loop or responsive neurostimulation can abort induced or spontaneous epileptiform discharges. **Objective:** To assess the effectiveness of a programmable cranially implanted closed-loop neurostimulation system in the control of seizures originating from an area relatively inaccessible by open craniotomy. **Method:** A patient with drug-resistant partial epilepsy had previously undergone open resection of the left frontal opercular cortex and the underlying insular area. Although subdural-depth electrode ictal recordings had been nonlocalizing, depth electrode insular stimulation had produced the patient's habitual aura. Postoperatively, there was a sustained 50% reduction in seizure frequency. The residual seizures were identical to the preoperative seizures. Repeat depth electrode monitoring revealed that the ictal focus was immediately posterior to the previously resected insular area. A closed-loop cranial internal pulse generator system including left anterior insular and posterior orbitofrontal depth electrodes was implanted. **Result:** There was an ad-

ditional 60% reduction of seizures. **Conclusion:** Preliminary observation indicates that responsive neurostimulation may be an effective alternative to higher-risk resective epilepsy surgery.

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Introduction

Uncontrolled open-loop stimulation studies in adults with medically intractable epilepsy have shown varying control of seizures with stimulation of the cerebellar cortex [1], cerebellar dentate nucleus [2], anterior thalamic nucleus [3], centromedian thalamic nucleus [4], caudate head [2], hippocampus [2, 5], and subthalamic nucleus [6]. The only controlled studies involved the cerebellar cortex [7] and thalamic centromedian nucleus stimulation [8], and neither showed that stimulation had a significant effect on clinical seizures. However, the vagus nerve stimulator, which provides scheduled cyclical open-loop stimulation to the left vagus nerve, has been shown to reduce seizures in several controlled clinical trials [9].

One study showed that stimulation-induced cortical afterdischarges could be terminated by applying respon-

sive stimulation [10]. The authors entertained the possibility that an implanted closed-loop device could both detect and terminate epileptiform activity. Subsequent clinical trials assessed patient response to closed-loop systems that provided stimulation contingent on seizure detection [11–13]. One multicenter study utilized an external responsive device that could be programmed to detect and deliver therapeutic stimulation to areas generating epileptiform activity. This study provided preliminary information that responsive stimulation was well tolerated and that some epileptiform discharges could be altered [12]. Based on these results, clinical trials with an implantable device that provided responsive neurostimulation (the RNS™ System) were begun.

Subjects included in the RNS System clinical investigations have been adults with medically intractable disabling partial-onset seizures localized to 1 or 2 epileptic foci. Safety and efficacy were examined in a recently completed pivotal clinical investigation [unpubl. data]. Experience with 1 subject participating in a previously completed multicenter feasibility clinical investigation [27] is provided here and suggests that the RNS System might be a useful treatment approach for patients whose seizure focus is within an area relatively difficult to access with open craniotomy.

Utilizing stereotactic depth electrodes, we identified a patient with residual postoperative seizures originating in the left anterior superior insular area. Because of the risk to language function when approaching the anterior insula in the language-dominant hemisphere [14, 15], and because stereotactic depth electrodes could be safely implanted in the insular area [16], we presented the surgical option of implanting a closed-loop stimulation device to this patient.

Materials and Methods

Candidacy, surgical technique, and the RNS System have been previously described [17]. As with other candidates for RNS System implantation, the current patient had focal seizures that had not responded adequately to multiple antiepileptic medications over an extended period. Also, as with other candidates, the present patient had had at least 4 disabling seizures per month over a 3-month period before final consideration for implantation.

The neurostimulator system consists of 3 components: (1) an internal pulse generator which contains electronics, a telemetry coil, a battery, and a connector port that accommodates one or two 4-contact electrodes; (2) quadripolar stereotactic depth electrodes with 1.27-mm diameter by 1.5-mm-long platinum-iridium contacts spaced 3.5 or 10 mm apart, and total lengths of 30 or 44 cm, and (3) a handheld computer with specialized programming

software and a telemetry wand that communicates with the internal pulse generator.

The RNS system continuously analyzes electrocorticography and triggers electrical stimulation when it detects specific characteristics programmed by the clinician as indicative of epileptiform activity. It also stores and can download diagnostic information that details detections and stimulations, including multi-channel stored electrocorticography. The neurostimulator system has a limited electrocorticography memory buffer. The number of electrocorticographies stored depends on the number of recording channels and the recording time selected. Typically, 2 bipolar recording channels are selected with a 60-second pretrigger and 30-second posttrigger duration, which allows 9 electrocorticographies to be stored. Any additional electrocorticographies overwrite the previous recordings. Electrocorticography storage can be triggered by any of several electrographic events, including seizure onset.

The neurostimulator system utilizes any of 3 seizure detection tools (line length, area, and half-wave tools) operating on 1 or 2 detection channels. The line length and area tools compare the electrographic activity contained within a short-term sample time window to that contained within a longer-term trend window. When activity within the sample window exceeds the trend activity by a specified percentage, detection occurs. The line length tool is more commonly used to detect high-frequency, low-amplitude activity that diverges in amplitude little from the baseline electrographic amplitude, but has significant summed line length [18]. The area tool is more commonly used for slower rhythmic, higher amplitude epileptiform activity with large integrated areas. The half-wave tool measures half-waves of specified duration, amplitude, and frequency bandwidth [19]. When an epileptiform discharge meeting these criteria is detected, programmed therapeutic stimulation is delivered.

Therapeutic stimulation consists of charge-balanced biphasic pulses with amplitude programmable from 0.5 to 12 mA, pulse width programmable from 40 to 1,000 μ s, frequency programmable from 1 to 333 Hz, and pulse trains or bursts programmable from 10 to 5,000 ms. Any of the electrode contacts or the pulse generator housing may be programmed as anode or cathode. After a pulse train therapy has been delivered, a redetection algorithm determines if the epileptiform activity is still present. If so, up to 4 additional therapies may be delivered per episode. Also, each therapy may consist of 1 or 2 pulse trains. The parameters of each therapy and each pulse train may be the same or varied. The neurostimulator system has a built-in charge density limit that will allow no more than 25 μ C/cm²/phase charge density to be delivered.

Case Report

The patient was a 33-year-old male whose seizures began at the age of 12 years. These were characterized by an aura of epigastric tightening followed by extension at the right elbow, grasping with the left hand, then kicking with 1 or both legs and vocalization. The seizures lasted 5–10 s during which the patient remained conscious with intact speech comprehension. Multiple antiepileptic medications had failed to significantly affect seizure frequency and intensity.

Fig. 1. MRI shows the area of increased signal in the left frontal operculum (arrow).

Fig. 2. Arrow points to contact 2 of the insular depth electrode. In addition, a 6×8 left frontal convexity subdural electrode, a 1×8 left mesial frontal depth electrode, and two 1×4 mesial frontal and two orbitofrontal 1×4 subdural strip electrodes were implanted.

Neurological examination was normal. Neuropsychological testing revealed a full-scale IQ score of 104, a verbal IQ score of 103 and a visuospatial IQ score of 106. Delayed verbal memory score was 114, and visuospatial memory score was 103. Intracarotid sodium amytal (Wada) testing revealed left language dominance with object recall of 4 of 8 items after left injection and 8 of 8 items after right injection.

Video EEG monitoring showed interictal discharges at F3 and F4. Multiple ictal EEG recordings did not localize the seizure focus. Brain MRI showed increased T_2 signal in the subcortical white matter of the left frontal opercular area (fig. 1). SISCOM (subtraction ictal SPECT coregistered to MRI) showed increased isotope uptake in the left mesial frontal, left insulo-opercular, and right insular areas.

Subsequent continuous video EEG monitoring utilized stereotactic depth electrodes in left mesial frontal and insular areas, as well as subdural electrodes including a 6×8 left frontal convexity grid, and anterior and posterior left orbitofrontal and mesial frontal 1×4 strip electrodes (fig. 2). The insular electrode was included because the patient described an aura of epigastric tightening [20], and because of hypermotor activity (kicking) [21, 22]. There was no localized interictal activity at any of the electrode contacts and ictal recordings revealed diffuse nonlocalized attenuation. Subsequent extraoperative stimulation studies showed that stimulation at contact 2 of the left insular electrode (fig. 2) produced the patient's habitual epigastric aura. Stimulation at contact 3 produced a cephalic sensation and stimulation at contact 1 produced no phenomena. Intraoperative stimulation map-

ping at the time of electrode implantation had produced no naming errors, although left language dominance was noted on previous Wada testing.

The patient returned to surgery. After removal of the electrodes, the left anterior frontal opercular cortex was resected to access the subjacent insula where stimulation had reproduced the patient's epigastric aura. This insular area was then resected (see sagittal reconstruction in fig. 3). Although language mapping of the more posterior frontal operculum (the area of subcortical increased T_2 signal) had not produced any language errors, this area was spared as recommended by Rasmussen [23]. Histopathologic examination of the opercular specimen revealed only gliosis. Histologic examination of the anterior insular tissue showed cortical dysplasia.

When the patient was re-evaluated 3 years later, his habitual seizure frequency had decreased by 50%. No epileptiform activity was discernible on interictal or ictal EEG. Subsequent magnetoencephalography showed multiple interictal epileptiform dipoles in the left anterior insular area (fig. 4). Stereotactic left orbitofrontal and anterior insular depth electrodes were placed to assess the possibility of additional epilepsy surgery. Multiple electrographic (and clinical) seizure onsets were recorded from contacts 4 and 5 of the insular electrode with rapid spread to contacts 6 and 7 of the orbitofrontal electrode (fig. 5). Further resection of the anterior insula through a transopercular approach was thought too risky to language function, so the patient was subsequently enrolled in the RNS System feasibility investigation.

Fig. 3. Post-depth electrode implant T₂-weighted MRI (later fused to stereotactic CT and T₁-weighted MRI obtained at the time of RNS implant). The depth electrode contacts are immediately posterior to the trajectories constructed for the RNS depth electrodes. The insular resection (arrow) is between the two trajectories on the sagittal reconstruction.

Fig. 4. Encircled white triangles represent interictal epileptiform magnetic dipoles located in the region of the left anterior superior insula.

Fig. 5. Anterior arrows point to contacts 6 and 7 of the left orbito-frontal depth electrode. Posterior arrows point to contacts 4 and 5 of the insular depth electrode.

Fig. 6. The anterior orbitofrontal and more posterior insular depth electrode contacts are numbered. The upper arrow points to the connector port of the RNS system, the middle arrow to the microprocessor, and the lower arrow to the battery.

Fig. 7. Example of aborted epileptiform activity recorded from channels 1 and 2 (recorded from insular depth electrode contacts 1–2 and 3–4, respectively). Label B indicates point of seizure detection. Beginning of therapeutic stimulation delivery is labeled Tr. Subsequent electrocorticography recording shows reversion to nonepileptiform pattern.

An MRI was obtained (fig. 3) prior to removal of the depth electrodes to document the exact site of the contacts involved in seizure localization. This study was later fused with stereotactic CT and contrast-enhanced magnetization-prepared rapid gradient echo MRI scans at the time the RNS System neurostimulator and two 4-contact stereotactic depth electrodes (10-mm contact spacing) were implanted (fig. 6).

The RNS System neurostimulator utilized 2 seizure detection tools: the line length [18] and half-wave tools [17]. The line length tool employed a detection threshold of 112% of baseline line length. The half-wave tool employed an amplitude threshold of 5% of peak spike amplitude, half-wave duration threshold of 5% of maximum, and a frequency range of 15–42 Hz. Cathodal stimulation was de-

livered through contacts 1–4 of the insular electrode. Stimulation parameters were as follows: current = 8 mA, frequency = 20 Hz, pulse width = 120 μ s/phase and pulse train duration = 50 ms. Figure 7 shows an example of an epileptiform discharge that received stimulation and did not develop into an electrographic or clinical seizure. Since implantation of the RNS System neurostimulator and leads, the seizure frequency has been reduced by an additional 60% (median 18 seizures/month before implantation, median 7 seizures/month over the most recent 2 years) for a total of 80% seizure reduction since the initial resective surgery. Figure 8 shows in graphic format the decrease in seizure frequency over the nearly 4-year postoperative period.

Fig. 8. The bar graph shows the seizure frequency both before (preop) and after implantation of the RNS System.

Conclusions

Studies on the effect of electrical stimulation on induced cortical afterdischarges have shown that afterdischarges can be terminated sometimes [10], and that there may be optimal parameters for this [24]. External responsive neurostimulation studies have revealed that closed-loop stimulation can alter some spontaneously occurring electrographic seizure activity [11, 12, 25]. Early seizure detection and stimulation of multiple contacts in the immediate vicinity of the seizure focus appears to increase the likelihood that the epileptiform activity can be suppressed [24]. An implantable device, the RNS System, has been tested in multicenter controlled clinical trials as an adjunctive therapy for adults with medically intractable

disabling partial seizures in order to assess safety and to determine efficacy [26]. The present report suggests that this closed-loop system may be effective in controlling medically intractable focal epilepsy that originates in areas that are relatively difficult to access with resective surgery.

Intractable focal epilepsy of insular origin may be more common than originally thought. It has been suggested that as many as 10% of seizures thought to be of mesial temporal origin may originate from the insula [20]. Since resection of such foci has inherent dangers, some have suggested stereotactic radiofrequency lesioning as an alternative [20]. Based on our initial experience with the currently reported patient, closed-loop cortical stimulation may prove to be a reasonable alternative.

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