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SHORT RESEARCH ARTICLE

Application of RNS in refractory epilepsy: Targeting insula

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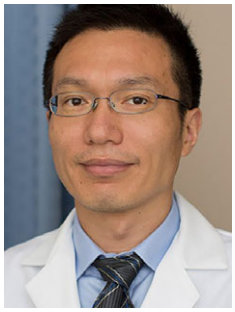

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Summary

Although responsive neurostimulation (RNS) is approved for treatment of resistant focal epilepsy in adults, little is known about response to treatment of specific cortical targets. We describe the experience of RNS targeting the insular lobe. We identified patients who had RNS implantation with at least one electrode within the insula between April 2014 and October 2015. We performed a retrospective review of preoperative clinical features, imaging, electrocardiogram (EEG), intraoperative electrocorticography (ECoG), and postoperative seizure outcome. Eight patients with at least 6 months of postimplant follow-up were identified. Ictal localization was inconclusive with MRI or scalp EEG findings. Intracranial EEG monitoring or intraoperative ECoG demonstrated clear ictal onsets and/or frequent interictal discharges in the insula. Four patients demonstrated overall 50–75% reduction in seizure frequency. Two patients did not show appreciable seizure improvement. One patient has experienced a 75% reduction of seizure frequency, and another is nearly seizure free postoperatively. There were no reported direct complications of insular RNS electrode placement or stimulation, though two patients had postoperative complications thought to be related to craniotomy (hydrocephalus and late infection). Our study suggests that insular RNS electrode placement in selected patients is relatively safe and that RNS treatment may benefit selected patients with insular epilepsy.

KEY WORDS: **Insula, Epilepsy, Responsive neurostimulator, RNS, Seizure outcome.**

Despite multiple antiepileptic drugs (AEDs), nearly one-third of patients still suffer from refractory epilepsy.[1] Responsive neurostimulation (RNS) delivers electrical stimulation in response to recorded electrographic seizures in a real-time manner. It is FDA-approved as an adjunctive therapy for adult partial-onset seizures with frequent disabling seizures and no more than two seizure foci.[2] Current studies show an overall 38% seizure reduction by a 12-week blinded follow-up. By the 1- and 2-year follow-up, there is a 44% and 53% seizure reduction, respectively.[2–4] Despite the proved overall benefit, the efficacy of neurostimulation relative to different epileptogenic foci (e.g., temporal and extratemporal) is unknown.

Failure to recognize insular seizures may account for seizure recurrence after temporal or frontal resection surgery.[5,6] Insular lobe resection is difficult because of the complicated accessibility and close proximity to eloquent areas. However, the insula may be accessed through a depth electrode, making patients with epilepsy originating from the insular lobe excellent RNS candidates.

Previously, one case report described the application of RNS targeting the insular lobe in a single patient.[7] However, relevant clinical information, including presurgical work-up, optimal stimulation parameters, and postoperative seizure outcome, is still poorly understood. In addition, postimplantation medication adjustments have not been discussed. We report a case series of RNS application targeting the insular cortex at a single level IV comprehensive

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epilepsy center. Our early experience may give insight into these questions.

Methods

Patient identification and characteristics

From our patient database, we identified patients who had undergone RNS placement with at least one electrode placed in the insula between June 2014 and October 2015 at the New York University (NYU) Langone Comprehensive Epilepsy Center. All patients had inpatient scalp video electroencephalograph monitoring (vEEG), a brain MRI, and neuropsychological assessment. Invasive monitoring with subdural grid and depth electrodes was performed in selected patients, depending on clinical indication. All patients were discussed in the multidisciplinary epilepsy conference to reach consensus before proceeding with the surgery. Intraoperative electrocorticography (ECoG) was done in all patients to guide optimal RNS electrode placement. Two patients had vagal nerve stimulation (VNS) placement prior to RNS implantation, and VNS remained activated during RNS treatment.

Surgical procedures

All insula RNS cases involved frameless stereotaxy (BrainLab) that specifically targeted the insula using RNS depth electrodes in a trajectory along the posterior to anterior axis or the superior to inferior axis or some diagonal axis rather than an orthogonal approach using a custom depth electrode cannula system. In patients who had a historical frontal resection, the insula depth electrode was placed entering the brain from the resection margin of the frontal resection. Bone access involved craniotomy or burr hole depending upon the circumstances and requirements of the RNS procedure. Whenever possible, old incisions were used, which therefore constrained the approaches for insula coverage. Otherwise, a posterior-to-anterior trajectory via an occipital approach or a superior-to-inferior trajectory via a frontal paramedical burr hole was used. The standard RNS procedure included placement of combination of 3–4 depths and strips via craniotomy or burr hole as well as craniectomy for the ferrule and generator assembly. Two electrodes that demonstrated the most robust epileptiform discharges on intraoperative ECoG were chosen to connect with the generator. One depth electrode was targeted on the insula in this cohort. Postoperative CT imaging was performed the day following the implant (Fig. S1A,B).

Outcome assessment

Patient baseline seizure frequency was obtained from multidisciplinary conference documents. Follow-up (6–20 months) seizure frequency was extracted from chart review. We report longitudinal outcome at 6-month intervals in this study. Auras and simple partial sensory seizures are not counted. A semiquantitative seizure frequency was adapted in this study as seizure frequency reduction of more than 75%, 50–75%, <50%, and no appreciated improvement.

Results

Demographic and clinical parameters

Eight patients (3 female, 5 male) were identified. The mean age at operation was 24 years (range 18–32). Five patients had previous resective surgery, with resection sites within the frontal, temporal, or insular lobes. Two patients had multiple subpial transections (MST), and 1 patient had an anterior corpus callosotomy in addition to resective surgery (Table 1).

Electrophysiological and image findings

All patients had at least one scalp vEEG recording. One patient's vEEG showed a focal seizure onset over the temporal region. Other patients demonstrated a nonlocalizable seizure onset, with diffuse, bisynchronous or unilateral broad seizure features (Table 1).

Six patients had intracranial EEG (IEEG) before the RNS implantation. Among them, 2 patients showed a definitive ictal onset within the insula. Three patients had additional independent or concurrent seizure foci from two different lobes (insular in addition to parietal, occipital, or temporal lobe). One patient had a diffuse electrographic onset that involved the insula. Two patients did not have IEEG prior to RNS implantation because of elevated infection risk and adhesions from multiple prior intracranial surgeries. Intraoperative ECoG was applied, and robust spike discharges were noted in the insula in all patients (Table 1).

The initial brain MRI results are summarized in Table 1. For patients who had previous resective epilepsy surgery, recent MRI showed postoperative changes, and therefore original MRI images prior to the surgery were also reviewed. In this cohort, 3 patients had normal MRI studies. Other study results included mesial temporal sclerosis, frontal atrophy, and nonspecific fluid attenuated inversion recovery (FLAIR) signal changes (Table 1).

Postoperative complications

One patient, who also had a concurrent temporal resection at the time of RNS placement, had postoperative hydrocephalus that resolved after a ventriculoperitoneal shunt placement. One patient had an intracranial infection identified 1 year after implantation that resulted in device removal. One patient sustained damage to the device ferrule due to head trauma, requiring replacement and lead revision. There was no clinical or radiological evidence of intracranial hemorrhage associated with the insular electrodes. No other subjects had complications from device implantation.

Table 1. Demographic and clinical characteristics of patients

Patient	Age (years)	Sex	Prior epilepsy surgery	Initial image finding	IEEG ictal onset	Scalp EEG ictal onset	RNS electrode placement (lobe)
1	22	Female	N/A	Normal	Left insular	Bilateral	Left insular,
					Parietal	Multifocal/diffuse	Parietal
2	26	Female	N/A	Normal	Left insular	Left frontocentral	Left insular,
			Temporal,		Occipital	Temporal	Occipital
3	22	Male	Insula, MST	Normal	Left insular	Central dominant	Left insular,
			Frontal, MST			Right parasagittal	Lateral temporal
4	32	Male	Anterior corpus callosotomy	Not available	N/A	Centroparietal temporal,	Right insular, frontal
					Diffuse left		Left insular,
5	24	Male	Temporal, frontal	Not available	Hemispheric	Left hemispheric	Parietal
				Left mesial			Left insular,
6	22	Male	Temporal	Temporal sclerosis	Left insular	Left frontocentral	Lateral temporal
				FLAIR signal	Left insular		Left insular,
7	25	Female	N/A	Over left insula	Mesial temporal	Left temporal	Hippocampus
8	18	Male	Frontal, temporal	Left frontal atrophy	N/A[a]	Left hemisphere	Left insular, frontal

[a]Prior to temporal and fontal resection, previous IEEG showed frontal and temporal seizure onset.EEG, electroencephalogram; FLAIR, fluid attenuated inversion recovery; IEEG, intracranial EEG; MST, multiple subpial transection; N/A, not applicable; RNS, responsive neurostimulation.

Treatment and seizure outcome

One patient reported three seizures postoperatively, and the RNS stimulation was not turned on during the follow-up period (19 months). The remaining 7 patients had stimulation activated within 1–10 weeks postoperatively. Several seizure onset patterns were identified in RNS ECoG recording, including rhythmic theta activity (Patients 1 and 8), burst of low-amplitude beta activity (Patient 6), as well as rhythmic spikes of delta, theta, or alpha frequencies (Patients 3, 4, 5, and 7). Review of recorded ECoG demonstrated presumed seizure interruption by RNS pulse stimulation in the insular cortex before further spread with some seizures (Fig. S1C,D). The range of stimulation parameters used varied. By the last clinic visit, the therapeutic settings ranged from 0.5 to 3 mA (current), 160 ms (pulse width), 100 ms (burst duration), 0.5–1.5 $\mu C/cm^2$ (charge density), and 100–200 Hz (frequency). Attempts to increase stimulation intensity beyond 2.5–3.5 $\mu C/cm^2$ resulted in increases in interictal activity recorded on ECoG in some patients, and higher stimulation intensities were not used.

Patients used between two and five AEDs prior to RNS implantation. By the last follow-up, 3 patients had a new AED added (acetazolamide, perampanel, and clobazam). Four patients had withdrawn previous AEDs (primidone, eslicarbazepine, vigabatin, and zonisamide). Seven patients had a medication dose adjustment (increase or decrease) during the postoperative period.

Among 7 patients whose RNS were activated, 1 patient showed reduction of seizure frequency by 75% at clinic visits (last visit 20 months postoperative). Four patients demonstrated an overall 50–75% reduction of seizures (last visit 6–18 months, respectively). Two patients did not show seizure improvement after RNS implantation (last visit 8 and 16 months, respectively) (Table 2). Of the 5 patients who demonstrated ≥50% improvement, 1 also had an addition of new AEDs, and 2 patients had previous AED dose increases following RNS implantation.

Discussion

In this retrospective case series, we describe 8 patients who underwent implantation of the RNS system for refractory focal epilepsy that included an epileptogenic focus in the insular cortex. The follow-up duration was 6–20 months, and RNS devices were activated in 7 patients at the time of last follow-up. One patient had prolonged seizure freedom postoperatively, and therefore the RNS device has not been activated at the time of last observation. A double-blind, randomized control trial of RNS showed seizure reduction by ~38% in the treatment group during the pivotal phase of the clinical trial.[2] In this group, patients experienced a highly variable reduction in seizure frequency (no improvement to nearly seizure free). However, 4 out of 7 (57%) patients were RNS responders (more than 50% seizure reduction) by the last clinic visit. The responder rate

Table 2. Seizure outcome

Patient	6 months	12 months	18 months	Last visit (time)
1	>75%	>75%	>75%	>75% (at 20 months)
2[a]	Seizure free	Seizure free	>75%	>75% (at 19 months)
3	>75%	>50%	<50%	<50% (at 18 months)
4[b]	>50%	>75%	N/A	>75% (at 15 months)
5	No improvement	No improvement	N/A	No improvement (at 16 months)
6	>50%	N/A	N/A	>50% (at 8 months)
7	No improvement	N/A	N/A	No improvement (at 8 months)
8	>50%	N/A	N/A	>50% (at 6 months)

[a]RNS is not activated.
[b]RNS is removed after the last visit.
N/A, not applicable; RNS, responsive neurostimulation.

was 50% (2 of 4) among patients who had 15–20 months of follow-up. Early seizure termination by RNS treatment was recorded in RNS ECoG. However, seizures may be refractory to RNS therapy, which can be due to insufficient stimulation delivery; therefore, adjustment of therapeutic stimuli parameters should be emphasized at each clinic visit. These findings are overall comparable to results of a multicenter, prospective open label study of a heterogeneous group of patients who received RNS, which showed 44% and 55% overall responder rate at 12 and 24 months follow-up, respectively.[3] The comparable outcome between our cohort and previously studied patients with variable epileptogenic foci suggests that the benefit of RNS is possibly not directly related to implantation sites. However, further large-scale subgroup analysis by anatomy location (such as frontal, temporal, occipital) may further clarify this question.

Furthermore, our experience with 2 patients demonstrates that activation of both VNS and RNS is feasible and safe. VNS has been used as an adjunctive treatment for refractory epilepsy, and a number of patients may have had VNS implantation before they are referred to RNS evaluation.[8] In the pivotal study, VNS generators were explanted prior to RNS implantation.[2] In this cohort, 2 patients had a VNS device implanted that remained active throughout the course of RNS treatment (VNS temporarily inactivated perioperatively). No side effects were observed in those 2 patients.

Insular lesionectomy has achieved a satisfactory seizure outcome (79% ILAE 1–3 outcome) in previous reports.[9] However, resection of the insular lobe is technically challenging and infrequently performed because of the risk of injury of the nearby eloquent cortex and dense vessel along the Sylvian fissure. Furthermore, resective surgery is performed only for patients with a well-circumscribed structural lesion, and nonlesional cases are often excluded from the procedure.[9] Because of the unfavorable risk-to-benefit ratio, some patients with insular onset seizures may be better candidates for RNS than resective surgery.

Our case series has several limitations. The number of patients is small, and long-term follow-up data are lacking. The study includes a heterogeneous group of patients: 2 patients have seizures arising from the insula; while multilobar (insular plus temporal, parietal, or occipital lobe) or diffuse seizure onsets were identified in other patients. In addition, 6 patients had medication adjustment (either medication switches or dose adjustment) that may also have contributed to seizure reduction. One patient showed significant seizure frequency reduction 4 months after implantation, which temporally coincided with the addition of new AEDs (perampanel and acetazolamide). The benefit of AEDs should not be underestimated. A previous study of patients with drug refractory epilepsy has shown 14% (nearly 5% per year) obtained a 6-month terminal seizure remission with medication adjustments over the 3 years of follow-up.[10] In addition, seizure occurrence and remission may fluctuate during the natural course of drug-resistant epilepsy.[11] Nevertheless, from our experience, RNS implantation within the insula is feasible and may provide meaningful seizure reduction when the ictal onset zone is determined from invasive monitoring. This treatment option can be particularly applicable and should be considered for those nonlesional cases who are not optimal candidates for resective surgery.

Disclosure of Conflict of Interest

Dr. Friedman has received an honorarium for educational materials from Neuropace. He also receives salary support for consulting and clinical trial–related activities performed on behalf of the Epilepsy Study Consortium, a nonprofit organization. Dr. Friedman receives no personal income for these activities. NYU receives a fixed amount from the Epilepsy Study Consortium toward Dr. Friedman's salary. Within the past year, the Epilepsy Study Consortium received payments for research services performed by Dr. Friedman from Alexza Pharmaceuticals, Acorda, GW Pharma, Eisai Medical Research, Pfizer, Upsher Smith, and Zynerba. He has also served as a paid consultant for UCB and LivaNova as well as participated in advisory boards for GW Pharmaceuticals and Supernus. He receives research support from UCB, NINDS, CDC, and the Epilepsy Foundation. The remaining authors have no conflicts of interest. We confirm that we have read the

Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. (A) Postoperative skull X-ray scan showing cortical strip leads (temporal, frontal, parietal) and one insular depth electrode. (B) Reconstruction MRI showing the depth electrode in the insula. (C and D) One seizure originating from the insula (channel 2 insular contact 3–4) recorded by RNS.