Responsive Neurostimulation for epilepsy

One-third of patients with epilepsy continue to have seizures despite antiepileptic drugs. Some of these refractory patients may not be candidates for surgical resection primarily because the seizure onset zones (SOZs) involve both hemispheres or are located in eloquent areas

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Stimulation devices are considered in patients with drug-resistant epilepsy and who are not surgical candidates. Responsive neurostimulation (RNS) is a cortically based stimulator activated by electrocorticography (ECoG) patterns. Stimulation is applied directly to the seizure focus. The vagal nerve stimulator AspireSR 106 is also a responsive device that, in addition to basal stimulation, is activated by tachycardia. Deep brain stimulation of the anterior nucleus of the thalamus is used in Europe for intractable epilepsy and yields similar response rates to RNS using duty cycle stimulation. Chronic subthreshold cortical stimulation is an experimental form of constant, low-level stimulation applied to a seizure focus [1)].

Patients with medically refractory temporal lobe epilepsy (TLE) are candidates for neuromodulation procedures. While vagus nerve stimulation (VNS) was historically the procedure of choice for this condition, the responsive neurostimulation system (RNS) has come into favor for its more targeted approach.

Controlled clinical trials in adults with medically intractable focal seizures treated with the RNS® System demonstrate that closed-loop responsive neurostimulation to the seizure focus reduces the frequency of disabling seizures, is well tolerated and is acceptably safe. Seizure reductions begin with initiation of treatment and continue over time, reaching median reductions of 75% after 9 years of treatment. Treatment with responsive cortical stimulation is also associated with improvement in quality of life and cognitive function related to the functional area being treated. In addition, the RNS System's chronic ambulatory electrocorticographic monitoring provides unprecedented insight into each patient's disease management, and into the study of epilepsy itself, in ways that may enhance the treatment of epilepsy in the future [2)].

This treatment was approved by the U.S. Food and Drug Administration (FDA) in 2013.

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Neuromodulation such as vagus nerve stimulation (VNS) and responsive neurostimulation (RNS) are safe and effective strategies for medically intractable epilepsy secondary to complex partial seizures, but researchers have yet to compare their efficacies.

Wang et al. retrospectively reviewed the records of all patients with TLE who underwent VNS or RNS placement at our institution from 2003 to 2018. The primary outcome was change in seizure frequency. Other outcomes included Engel score, change in anti-epileptic medications, and complications.

Twenty-three patients met inclusion criteria; 11 underwent VNS and 12 underwent RNS. At baseline, the 2 groups were statistically similar regarding age at surgery, epilepsy duration, and preoperative seizure frequency. At last follow-up, both groups displayed reduced seizure frequency (mean reduction of 46.3% for the VNS group and 58.1% for the RNS group, p = 0.49). Responder rate, Engel score, and change in medications were statistically similar between groups. Compared to 0.0% of the VNS group, 13.3% of the RNS group experienced infection requiring re-operation.

Despite their different mechanisms, VNS and RNS resulted in similar response rates for patients with TLE. We suggest that VNS should not be excluded as a treatment for patients with medically refractory TLE who are not candidates for resective or ablative procedures [3].

The goal of a study of Ellens et al. was to compare VNS and RNS efficacy at reducing seizure frequency and complication rates in subjects with medically intractable epilepsy secondary to complex partial seizures.

This is a retrospective chart review of 30 patients with medically intractable complex partial epilepsy, who underwent either VNS or RNS placement at a single institution between June 2012 and January 2016. There was a mean follow-up of 19 months. Seizure frequency reduction and complications were identified.

The median seizure frequency reduction was similar for VNS (66%) and RNS (58%). There was no major morbidity or mortality, and the frequency of minor complications was similar between VNS (15%) and RNS (18%).

They found that VNS and RNS reduced the median seizure frequency similarly with no difference in morbidity or mortality. Further prospective studies are warranted as VNS and RNS therapy improves over time [4].

Systematic reviews

Boon et al., conducted a systematic review on the currently available neurostimulation modalities primarily with regard to effectiveness and safety.

For vagus nerve stimulation (VNS), there is moderate-quality evidence for its effectiveness in adults with drug-resistant partial epilepsies. Moderate-to-low-quality evidence supports the efficacy and safety of deep brain stimulation (DBS) and responsive neurostimulation (RNS) in patients with DRE. There is moderate-to-very low-quality evidence that transcranial direct current stimulation (tDCS) is effective or well tolerated. For transcutaneous vagus nerve stimulation (tVNS), transcranial magnetic stimulation (TMS) and trigeminal nerve stimulation (TNS), there are insufficient data to support the

efficacy of any of these modalities for DRE. These treatment modalities, nevertheless, appear well tolerated, with no severe adverse events reported.

Head-to-head comparison of treatment modalities such as VNS, DBS and RNS across different epileptic syndromes are required to decide which treatment modality is the most effective for a given patient scenario. Such studies are challenging and it is unlikely that data will be available in the near future. Additional data collection on potentially promising noninvasive neurostimulation modalities like tVNS, TMS, TNS and tDCS is warranted to get a more precise estimate of their therapeutic benefit and long-term safety [5)].

Jobst BC, Kapur R, Barkley GL, Bazil CW, Berg MJ, Bergey GK, Boggs JG, Cash SS, Cole AJ, Duchowny MS, Duckrow RB, Edwards JC, Eisenschenk S, Fessler AJ, Fountain NB, Geller EB, Goldman AM, Goodman RR, Gross RE, Gwinn RP, Heck C, Herekar AA, Hirsch LJ, King-Stephens D, Labar DR, Marsh WR, Meador KJ, Miller I, Mizrahi EM, Murro AM, Nair DR, Noe KH, Olejniczak PW, Park YD, Rutecki P, Salanova V, Sheth RD, Skidmore C, Smith MC, Spencer DC, Srinivasan S, Tatum W, Van Ness P, Vossler DG, Wharen RE Jr, Worrell GA, Yoshor D, Zimmerman RS, Skarpaas TL, Morrell MJ. Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas. Epilepsia. 2017 Jun;58(6):1005-1014. doi: 10.1111/epi.13739. Epub 2017 Apr 7. PubMed PMID: 28387951.

Case series

performed a prospective single-center study of consecutive refractory epilepsy patients who underwent RNS system implantation in the anterior (ANT) and centromedian (CM) thalamic nuclei from September 2015 to December 2020. Patients were followed postoperatively to evaluate seizure freedom and complications.

Results: Twenty-three patients underwent placement of 36 RNS thalamic leads (CM = 27 leads, ANT = 9 leads). Mean age at implant was 18.8 ± 11.2 years (range 7.8-62 years-old). Two patients (8.7%) developed infections: 1 improved with antibiotic treatments alone, and 1 required removal with eventual replacement of the system to recover the therapeutic benefit. Mean time from RNS implantation to last follow-up was 22.3 months. Based on overall reduction of seizure frequency, 2 patients (8.7%) had no- to <25% improvement, 6 patients (26.1%) had 25-49% improvement, 14 patients (60.9%) had 50-99% improvement, and 1 patient (4.3%) became seizure-free. All patients reported significant improvement in seizure duration and severity, and 17 patients (74%) reported improved post-ictal state. There was a trend for subjects with SOZs located in the temporal lobe to achieve better outcomes after thalamic RNS compared to those with extratemporal SOZs. Of note, seizure etiology was syndromic in 12 cases (52.2%), and 7 patients (30.4%) had undergone resection/disconnection surgery prior to thalamic RNS therapy.

Conclusion: Thalamic RNS achieved ≥50% seizure control in ~65% of patients. Infections were the most common complication. This therapeutic modality may be particularly useful for patients affected by aggressive epilepsy syndromes since a young age, those whose seizure foci are located in the mesial temporal lobe, and those who have failed prior surgical interventions [6)].

The pulvinar has remained largely unstudied as a neurostimulation target to treat refractory epilepsy.

Because the pulvinar has connections with the posterior quadrant, neurostimulation may be effective if applied to seizures originating in this area. Burdette et al. performed a retrospective chart review of patients with regional neocortical epilepsy onsets in the posterior quadrant treated with Responsive neurostimulation. Demographics, epilepsy history, clinical seizure frequencies, and neuropsychological testing results were obtained from the chart. Electrocorticogram (ECoG) records stored by the RNS System were reviewed to evaluate electrographic seizure onset patterns. The patients were followed for 10, 12.5, and 15 months. All patients were responders (≥50% seizure reduction), and two of the three patients experienced a ≥90% reduction in seizures at the last follow-up. Pre- and postsurgical neuropsychological evaluations were compared for two of the patients, and there was no evidence of cognitive decline found in either patient. Interestingly, mild cognitive improvements were reported. The third patient had only postimplant neuropsychological testing data available. Findings for this patient suggested executive dysfunction that was present prior to the RNS System which did not worsen with surgery. A visual inspection of ECoGs revealed near-simultaneous seizure onsets in neocortical and pulvinar leads in two patients. Seizure onsets in the third patient were more variable. This is the first published report of brain-responsive neurostimulation targeting the pulvinar to treat refractory regional onset epilepsy of posterior quadrant origin [7) 8)].

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