Implant Short Circuits Some Epileptic Seizures

VITALS

Major Findings: Seizures declined by a mean of 29% during active stimulation with the device over the first 12 weeks, compared with a 14% reduction during sham activation.

Source of Data: Multicenter, randomized, sham-controlled clinical trial of 191 patients with medically intractable partial onset seizures. ClinicalTrials.gov identifier NCT00264810.

Disclosures: Dr. Morrell is the chief medical officer of NeuroPace, which developed the system and funded the trial.

BY DIANA MAHONEY

BOSTON — Patients with treatment-resistant epilepsy can significantly reduce their frequency of seizures with the use of an implantable device that detects pre-seizure electrical activity and preemptively aborts seizures, the results of a multicenter randomized controlled trial suggest.

In 191 patients with medically intractable partial onset seizures who were implanted with the neurostimulator, seizures declined by a mean of 29% during active stimulation with the device, compared with a 14% reduction during sham activation, Dr. Martha J. Morrell reported at the annual meeting of the American Epilepsy Society.

In the later, open-label phase of the study in which all of the patients received the active stimulation, nearly half of the 171 patients for whom 12 weeks of data were available experienced at least a 50% reduction in seizure frequency relative to baseline, said Dr. Morrell, clinical professor of neurology at Stanford (Calif.) University and chief medical officer of NeuroPace, developer of the Responsive Neurostimulator System (RNS).

The cranially implanted RNS device differs from conventional, "open loop" brain stimulation technologies that involve the scheduled delivery of electrical stimulation to specific brain regions independent of brain activity.

The responsive neurostimulation system comprises electrodes that are surgically implanted in epileptic regions of the brain and connected to the computerized, battery-powered neurostimulator, which is embedded in the patient's skull. The device is programmed to detect and disrupt significant electrical events.

"The programming is done wirelessly by the physician via a laptop computer," Dr. Morrell said. "It's highly modifiable in that the physician can view the patient's electrocorticographic activity in real-time and change the [signal-detection] criteria at any time based on individual patient characteristics."

Because the neurostimulation occurs in response to aberrant electrical activity in the patient's brain, fewer electrical impulses are being delivered to the brain than would occur with continuous stimulation. This in turn diminishes the possibility of treatment-related adverse events, Dr. Morrell explained.

In an initial feasibility study of 65 patients, the responsive neurostimulation system demonstrated excellent safety, tolerability, and preliminary evidence of efficacy, Dr. Morrell said.

The preliminary efficacy evidence from that study showed that a minimum 50% reduction in seizure frequency was experienced by 43% of the patients with complex partial seizures and 35% of those with total disabling seizures (Neurotherapeutics 2008;5:68-74).

In the double-blind pivotal trial, the 191 patients were randomized to active or sham therapy. All of the patients were 18-70 years of age (median age 35 years), and all had partial onset epilepsy localized to one or two foci and had failed at least two antiepileptic medications.

The patients were taking an average of three antiepileptic medications to attempt seizure control, and approximately 34% of the patients had been treated previously with vagus nerve stimulation, 33% had prior surgical resection, and 16% had been treated with both.

Of the 191 patients implanted with the responsive neurostimulator device, 50% had mesial temporal seizure onset, 42% had neocortical seizure onset, and 8% had both, Dr. Morrell said in a press briefing at the meeting.

The trial consisted of an initial 12-week period prior to system implantation during which baseline seizure activity was collected, followed by a 12-week blinded period when participants were randomly assigned to have the responsive stimulation activated or left inactive, she said.

At each of the 31 trial sites, the patients and one neurologist were blinded to the stimulation status, while a separate neurologist programmed the devices to maintain the study blinding. The responsive stimulation was optimized in the treatment over the next four weeks, followed by 84 days of data collection, Dr. Morrell said.

The responsive neurostimulation system has not yet received Food and Drug Administration approval, but NeuroPace plans to submit a premarket approval application early this year, she said. ■

MY TAKE

Devices Likely to Improve Over Time

The development and use of stimulation devices for medically refractory epilepsy represents an altogether new approach when surgery is not possible and pharmacology is ineffective. Open loop devices that deliver electrical stimulation on a duty cycle include the vagal nerve stimulator (Cyberonics) and the thalamic deep brain stimulator (Medtronic).

DR. NOE

DR. DRAZKOWSKI

The Responsive Neurostimulator device (NeuroPace), the first closed loop stimulator, is distinctly different than the other devices. Once it is permanently implanted using depth or surface leads, the RNS device detects and analyzes EEG/electrocorticography on a continuous basis. The device is programmed to "recognize" an individual's unique ictal onset through various algorithms. Once the abnormal signal is detected, the device responds quickly to deliver a small electrical potential in an attempt to abort the abnormal EEG activity before it can spread and become a clinical seizure.

Results for both the randomized, blinded portion and long-term, open-label portion of the pivotal RNS showed statistically significant reductions in seizure frequency with acceptably low rates of complications. With time, device technology is likely to be refined and improved, both through technical advances and additional clinical data.

DR. KATHERINE NOE *and* DR. JOSEPH DRAZKOWSKI *are epilepsy specialists at the Mayo Clinic, Scottsdale, Ariz. They were both investigators in the RNS trial.*

Online Tool Could Streamline Surgical Referrals for Epilepsy

VITALS

Major Findings: Using a decision-support tool, nearly 21% of 2,646 clinical scenarios created from different combinations of patient-level factors were considered appropriate for evaluation for epilepsy surgery. None of the surgeries was rated as unnecessary.

Data Source: An expert panel's use of a decision-support tool.

Disclosures: The investigator had no relevant disclosures or conflicts of interest.

BY DIANA MAHONEY

BOSTON — An online decision-support tool may help to close the protracted gap between seizure onset and referral for surgery in patients with medically intractable epilepsy, based on results obtained by an expert panel.

The user-friendly tool is designed for use by clinicians who treat epilepsy patients but may not be epilepsy specialists, according to Dr. Nathalie Jetté, who developed the tool with her colleagues at the University of Calgary (Alta.)

The tool rates the appropriateness and necessity of referring individual patients for a surgery evaluation based on factors such as age, epilepsy duration, seizure type, frequency and severity of seizures, the number of adequate epilepsy drug trials, and EEG and MRI findings, Dr. Jetté said at the annual meeting of the American Epilepsy Society.

Despite surgical success rates as high as 90% for patients with medically intractable temporal lobe epilepsy, the average time between seizure onset and surgery for these patients is 9 years for children and 19 years for adults, according to Dr. Jetté.

Based on a literature review and on discussion during a face-to-face meeting, an expert panel rated clinical scenarios for their appropriateness for an epilepsy surgery evaluation, Dr. Jetté said.

"The scenarios were rated on a scale from 1 to 9, where 1 was the most inappropriate and 9 was the most appropriate. After extensive discussion, all of the scenarios were re-rated, and those that were appropriate for referral [rated a 7 or higher] were re-rated for necessity," she said.

For rating purposes, referral was considered a necessity if the presumed benefits exceeded the risks by a sufficient margin; if failing to refer the patient would be improper care; if there was a reasonable chance the referral would benefit the patient; and if the magnitude of the expected benefit "was not small," she said.

Of 2,646 clinical scenarios, nearly 21% received a rating of at least 7 and were considered appropriate for surgical referral. About 17% were considered uncertain for appropriateness because they were rated 4-6, and nearly 62% were deemed inappropriate because they were rated 1-3, Dr. Jetté said.

In practice, a patient who failed one antiepileptic drug (AED) would be inappropriate for referral, but a patient who failed two AEDs and had an abnormal MRI and EEG would typically be an appropriate candidate for surgical evaluation, she explained. With respect to necessity, "none of the appropriate cases were rated as unnecessary," she said. ■