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.

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 preseizure electrical activity and preemptively aborts seizures.

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 RNS delivers stimulation in response to a detected event," said Dr. Morrell, noting that the treatment is "individualized and dynamic" in that it uses computer technology to recognize and respond to patterns of brain activity specific to individual patients' seizure patterns.

The RNS 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, which continuously monitors the electrical activity of the patient's brain, is programmed by a neurologist to detect and disrupt significant electrical events. "The programming is done wirelessly 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."

Up to two leads, each containing four electrodes, can be connected to the neurostimulator, so the system can monitor and deliver responsive stimulation to two distinct epileptogenic zones independently, she noted.

Because the neurostimulation occurs in response to aberrant electrical activity in the 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.

In an initial feasibility study of 65 patients, the responsive neurostimulation system demonstrated excellent safety, tolerability, and preliminary evidence of efficacy, Dr. Morrell said. "There were no serious device-related adverse events, and stimulation-related symptoms experienced by several subjects were addressed by adjusting the stimulation settings."

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. The patients were between 18 and 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 about 34% of the patients had been treated previously with vagus nerve stimulation, 33% had prior surgical resection, and 16% had been treated with both.

"These patients tended to be very ill. Most of them had epilepsy for more than 20 years, and many were having at least three seizures per 28-day period—often many more than that," Dr. Morrell said.

Of the 191 patients implanted with the 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 in order 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. At the end of the blinded efficacy period, stimulation was activated for all of the study participants for two years post-implantation, Dr. Morrell said.

In addition to the statistically significant reduction in seizure frequency in the active therapy group relative to those in the sham therapy condition, there were no serious, unanticipated device-related adverse events during the trial, nor was there a difference between the two groups with respect to the rate of adverse events, including depression, memory impairment, and anxiety, Dr. Morrell reported.

The findings suggest that responsive neurostimulation might be a promising treatment option for individuals with seizures that are resistant to conventional antiepileptic therapy. Importantly, the apparent increase in the number of patients experiencing at least a 50% reduction in seizure frequency relative to baseline during the open-label phase of the study suggests the system might become more effective over time, she noted.

The RNS has not yet received Food and Drug Administration approval, but NeuroPace plans to submit a premarket approval application to the FDA in early 2010, Dr. Morrell said. ■

MY TAKE

A New Kind of Stimulation

The development and use of stimulation devices for medically refractory epilepsy represents an altogether new approach for these patients 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), which is FDA-approved for refractory partial epilepsy, and the thalamic deep brain stimulator (Medtronic), which is FDA-approved for Parkinson's disease and essential tremor and is currently seeking FDA approval for refractory partial epilepsy. The RNS is the first closed loop stimulator and is distinctly different from other investigational and FDA-approved devices used to treat patients with epilepsy. The fact that in this day and age one can successfully and safely detect seizures using an implantable device on a long-term basis may provide hope for future advancements. With time, device technology is likely to be refined and improved, both through technical advances and as additional data are gathered and further studies are completed. Clinical experience will also help define proper patient selection, expectations, and effectiveness.

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

Algorithm to Predict Seizures Via Scalp EEG Under Study

BALTIMORE — An algorithm that analyzes recordings from a scalp, rather than an intracranial, EEG has been demonstrated to predict seizures with odds significantly greater than chance.

Dr. J. Chris Sackellares, chief scientific officer of Optima Neuroscience Inc., Gainesville, Fla., presented these findings at the annual meeting of the American Neurological Association.

At regular intervals, the algorithm sequentially calculates a pattern match regularity statistic—a measure of how ordered an electrical signal is—in four different channel groups located on patients' scalps.

Comparisons of the electrical activity in the four channels are used to predict seizures by detecting when the electrical activity of certain channels begins to converge on specific pattern match regularity statistics over time, indicating that a seizure is imminent.

Dr. Sackellares and his colleagues tested their algorithm in 51 patients with temporal lobe epilepsy. They captured 159 seizures and analyzed 93 segments of scalp EEG recordings. Each segment recording lasted a mean of 26 hours, with a total length of 48 hours per patient.

The researchers' automated prediction algorithm detected seizures with 95% sensitivity, generating one false-positive result every 8.6 hours, compared with a random predictor model that had an overall sensitivity of 83% and a rate of one false-positive result every 2.5 hours in individual patients.

The algorithm could detect seizures with nearly 70% sensitivity and a false-positive rate of about 0.22 per hour. The prediction was not sensitive enough for use in inpatient monitoring units or ambulatory EEC recording.

The study was supported by a grant from the National Institute of Neurological Disorders and Stroke.

—Jeff Evans

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