

By Robert S. Fisher MD, PhD

Electrical stimulation of brain has been much discussed as a possible treatment for epilepsy, but large controlled trials have only been completed in the past year. The SANTE trial, sponsored by Medtronic and led by Dr. Robert Fisher of Stanford, tested safety and efficacy of stimulation of the anterior nucleus of thalamus in epilepsy. The anterior nucleus is believed to play a “pacemaker” role for brain electrical activity in the frontal and temporal lobes. Eligible patients were age 18 to 65, with partial seizures, with or without secondary generalization. The average seizure frequency was 20 per month at baseline. 110 patients were implanted and followed for up to four years of stimulation. A three-month baseline with stable medications was recorded and then deep brain stimulating leads were placed into left and right anterior thalami. Leads were connected subcutaneously to a dual-channel programmable stimulator on the chest wall. After a month of recovery, subjects were randomized to 0 or 5V of stimulation, at 145 pps, on for 1 minute and off for 5 minutes. Subjects could not perceive the stimulation or tell accurately if they were in the active or placebo group. For the final month of stimulation, seizures were reduced by a median 40% in the stimulator group vs. 15% in the control group, a significant difference in favor of stimulation. Patients who had not benefited from prior epilepsy surgery or implantation of a vagus nerve stimulator improved with brain stimulation. During the blinded phase, complex partial seizures and seizures prospectively designated as most severe significantly improved in the stimulated group. Seizure-provoked injuries were significantly better in the blinded phase with stimulation. At month 4 after implantation, all patients were set to stimulation at 5 V, and attempts were made for an additional 9 months to hold medications constant. Seizure frequency continued to decline such that, by three years of stimulation, median seizure frequency was reduced to one-third of baseline levels. Approximately 13% of patients were seizure-free for six months or longer. Responder rate, quality of life and seizure severity scores did not significantly improve in the blinded phase, but all these measures did improve compared to baseline in the open-label phase.

During the study, there were five deaths, one in the baseline phase and four after stimulation. None were attributed to stimulation or the implantation procedure. Brain hemorrhages were visible by MRI or CT in five patients, but none were clinically significant. There were no severe unanticipated device-related adverse events. Stimulation was generally well tolerated.

Stimulation of the anterior nucleus of thalamus is an effective therapy for patients with medically refractory seizures, although it is not a curative procedure. Report of this trial is in press in the journal *Epilepsia*, scheduled to be available online by March, 2010. During that same month, the FDA will consider application for licensing. Yet to be accomplished is determination of the overall place of deep brain stimulation in the treatment of people with epilepsy. More needs to be known about the mechanisms of deep brain stimulation, optimal stimulation parameters and methods for predicting likely responders. Future studies may also show a role for deep brain stimulation as therapy for other adult and pediatric seizure types.