

EPILEPSY TREATMENT STIMULUS PACKAGE? DEEP BRAIN STIMULATION IN TREATMENT-RESISTANT FOCAL EPILEPSY

Electrical Stimulation of the Anterior Nucleus of Thalamus for Treatment of Refractory Epilepsy. Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, Oommen K, Osorio I, Nazzaro J, Labar D, Kaplitt M, Sperling M, Sandok E, Neal J, Handforth A, Stern J, DeSalles A, Chung S, Shetter A, Bergen D, Bakay R, Henderson J, French J, Baltuch G, Rosenfeld W, Youkilis A, Marks W, Garcia P, Barbaro N, Fountain N, Bazil C, Goodman R, McKhann G, Babu Krishnamurthy K, Papavassiliou S, Epstein C, Pollard J, Tonder L, Grebin J, Coffey R, Graves N; SANTE Study Group. *Epilepsia* 2010;51(5):899–908. **PURPOSE:** We report a multicenter, double-blind, randomized trial of bilateral stimulation of the anterior nuclei of the thalamus for localization-related epilepsy. **METHODS:** Participants were adults with medically refractory partial seizures, including secondarily generalized seizures. Half received stimulation and half no stimulation during a 3-month blinded phase; then all received unblinded stimulation. **RESULTS:** One hundred ten participants were randomized. Baseline monthly median seizure frequency was 19.5. In the last month of the blinded phase the stimulated group had a 29% greater reduction in seizures compared with the control group, as estimated by a generalized estimating equations (GEE) model ($p = 0.002$). Unadjusted median declines at the end of the blinded phase were 14.5% in the control group and 40.4% in the stimulated group. Complex partial and “most severe” seizures were significantly reduced by stimulation. By 2 years, there was a 56% median percent reduction in seizure frequency; 54% of patients had a seizure reduction of at least 50%, and 14 patients were seizure-free for at least 6 months. Five deaths occurred and none were from implantation or stimulation. No participant had symptomatic hemorrhage or brain infection. Two participants had acute, transient stimulation-associated seizures. Cognition and mood showed no group differences, but participants in the stimulated group were more likely to report depression or memory problems as adverse events. **DISCUSSION:** Bilateral stimulation of the anterior nuclei of the thalamus reduces seizures. Benefit persisted for 2 years of study. Complication rates were modest. Deep brain stimulation of the anterior thalamus is useful for some people with medically refractory partial and secondarily generalized seizures.

COMMENTARY

Despite the available pharmacologic treatments for epilepsy, approximately one-third of patients continue to have seizures and alternative treatment approaches are necessary (1). For many, resective surgery can be an effective method of achieving seizure freedom, however success is predicated on identification of the ictal onset zone through invasive or noninvasive means. Patients with multifocal or poorly localized onsets as well as patients with ictal onset zones in eloquent cortex (i.e., motor, sensory, language, or visual functional areas) are generally not candidates for resective surgery. In order to improve outcomes for these patients, alternative treatments are required.

For decades, the effects of electric stimulation on brain activity have been studied. In 1952, desynchronizing effects of vagal nerve stimulation were noted on feline sleep spindles as well as on a strychnine model of epileptiform activity (2). Direct stimulation of the cerebellum was reported to be effective in treating epilepsy in noncontrolled studies (3), but subsequent controlled studies in a total of 17 patients failed to show significant effects (4,5). In 1997, vagal nerve stimulation was approved for treatment-resistant epilepsy (6,7). Early investigations of the thalamus in animal models of epilepsy demonstrated the potential for both pharmacologic (8) and electrical stimulation induced (9) disruption of seizures.

The Fisher et al./SANTE study investigated the effectiveness of bilateral stimulation of the anterior nuclei of the thalamus by enrolling 157 patients with treatment-resistant epilepsy; of these, 110 patients underwent bilateral implantation of deep brain stimulation (DBS) electrodes in the anterior nucleus of the thalamus. At the end of the 3 months of blinded, randomized treatment, the median percent reduction in seizure frequency was approximately three times greater (40.4%) for the active stimulation group than for the control group. Patients with seizures arising from the temporal lobe(s) ($n = 66$) had significant reductions in seizures compared to baseline, whereas those with frontal ($n = 30$), parietal ($n = 5$), or occipital ($n = 4$) onsets did not demonstrate significant reductions. A trend toward improvement was seen for those with multifocal or diffuse ($n = 10$) ictal onsets. Open-label follow-up after the first 12 months, during which time stimulation parameters and medications could be changed at the physician's discretion, was associated with a 41% decrease in seizures at 13 months ($n = 99$) and a 56% decrease in seizures at 25 months ($n = 81$). The responder rates (i.e., 50% or greater reduction in seizures from baseline) for these time points were 43% and 54%, respectively. While seizure freedom was achieved for at least 6 months in 14 patients, eight patients were seizure free for a year or more, four for 2 or more years, and one for over 4 years.

Although no direct comparisons with vagal nerve stimulation have been made, these findings can be considered in

light of the results of two earlier vagal nerve stimulation trials (6,7). The blinded phases of both trials were conducted over a 3-month period and used a low level of stimulus intensity as a control. In the Vagus Nerve Stimulation Study Group trial, treatment was associated with a 24.5% reduction from baseline compared to 6.1% in the control arm (7). In a study by Handforth et al., baseline reductions were 28% and 15%, respectively (6). Between the two studies, only one patient was seizure free (combined $n = 144$) during the blinded phase. Results from an add-on trial of lacosamide (a recent addition to the epilepsy pharmacopeia) indicated median reductions in seizure frequency per 28 days of 39% at 400 mg/day and 40% at 600 mg/day of the drug compared to 10% for placebo (10). As these data demonstrate, the overall response to DBS is at least comparable to existing medical and device-based treatment modalities. With the exception of resective surgery in well-selected candidates, neither DBS nor any current treatment achieves seizure freedom in more than a small percentage of treatment-resistant patients.

Overall, adverse event occurrences were considered modest for DBS. In total, 808 adverse events were reported; 29.5% were considered to be device related. The most common of these were paresthesias (18.2%), implantation site pain (10.9%), and infections (12.7%). Asymptomatic hemorrhages were noted in 4.5% of patients. Both depression and memory complaints were significantly increased in the stimulation group compared to the control (i.e., eight vs. one for depression and seven vs. one for memory). Depressive symptoms resolved in four of the eight subjects and memory complaints resolved for all subjects. Notably, neuropsychologic testing scores for mood and cognition did not differ between groups at the end of the blinded phase.

Epilepsy-related complications included new seizure types during the blinded phase in six patients (four in the stimulation group and two in the control group). Nine patients had an increase in seizures compared to baseline at the end of 25 months of stimulation. Status epilepticus occurred in five patients: two following implantation and prior to initiation of stimulation, one during blinded stimulation in the active group, one following initiation of stimulation after the blinded phase (i.e., confusion and epileptiform changes associated with turning on the stimulator, which resolved 5 days after stimulation cessation), and one following discontinuation of stimulation. In addition, one patient experienced simple partial seizures corresponding to the stimulation cycle (210 seizures) following initiation of stimulation, which resolved when stimulation was stopped and did not recur when stimulation was restarted at a reduced voltage. Additional data will be necessary to identify epilepsy or seizure types that may be susceptible to exacerbation through stimulation.

As with any new therapy, identification of the ideal candidate can be a challenge. The data presented suggest that DBS

is most effective in patients with temporal lobe epilepsy, as opposed to extratemporal, neocortical epilepsy. Additional data that further characterize the seizure types and ictal onset zones that respond best to DBS are necessary to maximize benefit to patients. The observed statistically significant improvements in complex partial seizures invite speculation as to the physiologic impact of DBS on seizures: does DBS halt the ictal evolution? This effect could manifest in some patients as a decrease in more severe seizures (as was observed), with a relative preservation or even increase in auras and simple partial seizures, and it suggests a potential role for DBS in the treatment-resistant idiopathic or symptomatic generalized epilepsies. Although no clear reduction in seizures was seen with changes to stimulation parameters in the open-label phase, these adjustments were not systematically studied, and future studies may lead to further optimization of the stimulation paradigms and ultimately improve seizure control. Although challenges and questions remain, the findings of the SANTE study group represent a step forward for novel alternatives to systemic pharmacotherapy for treatment-resistant epilepsy. One hopes this will be the first of many steps for DBS as well as other therapies.

by Chad Carlson, MD

References

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314–319.
2. Zanchetti A, Wang SC, Moruzzi G. The effect of vagal afferent stimulation on the EEG pattern of the cat. *Electroencephalogr Clin Neurophysiol* 1952;4:357–361.
3. Cooper IS, Amin I, Gilman S. The effect of chronic cerebellar stimulation upon epilepsy in man. *Trans Am Neurol Assoc* 1973;98:192–196.
4. Van Buren JM, Wood JH, Oakley J, Hambrecht F. Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy. *J Neurosurg* 1978;48:407–416.
5. Wright GD, McLellan DL, Brice JG. A double-blind trial of chronic cerebellar stimulation in twelve patients with severe epilepsy. *J Neurol Neurosurg Psychiatry* 1984;47:769–774.
6. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilmartin RC, Labar DR, Morris GL 3rd, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW. Vagus nerve stimulation therapy for partial-onset seizures: A randomized active-control trial. *Neurology* 1998;51:48–55.
7. VNS Study Group, T. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. *Neurology* 1995;45:224–230.
8. Mirski MA, Ferrendelli JA. Anterior thalamic mediation of generalized pentylenetetrazol seizures. *Brain Res* 1986;399:212–223.
9. Mirski MA, Rossell LA, Terry JB, Fisher RS. Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. *Epilepsy Res* 1997;28:89–100.
10. Ben-Menachem E, Biton V, Jatuzis D, Abou-Khalil B, Doty P, Rudd GD. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. *Epilepsia* 2007;48:1308–1317.