EPILEPSY CURRENTS

Current Literature

In Clinical Science

Trigeminal Nerve Stimulation May Not Be Effective for the Treatment of Refractory Partial Seizures

Randomized Controlled Trial of Trigeminal Nerve Stimulation for Drug-Resistant Epilepsy.

DeGiorgio CM, Soss J, Cook IA, Markovic D, Gornbein J, Murray D, Oviedo S, Gordon S, Corralle-Leyva G, Kealey CP, Heck CN. *Neurology* 2013;80:786–791.

OBJECTIVE: To explore the safety and efficacy of external trigeminal nerve stimulation (eTNS) in patients with drug-resistant epilepsy (DRE) using a double-blind randomized controlled trial design, and to test the suitability of treatment and control parameters in preparation for a phase III multicenter clinical trial. METHODS: This is a double-blind randomized active-control trial in DRE. Fifty subjects with 2 or more partial onset seizures per month (complex partial or tonic-clonic) entered a 6-week baseline period, and then were evaluated at 6, 12, and 18 weeks during the acute treatment period. Subjects were randomized to treatment (eTNS 120 Hz) or control (eTNS 2 Hz) parameters. RESULTS: At entry, subjects were highly drug-resistant, averaging 8.7 seizures per month (treatment group) and 4.8 seizures per month (active controls). On average, subjects failed 3.35 antiepileptic drugs prior to enrollment, with an average duration of epilepsy of 21.5 years (treatment group) and 23.7 years (active control group), respectively. eTNS was well-tolerated. Side effects included anxiety (4%), headache (4%), and skin irritation (14%). The responder rate, defined as >50% reduction in seizure frequency, was 30.2% for the treatment group vs 21.1% for the active control group for the 18-week treatment period (not significant, p = 0.31, generalized estimating equation [GEE] model). The treatment group experienced a significant within-group improvement in responder rate over the 18-week treatment period (from 17.8% at 6 weeks to 40.5% at 18 weeks, p = 0.01, GEE). Subjects in the treatment group were more likely to respond than patients randomized to control (odds ratio 1.73, confidence interval 0.59-0.51). eTNS was associated with reductions in seizure frequency as measured by the response ratio (p = 0.04, analysis of variance [ANOVA]), and improvements in mood on the Beck Depression Inventory (p = 0.02, ANOVA). CONCLUSIONS: This study provides preliminary evidence that eTNS is safe and may be effective in subjects with DRE. Side effects were primarily limited to anxiety, headache, and skin irritation. These results will serve as a basis to inform and power a larger multicenter phase III clinical trial. CLASSIFICATION OF EVIDENCE: This phase II study provides Class II evidence that trigeminal nerve stimulation may be safe and effective in reducing seizures in people with DRE.

Commentary

Stimulatory devices offer a novel approach for the treatment of refractory partial seizures. Both peripheral and central stimulatory devices that provide either continuous or responsive stimulation have been studied. Currently the only approved device is the vagus nerve stimulator (VNS). Stimulatory devices may provide a safe and well-tolerated means of reducing seizures for patients with refractory seizures.

Trigeminal nerve stimulation (TNS) is a neuromodulatory device that has been studied in animal and pilot clinical trials. The original article investigating its potential antiepileptic properties was an animal study evaluating its effect on pentylenetetrazole-induced seizure activity in awake rats (1). Continuous unilateral stimulation of the trigeminal nerve reduced electrographic seizure severity and duration activity in a frequency-dependent fashion at frequencies >100 Hz. Bilateral trigeminal stimulation was more effective than unilateral stimulation. A proof-of-concept clinical trial investigated safety and efficacy among seven subjects using transcutaneous stimulation of the infraorbital and supraorbital branches of the trigeminal nerve (2). In this study, TNS was well tolerated, and four of seven subjects who completed ≥3 months had a ≥50% reduction in seizure frequency. Another study evaluated its effect in depression and found significant improvement in clinician- and individual-rated depression scales among five subjects (3). There has not previously been a randomized, blinded, controlled trial among persons with refractory epilepsy.

DeGiorgio and colleagues completed a phase-2 randomized, double-blind, multicenter trial evaluating external TNS (eTNS) among subjects with drug-resistant partial-onset epilepsy (having two or more complex partial or generalized tonic seizures per month for 2 consecutive months) (4). Subjects were randomized to either active treatment (frequency of 120

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Hz and pulse duration <250 μs) or control parameters (frequency, 2 Hz; duty cycle, 2 seconds on and 90 seconds off; and pulse duration, 50 μs). The active settings were derived from results from both the animal study in a pentylenetetrazole model of epilepsy as well as the open-label proof-of-concept study. The control parameters were extrapolated from settings used in VNS trials. A novel bipolar transcutaneous gel-based electrode, specifically designed to contact the right and left branches of the ophthalmic and supratrochlear nerves to provide bilateral stimulation, was utilized. Subjects were enrolled at the University of Southern California (USC) and the University of California–Los Angeles (UCLA) using block randomization. After completing a 6-week baseline period, subjects were evaluated at 6, 12, and 18 weeks.

Three primary endpoints were defined: 1) change in seizure frequency, 2) responder rate defined as ≥50% reduction in seizure frequency, and 3) time to fourth seizure. Because there were three primary outcomes, a Bonferroni correction was utilized giving a significance level of $p = 0.0167$ (0.05/3). Secondary measures included mood as measured by Beck Depression Index and response ratio.

Overall, subjects had refractory epilepsy with an average of 8.7 seizures per month and had failed an average of 3.35 antiepileptic drugs (AEDs) prior to enrollment. As in prior studies (2, 3), eTNS was well tolerated, with the most common reported side effect being skin irritation (14%) followed by anxiety (4%) and headache (4%).

There were no significant differences between the active group and control group in any of the three predefined primary end points. There was, however, a significant within-group difference improvement in responder rate over the 18-week treatment period. At 6 weeks, the responder rate was 17.8%, which then increased to 40.5% at 18 weeks, giving a significant within-group improvement ($p = 0.01$). It is, however, unclear how the responder rates at the serial evaluation periods were derived. The reported percentages could reflect a cumulative response between the different evaluation periods or may have reflected a more limited time period. The secondary outcome, response ratio, was also not significantly different between the active and control groups. Similar to the responder rate, there was a significant within-group difference ($p < 0.04$). Mood was improved with eTNS treatment compared with control (within- and between-group differences, $p < 0.02$).

Although interesting, these data do not support the effectiveness of eTNS for the treatment of refractory partial seizures. The device was well tolerated with minimal side effects. As no predefined primary end point was met, it is unclear how as suggested in the manuscript, this study provides preliminary evidence that eTNS may be effective as treatment for refractory partial seizures. In addition, although the study was designed to provide class II evidence for the safety and efficacy of eTNS as therapy for partial seizures, this evidence was not found in this study because of the lack of significant findings in any of the primary end points. Of interest, depression did improve with eTNS. Future larger scale trials with larger sample sizes may provide evidence to support the effectiveness of trigeminal nerve stimulation for the treatment of refractory partial seizures. Future trials evaluating the effectiveness of trigeminal nerve stimulation for the treatment of depression should also be considered.

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References

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