

VAGUS NERVE STIMULATION FOR GENERALIZED EPILEPSY? . . . SHOW ME THE EVIDENCE!

Is Vagus Nerve Stimulation a Treatment Option for Patients with Drug-Resistant Idiopathic Generalized Epilepsy?

Kostov H, Larsson PG, Røste GK. *Acta Neurol Scand Suppl* 2007;187:55–58. **BACKGROUND:** The value of vagus nerve stimulation (VNS) for treating patients with drug-resistant idiopathic generalized epilepsy (IGE) is not well documented. **PATIENTS AND METHODS:** Twelve patients (2 males, 10 females) with a mean age of 31 years (11–48 years) and with drug-resistant IGE had VNS implanted in the period 1995–2006. All had generalized seizures documented by video-electroencephalogram. Mean follow-up period was 23 months (9–54 months). **RESULTS:** There was a total seizure reduction of 61% ($p = 0.0002$). There was 62% reduction of generalized tonic-clonic seizures ($p = 0.0020$), 58% of absences ($p = 0.0003$), and 40% of myoclonic seizures ($p = 0.0156$). Eight patients were considered responders (>50% seizure reduction); two of these patients became seizure-free. Five out of seven patients with juvenile myoclonic epilepsy were responders. At the last follow-up visit, the patients had reduced the antiepileptic drug (AED) usage from an average of 2.3 to 1.7 AED per patient ($p = 0.0625$). Two patients are currently being treated with VNS therapy only. Nine patients reported side effects, which were mostly mild and tended to diminish over time. **CONCLUSION:** Our results indicate that adjunctive VNS therapy is a favorable treatment option for patients with drug-resistant IGE. Rapid cycling seems worth trying in some of the nonresponders.

COMMENTARY

In 1999, the Therapeutics and Technology Assessment (TTA) subcommittee of the American Academy of Neurology published a guideline for the use of vagal nerve stimulation (VNS) in epilepsy. On the bases of two multicenter randomized studies, the TTA found VNS to be an acceptable therapy for adults and adolescents over 12 years of age with medically intractable partial seizures who are not candidates for potentially curative surgical resections, such as lesionectomies or mesial temporal lobectomies (1). The two studies compared the antiepileptic effect of high versus low intensity stimulation (frequency: 20–50 vs 1–2 Hz; pulse-width: 500 microseconds vs 130 microseconds; on time: 30–90 seconds vs 30 seconds; off time: 5–10 minutes vs 60–180 minutes; current: 0.25–3.0 mA vs 0.25–2.75mA) during a 3-month period, while maintaining a constant use of concomitant antiepileptic drugs (AEDs) (2,3). Relative to a 3-month baseline seizure frequency, patients randomized to high stimulation had a significantly greater reduction in seizures than patients randomized to the low stimulation group (24% vs 6% and 28% vs 15% in the first and second study, respectively). Since the publication of the TTA guidelines, there have been several open trials reporting on VNS for the treatment of Lennox–Gastaut syndrome and pharma-

coresistant idiopathic generalized epilepsy (IGE)—one of which is the article by Kostov et al. reviewed here. Unfortunately, no new recommendations would come from updating the 1999 guidelines today, as the methodology used in all of these studies fails to meet the necessary criteria to establish a positive recommendation for the use of VNS for these types of epilepsy. Thus, should the published data on the use of VNS for generalized epilepsies be ignored?

The available data on the impact of VNS in Lennox–Gastaut syndrome consist of two retrospective studies and one prospective open trial in which seizure rate reductions ranged from 27 to 64 percent (4–6). The first retrospective study included 13 patients (mean age 16.7 years), for whom VNS yielded a median seizure rate reduction of 52% (range, 0–93%; $p = 0.04$) during the first 6 months of treatment (4). A second retrospective study of 50 children from six epilepsy centers (median age 13 years) found median reductions in total seizures of 58% at 6 months (5). In the only prospective study of 16 children during which AEDs were held constant, a reduction in seizure frequency of 50% or greater was identified in 25% of the patients (6). This study also compared measures of behavior, mood, and cognitive functions, and the data suggested a moderate improvement in all three areas. Furthermore, the scores for mood and mental age improved independent of seizure control. Of note, the latter study, which was methodologically sounder, yielded the least impressive seizure reduction results. These data have been sufficient to convince

many epilepsy centers to consider VNS for the treatment of Lennox–Gastaut syndrome ahead of corpus callosotomy. In the case of pharmacoresistant IGE, two small open trials (one of which is the prospective trial by Kostov and colleagues) reported a seizure frequency reduction ranging from 57 to 62 percent (7). Two other prospective studies reported on the use of VNS in open trials in a mixed group of 16 (8) and 24 (9) patients with refractory IGE or Lennox–Gastaut syndrome. There was a median overall seizure rate reduction of 46% and 43%, respectively.

The structures in the brain affected by VNS play important roles in the pathogenic mechanisms of partial and generalized epilepsies and, theoretically, effects on these structures ought to support use of VNS as a viable treatment. Such is the case for the thalamocortical networks. For example, in a study with O₁₅-H₂O-PET, VNS was found to activate the thalamus in patients with refractory partial epilepsy; the highest seizure rate reductions occurred in patients who had the greatest increases in thalamic blood flow (10).

Similarly, neuroimaging studies on humans with IGE have documented structural and functional abnormalities in the thalamus. For example, proton magnetic resonance spectroscopic imaging, measuring N-acetylaspartate (NAA), choline-containing compounds, and creatine (Cr) was used in 20 patients with IGE and 20 age-matched healthy subjects. Measurements were made in the thalamus, insular cortex, the posterior temporal lobe white matter, and the splenium of the corpus callosum. A reduction in the mean NAA/Cr was found in the thalamus of IGE patients but not in other examined areas (11). In addition, there was a significant negative correlation between thalamic NAA/Cr and duration of epilepsy, but no differences were found between patients with persistent or controlled seizures. The investigators suggested that the results provided evidence of progressive thalamic neuronal dysfunction in patients with IGE, supporting the notion of abnormal thalamocortical circuitry as a substrate of seizure generation in this form of epilepsy.

Furthermore, VNS increases the secretion of norepinephrine in various structures of the brain. The pathogenic role of norepinephrine has been demonstrated in several animal models of generalized epilepsy, particularly in two strains of genetically epilepsy-prone rats (GEPR-3 and GEPR-9) (12). Of note, the GEPR-9 strain displays more severe seizures and has greater norepinephrine deficits in several brain areas (i.e., cerebellum, pons-medulla, thalamus, and possibly the temporal cortex and olfactory bulbs). Suppression of convulsions was obtained with intracerebroventricular injections of norepinephrine in both strains, while intraventricular norepinephrine tissue grafts were successful in reducing seizure severity of audiogenic seizures. By the same token, in exper-

imental animal models of epilepsy, the anticonvulsant effect of VNS was associated with noradrenergic mechanisms (12). Indeed, chronic depletion of norepinephrine with bilateral infusion of 6-hydroxydopamine into the noradrenergic neurons of the locus coeruleus in the rat significantly prevented or reduced the anticonvulsant effect of VNS against electroshock or pentylenetetrazol-induced seizures.

Clearly, there are enough experimental and clinical data to suggest that VNS could be an effective therapy for generalized epilepsies. However, pivotal studies are missing and no definite recommendation can be made until they are carried out and shown to demonstrate a therapeutic effect. The medical and scientific communities are waiting for such recommendations.

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