

Pilot Study of Trigeminal Nerve Stimulation (TNS) for Epilepsy: A Proof-of-Concept Trial

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Summary: The safety and preliminary efficacy of trigeminal nerve stimulation (TNS) for epilepsy was evaluated in a pilot feasibility study of transcutaneous stimulation of the infraorbital and supraorbital branches of the trigeminal nerve. TNS was well tolerated. Four (57%) of seven subjects who completed ≥ 3 months

experienced a $\geq 50\%$ reduction in seizure frequency. The results of this pilot study support further investigation into the safety and efficacy of TNS for epilepsy. **Key Words:** Trigeminal nerve stimulation—Epilepsy—Neurostimulation.

Thirty to forty percent of adults with epilepsy are refractory to antiepileptic drug (AED) treatment (1). For those for whom AEDs fail, epilepsy surgery is extremely effective. Unfortunately, many patients are not ideal surgical candidates or have limited access to specialized epilepsy centers. For such patients, neurostimulation is a promising adjunct to AEDs (2). Trigeminal nerve stimulation (TNS), via cutaneous branches in the face, offers the opportunity of a minimally invasive method of neurostimulation. Response can be assessed before surgical implantation with self-adhesive cutaneous electrodes (3,4).

In their seminal report, Fanselow et al. (3) found that TNS significantly reduced pentylenetetrazol-induced seizures in rats. Seizure severity and duration were reduced in a frequency-dependent fashion at frequencies > 100 Hz (3). Bilateral stimulation was more effective than unilateral stimulation, and stimulation was well tolerated (3).

Recently, we reported the first two humans to be treated with TNS for epilepsy (4). We now present the results of a pilot feasibility study of TNS in seven subjects with intractable epilepsy who completed at least the first-month treatment visit, including the two subjects reported previously (4).

METHODS

Research committee approval was obtained for a pilot study of TNS. Inclusion and exclusion criteria were ages 18–65 years; three or more complex partial or generalized tonic-clonic seizures per month; no significant cardiac or medical conditions; the ability to maintain accurate seizure calendars; no history of trigeminal neuralgia or facial pain; no implantation of a vagus nerve stimulator; and exposure to at least two AEDs, in appropriate doses, including at least one trial of levetiracetam, topiramate, or zonisamide.

Stimulation was supplied using an Food and Drug Administration (FDA)-approved neurostimulator at 120 Hz, 250 μ s, ≤ 30 s on and 30 s off (EMS 400 Wisdomking.com, Oceanside, CA, U.S.A.). The stimulator delivers an asymmetrical biphasic square wave pulse adjustable from 0 to 100 mAs. The 1.25-inch disposable, hypoallergenic, silver-gel, self-adhesive, stimulating electrodes were used (Superior Silver-Permagel Electrodes, Tyco Healthcare/Uni-Patch, Wabasha, MN, U.S.A.). Power was supplied by 9-volt lithium medical-grade batteries (Eveready Energizer L522, Energizer, St. Louis, MO, U.S.A.). Subjects replaced the battery every other day and electrodes daily.

Initially, infraorbital stimulation was used, (subjects 1–3), with right-sided stimulation alternating every other day with left-sided stimulation. The 1.25-inch hypoallergenic silver gel discs were applied over the face, with the positive electrode placed over the infraorbital foramen, and the negative electrode placed $\frac{1}{2}$ to 1 inch posterolateral, in line with the nasolabial fold. Supraorbital stimulation allowed

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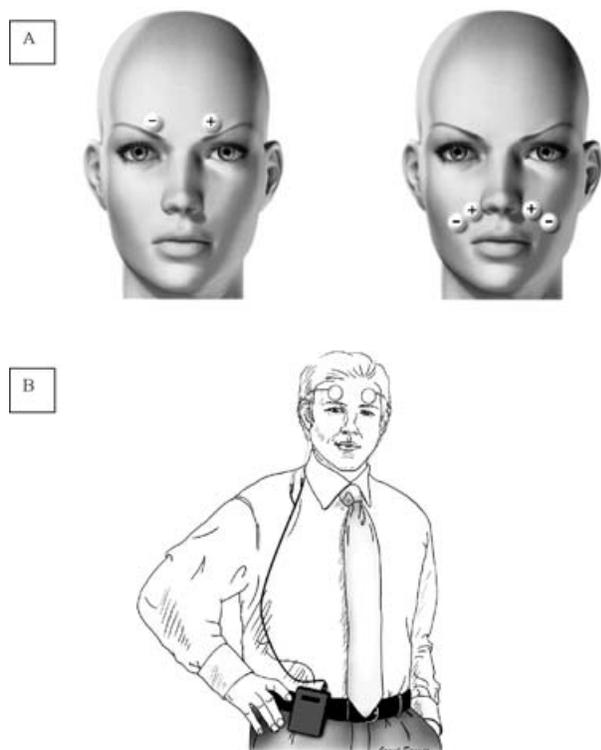


FIG. 1. A: Schematic of electrode placement for infraorbital and supraorbital electrodes. The positive electrodes are situated directly over the palpable supraorbital and infraorbital foramen. **B:** Drawing showing a subject with the electrodes placed over the supraorbital foramen for stimulation of the first division of the trigeminal nerve (supraorbital nerve). Subjects preferred supraorbital nerve stimulation, because the stimulating electrodes could be covered by a cap or hat. Bilateral stimulation was achieved by placement of one electrode over each foramen.

bilateral simultaneous stimulation with the use of only two electrodes. See Fig. 1.

After informed consent, subjects meeting all inclusion criteria were enrolled. During a 4-week prospective pretreatment baseline, subjects kept a diary of all seizures and quantified the date and character of each seizure. Diaries were verified, and all complex-partial or generalized tonic-clonic seizures were counted and validated by the study physician. An average daily seizure frequency for the sum of all complex partial or generalized tonic-clonic seizures was calculated at each study visit. At no time during baseline or the 3-month or 6-month treatment period were AED changes allowed: changes in AEDs resulted in exit from the study.

RESULTS

Ten subjects have been enrolled in this ongoing pilot study; data are complete on seven subjects. One exited after 2 weeks because of poor compliance and the need to adjust his AEDs. Two subjects have not yet completed the first 1-month follow-up visit.

On the first day of stimulation, the tolerability of acute TNS was assessed. Output current was gradually increased to identify the threshold for perception and pain. In the first three subjects, unilateral infraorbital stimulation was initiated. All subsequent subjects underwent bilateral supraorbital stimulation (supraorbital was preferred because electrodes could be concealed, and stimulation could be delivered bilaterally by using two electrodes).

Each subject's response to initial stimulation was assessed after a 1-month prospective baseline period. On the first day of stimulation, the output current was gradually increased, and the subject's perception was assessed on a 0–10 intensity scale. At first perception of sensation, patients reported a mild tingling in the canine teeth (infraorbital stimulation) or the scalp (supraorbital stimulation). As current was increased, patients consistently reported progressively increased tingling. At device settings >4 (output currents generally >20 mA), stimulation became progressively uncomfortable, and the current was reduced. Subjects indicated that stimulation between output settings of 2 and 4 (<20 mA) were comfortable. These settings were chosen for stimulation. Tolerance to stimulation generally tended to improve with time. Patients were able to carry out their normal activities of living without discomfort and minimal awareness of stimulation. No subject discontinued treatment because of discomfort.

On the first day of stimulation, heart rate and systolic and diastolic blood pressure were monitored every 5 min for 1 h. No blood pressure, pulse, or ECG changes were detected during stimulation. After 24 h of stimulation, blood pressure and heart rate were again monitored every 5 min for 60 min during stimulation, and again, no acute effects on vital signs were identified.

Throughout the study, TNS was well tolerated, and subjects reported that the hypoallergenic adhesive electrodes were easy to apply and maintain. Tingling or pressure in the forehead or canine teeth was reported, but these were minimized by a reduction in current. Overall, patients preferred supraorbital stimulation to infraorbital stimulation, as they could wear a cap or hat to cover the electrodes.

Six subjects used the stimulator 24 h/day; subject 7, because her seizures only occurred at night or in the early morning, elected to undergo stimulation at night for a total of 12 h/day.

Table 1 summarizes average daily seizure frequencies during baseline and the treatment period for the seven subjects who completed at least the 1-month treatment follow-up visit. Overall, the average change in seizure frequency was –43.7% at the last treatment visit. Four (57%) of seven responded with a $\geq 50\%$ reduction in seizure frequency at 3 months, and four of five who completed 6 months had a $> 50\%$ reduction in seizure frequency. Because of the small sample size, these differences were not significant (Wilcoxon signed rank).

TABLE 1. Summary of results in the seven subjects who completed at least the 1-month follow-up visit

Subject number	Average daily seizure frequency			% Reduction in seizure frequency
	Prospective baseline	3 mo	6 mo	
1	0.375	0.16	0.23	-38.6%
2	1.94	0.56	0.47	-75.7%
3	0.44	0.44	0.19	-56.8%
4	0.77	1.07	Exited after completing acute 3-mo study because of lack of efficacy	+39.5%
5	0.176	0.07	Exited after completing acute 3-mo study; did not wish to wear electrodes and desired VNS	-60.2%
6	0.26	0.09	0.04	-84.6%
7	0.20	0.20	0.14	-30.0%
Average daily seizure frequency	0.59	0.37	0.21	Average percentage reduction, -43.7%

Percentage reduction in seizure frequency is at the last completed visit (3 or 6 months).

DISCUSSION

The data from this pilot study indicate that transcutaneous stimulation of the supraorbital and infraorbital divisions of the trigeminal nerve was safe and well tolerated for the duration of the 3- and 6-month treatment periods. After adjustment in output current on day 1 of stimulation, all subjects tolerated high-frequency TNS without significant pain or discomfort. Most subjects expressed a preference for supraorbital stimulation, because of the ability to conceal the electrodes with a cap or hat.

Although the sample size is small in this pilot study, preliminary efficacy data indicate that four (57%) of seven experienced a $\geq 50\%$ reduction in seizures. Interpretation of the efficacy data must be approached with caution, as the sample size was small, and this is an open-label study, prone to possible placebo effects. Nevertheless, the data from this pilot exploratory study support further investigation of TNS for epilepsy.

Evidence from animals indicates that the trigeminal nerve and related structures play a role in seizure inhibition. The trigeminal nucleus has extensive projections to the nucleus tractus solitarius (NTS) and the locus ceruleus, structures known to modulate seizures (5–7). Stimulation of the medial portion of the NTS in cats delays the onset of overt seizures induced by amygdala stimulation (8). In the penicillin model, stimulation of the locus ceruleus suppresses focal epileptic discharges (9). The locus ceruleus is also believed to play a central role in the anticonvulsant effect of vagus nerve stimulation (10). Given the projections of both the trigeminal nerve and vagus nerve to NTS and locus ceruleus, a unifying hypothesis linking the antiepileptic effects of vagus nerve stimulation and TNS is intriguing and should be further explored.

TNS is a promising new treatment. TNS has theoretical advantages: it is minimally invasive, and it can be applied bilaterally. Efficacy and tolerability can be assessed non-invasively before a permanent device is implanted. If this

unifying hypothesis is true, then studies can be designed so that subjects first receive transcutaneous stimulation and then, if they respond, an implantable device. The cost of transcutaneous TNS is also favorable: stimulators cost $\sim \$180.00$ each, and the monthly retail cost of batteries and electrodes is $\sim \$150$ – $\$170.00$ /month.

We believe that the results of this pilot study justify further investigation into the safety and efficacy of TNS for epilepsy. We are now planning further studies of both transcutaneous and implantable TNS for epilepsy.

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