TRIGEMINAL NERVE STIMULATION FOR EPILEPSY: LONG-TERM FEASIBILITY AND EFFICACY

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Table Laboratory values at admission

Hematologic and chemical values		Serum virology
Analyte	**Value**	**Results**
Hematocrit	25%	HIV negative
Mean corpuscular volume	102 μm^3	HTLV-I negative
White cell count	18,300/mm^3	HCV negative
Neutrophils	77%	HBsAg negative
Lymphocytes	9.2%	EBV negative
Eosinophils	4%	CMV negative
Platelet count	232,000/mm^3	HSV-1 negative
Fibrinogen	390 mg/dL	HSV-2 negative
Prothrombin time	31 s	
Urea nitrogen	19 mg/dL	
Creatinine	1.1 mg/dL	
Ammonia	42 mmol/mL	
Glucose	86 mg/dL	
Total bilirubin	12.8 mg/dL	
Conjugated bilirubin	8.1 mg/dL	
Aspartate aminotransferase	161 U/L	
Alanine aminotransferase	64 U/L	

HTLV = human T-cell lymphotrophic virus; HCV = hepatitis C virus; EBV = Epstein-Barr virus; CMV = cytomegalovirus; HSV = herpes simplex virus.

IgG. Third, serum contained increased HHV-6 IgM. Remarkably, HHV-6 is closely related to CMV, the second most commonly found infection preceding Guillain-Barré syndrome, and its most common viral trigger.[6] The normal CSF protein content in our patient seemingly contrasts with evidence that about 80% of patients with AIDP have raised CSF protein concentrations. One explanation is that we collected our patient's CSF sample in the early days of illness, a time when protein content is often normal.[7] Measurement of potassium, phosphate, and porphyrin metabolism products helped to exclude alternative diagnoses. Stool sample cultures excluded *Campylobacter jejuni* enteritis. In addition, the neurologic examination on admission failed to disclose the cognitive disturbances typical of some alcohol-related acute reactions, thus arguing against a history of alcohol abuse, and lacked the signs of distal symmetric axonal polyneuropathy typically found in heavy chronic alcohol users.

Viral reactivation of a latent HHV-6 infection may be among the causative or precipitating factors of acute inflammatory PNS diseases.

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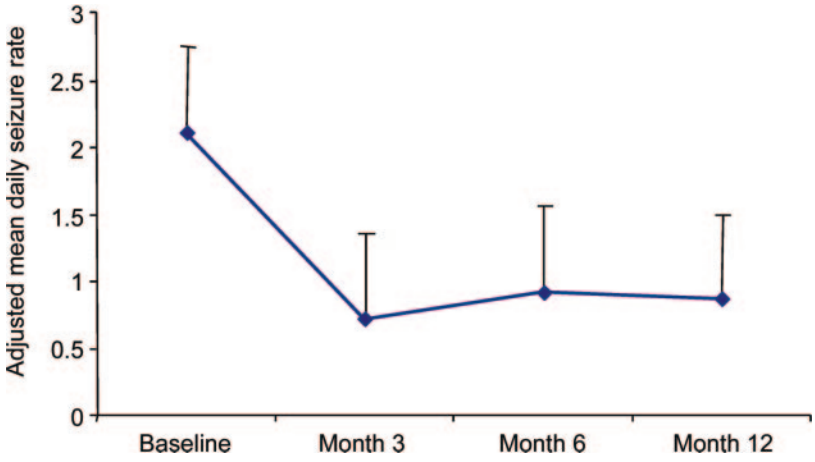
Neurostimulation has emerged as a viable alternative for intractable epilepsy. Trigeminal nerve stimulation (TNS), a novel form of neurostimulation, has an antiepileptic effect in a rodent model.[1] The superficial location of trigeminal branches allows for minimally invasive approaches, allowing assessment of response prior to a permanent device.[2] We report the long-term safety and efficacy of external TNS for epilepsy.

Methods. Research committee approval was obtained for an open study of external TNS in epilepsy. Informed consent was obtained before enrollment. Inclusion/exclusion criteria were age 18–65 years, ≥3 complex-partial/generalized tonic-clonic seizures/month, no progressive medical conditions, and exposure to ≥2 antiepileptic drugs (AEDs). Subjects enrolled in a 4-week pretreatment baseline, and were

Figure Adjusted mean daily seizure rate across time



Bars indicate standard error = 0.64.

evaluated at 1, 2, 3, 6, and 12 months. AEDs remained unchanged unless essential for patient safety. Neurostimulation was initially supplied using the analog EMS Model 400, and later a digital EMS model 7500.[2] Stimulation settings were as follows: frequency 120 Hz, 250 μs, ≤30 seconds on, ≤30 seconds off for 12–24 hours/day, and 1.25-inch disposable, silver-gel, adhesive electrodes were utilized, spaced 2 inches apart. Subjects 1–3 were initiated with infraorbital stimulation (V_2), but subjects found this awkward for chronic use. Since then, we have stimulated the ophthalmic nerve (V_1) in all subjects, which allows bilateral stimulation and can be concealed by a cap. See figure e-1 on the *Neurology*® Web site at www.neurology.org for a diagram of the device and electrode placement.

Statistical analysis. We compared mean seizure rates over time using a repeated measure analysis of variance (ANOVA) model. After confirming that missing data were missing at random, we used multiple imputation to replace missing values for daily seizure rate with a set of imputed values in patients who did not complete the study. The imputation was carried out under the repeated measure ANOVA model. The resulting variances of the means reflect not only the variation in the observed data but also the added uncertainty of using partially imputed information. It is preferable to impute missing values rather than omit patients with incomplete data entirely. Four imputed values were generated for each missing value. All analyses were carried out using SAS version 9.1. A p value of 0.05 was chosen for significance.

Supplemental data at www.neurology.org

Results. Thirteen subjects completed the 4-week prospective baseline. Twelve completed 3 months, 10 completed 6 months, and 7 completed 12 months (table e-1). Short-term results from the first seven subjects reported previously are included in this analysis.[2] The figure shows results at 3, 6, and 12 months. At 3 months, mean seizure frequency was reduced from a baseline of 2.1 seizures/day to 0.71 seizures/day (66% reduction, $p = 0.034$, standard error 0.64). At 6 months, mean seizure frequency was 0.92 seizures/day (56% reduction, $p = 0.073$, standard error 0.64). At 12 months, mean seizure frequency was 0.86 seizures/day (59% reduction, $p = 0.058$, standard error 0.64). Five subjects experienced greater than 50% reduction at 6 and 12 months; one subject had >90% reduction at 12 months.

TNS was well tolerated. Side effects included skin irritation in five subjects, which improved by reducing stimulation to 12–16 hours/day, or with hydrocortisone 1% cream. Tingling, forehead pressure, and headache were reported, but improved with reduction of current. No effect on pulse, blood pressure, or ECG was detected.

Discussion. External stimulation of the trigeminal nerve (V_1 and V_2) was well tolerated, with a mean reduction in seizure frequency of 59% at 12 months. The results of this study build upon data in an animal model, and our short-term report in humans.[1,2]

Why stimulate the trigeminal nerve for epilepsy? The trigeminal nerve has three bilateral cutaneous branches.[3] These afferent branches (V_1–V_3) exit foramen 1.25–1.5 inches lateral of the midline, and project to the trigeminal ganglion and the trigeminal nucleus, which projects to the nucleus tractus solitarius and locus ceruleus, all of which play a role in inhibition of seizures.[4-7] The antiepileptic effect of the trigeminal nerve and related structures has been confirmed in animal models.[1,4,5] Stimulation of the locus ceruleus suppresses epileptic discharges induced by cobalt and penicillin, and plays a central role in the mechanism of VNS.[6,7] In a pentylenetetrazole model, high-frequency stimulation of the trigeminal nerve significantly reduced seizure severity and frequency.[1] Bilateral stimulation was more effective than unilateral stimulation, and high frequency stimulation was more effective than low frequency stimulation.[1]

The data provide a foundation for future randomized studies of TNS in humans. Based on the long-term feasibility and efficacy of this study, we have embarked on a randomized controlled study of high vs low frequency stimulation of the ophthalmic branch (V_1) of the trigeminal nerve for intractable epilepsy.

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AUTHOR CONTRIBUTIONS

Daniela Markovic performed the statistical analysis.

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