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Brief Communication

Transcutaneous auricular vagus nerve stimulation as a complementary therapy for pediatric epilepsy: A pilot trial

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ABSTRACT

Objective: We investigated the safety and efficacy of transcutaneous auricular vagus nerve stimulation (ta-VNS) for the treatment of pediatric epilepsy.
Methods: Fourteen pediatric patients with intractable epilepsy were treated by ta-VNS of the bilateral auricular concha using an ear vagus nerve stimulator. The baseline seizure frequency was compared with that after 8 weeks, from week 9 to 16 and from week 17 to the end of week 24, according to the seizure diaries of the patients.
Results: One patient dropped out after 8 weeks of treatment due to lack of efficacy, while the remaining 13 patients completed the 24-week study without any change in medication regimen. The mean reduction in seizure frequency relative to baseline was 31.83% after week 8, 54.13% from week 9 to 16 and 54.21% from week 17 to the end of week 24. The responder rate was 28.57% after 8 weeks, 53.85% from week 9 to 16 and 53.85% from week 17 to the end of week 24. No severe adverse events were reported during treatment.
Conclusion: Transcutaneous auricular VNS may be a complementary treatment option for reducing seizure frequency in pediatric patients with intractable epilepsy and should be further studied.

1. Introduction

An estimated 10.5 million children worldwide under 15 years of age have active epilepsy. Population-based studies on childhood-onset epilepsy indicate annual incidence rates of 61–124 per 100000 in developing countries and 41–50 per 100000 in developed countries [1].

In 1997, vagus nerve stimulation (VNS) was approved as an adjunct therapy for treatment of refractory seizures in patients older than 12 years. Short-term and long-term studies have shown that VNS is an effective method for seizure frequency reduction in adults [2–4], but few studies have assessed the efficacy of VNS against pediatric epilepsy. Results from small observational studies suggest that VNS may be more effective in children than in adults and that the therapeutic benefits are achieved more rapidly [5,6]. Indeed, VNS in pediatric patients is associated with fewer epilepsy-related events and improved quality of life, as well as cost savings and reduced use of medical resources [7].

The auricular branch of the vagus nerve (ABVN) innervates the auricular concha and so provides non-invasive access to the vagus nerve (VN). Several studies have suggested stimulation of the ABVN for the treatment of epilepsy [8–10]. In animal experiments, we observed equivalent antiseizure effects of transcutaneous auricular vagus nerve stimulation (ta-VNS) and direct cervical VNS [11]. A preliminary trial reported an overall reduction of seizure frequency in five of seven patients after 9 months of ta-VNS and verified the long-term safety of ta-VNS [12].

In this preliminary study, we examined the efficacy and clinical outcome of ta-VNS in patients no more than 12 years old with medically refractory epilepsy.

2. Methods

2.1. Patients

Patients were enrolled in Xuanwu Hospital, Tiantan Hospital, and Beijing Children's Hospital, all institutions affiliated with Capital Medical University. The patients were defined as having medically refractory seizures based on the failure of two or more antiepileptic drugs (AEDs). Patients were included based on the following inclusion criteria: a) diagnosed with epilepsy, b) 12 years old or younger, c) following a constant drug regimen (number and dose) for at least eight weeks prior to ta-VNS, and d) willing and able to document seizure frequency until the completion of the study or having guardians willing and able to document seizure frequency until the completion of the study. Patients

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were excluded a) if they had already received VNS therapy or b) if their epilepsy was accompanied by a progressive central nervous system disease or severe heart, liver, kidney, or blood diseases.

The patients were required to maintain the same drug regimen throughout the study. The study was approved by the Ethics Committee of the Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences. Written informed consent was obtained from the patients and their guardians.

2.2. Study design

Each guardian was given a diary and a home ta-VNS device. The subjects and their guardians were carefully instructed on the use of the ta-VNS device. The diary was used to record the frequency of seizures, usage of the ta-VNS instrument, and any adverse events associated with ta-VNS. The seizure frequency of each subject was assessed at baseline and after 8 weeks, from week 9 to 16 and from week 17 to the end of week 24. Correlations between seizure frequency reduction after 24 weeks of ta-VNS and age, gender, seizure type, seizure duration, and initial seizure frequency at baseline were also investigated.

2.3. Transcutaneous auricular VNS

Transcutaneous stimulation was performed on bilateral auricular conchae using an ear vagus nerve stimulator (TENS-200, Suzhou, China) attached by two pairs of electrode clips (Fig. 1). The electrode clips are made of conductive rubber and are 5 mm in diameter. For ta-VNS, one electrode was clipped on the concha cavity and the other on the concha cymba. The stimulation frequency of the ta-VNS was 20 Hz, and the intensity was increased gradually from 0.4 mA to 1.0 mA according to patient tolerance. Transcutaneous stimulation was performed three times a day, 30 min per session. Professional technicians trained the patients and their caregivers on the proper use of the stimulator.

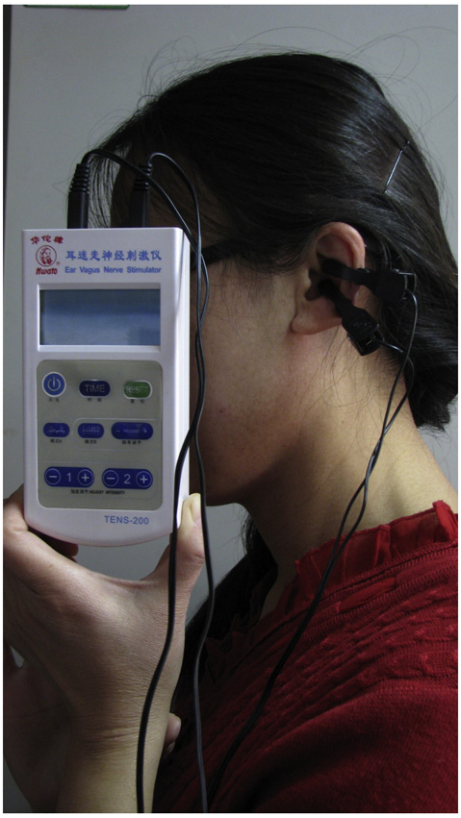

Fig. 1. The ta-VNS device, the stimulator clips, and the stimulation positions at the concha cavity and the concha cymba.

2.4. Outcome assessment

The primary treatment outcome measure was the change in seizure frequency from baseline to that after 8 weeks, from week 9 to 16 and from week 17 to the end of week 24 of ta-VNS treatment as recorded in the patient's seizure diary. Seizure outcomes were expressed by a modified Engel scale [13]. According to the effect of ta-VNS, patients were assigned to one of four outcome groups: I — seizure-free, II — frequency reduction ≥90% but <100%, III — reduction ≥50% but <90%, and IV — reduction ≥0 but <50%. Patients exhibiting a seizure frequency reduction of ≥50% (outcome groups I–III) were considered responders, and group IV patients were considered nonresponders.

2.5. Data analyses

The raw data from the seizure diaries and medical records were entered into Microsoft Excel (Office 2010). All statistical calculations were performed using SPSS v.14.0 (SPSS, Inc., Chicago, IL). The seizure frequency was counted over 8-week epochs. The mean numbers of seizures after 8 weeks, from week 9 to week 16 and from week 17 to the end of week 24, were compared with baseline frequency by paired sample t-tests. Categorical data were compared by chi-square tests. The correlations between seizure frequency reduction class (groups I–IV) after 24 weeks of ta-VNS and the clinical parameters of age, gender, seizure type, seizure duration, and seizure frequency at baseline were evaluated by Pearson's correlation test. A P-value<0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Fourteen patients with epilepsy (11 males and 3 females) of mean age 7.64 years (range: 1–12 years) were enrolled in this study to evaluate the therapeutic efficacy of ta-VNS (Table 1). Three patients were 2 to 4 years old (21.43%), four were 5 to 8 years old (35.71%), and seven were 9 to 12 years old (42.86%). Three patients had complex partial seizures with secondary generalization (21.43%), four had generalized seizures (28.57%), one had simple partial and generalized seizures (7.14%), one had simple partial seizures (7.14%), and five had complex partial seizures (35.71%). The median seizure frequency at baseline was 25.25 events per week (range: 0.75–75).

3.2. Seizure frequency reduction by ta-VNS

One patient discontinued treatment due to lack of treatment effect after 8 weeks. The remaining 13 patients completed the entire 24-week study with no changes in medication. After 8 weeks of ta-VNS, one patient was seizure-free (class I), two patients experienced seizure frequency reductions of no less than 90% (class II), one patient experienced a seizure frequency reduction of ≥50% but <90% (class III), while the remaining 9 patients experienced reductions of <50% (class IV, classified as nonresponders). Four patients were seizure-free by the end of week 16, one patient experienced a seizure frequency reduction of more than 90%, two patients experienced seizure frequency reductions of less than 90% but more than 50%, and six patients experienced seizure frequency reductions of less than 50%. By the end of the 24-week ta-VNS study, four patients were seizure-free, one patient achieved a reduction of more than 90%, two patients achieved a reduction of less than 90% but more than 50%, and six patients achieved a reduction of less than 50% (Fig. 2). The mean number of seizures during the baseline prior to ta-VNS was 26.04±8.37 per week, falling to 16.38±6.48 per week during the first 8 weeks, to 8.89±3.77 per week during the second 8-week