Version number: 5.0; Version date: 2024.02.03
Research unit: Southern Medical University Southern Hospital

Study protocol

Title	Noninvasive vagus nerve stimulation for the prevention and treatment of primary headache: a randomized, double-blind, single-center clinical study.
Application	Department of Neurology, Nanfang Hospital, Southern Medical University
Purpose	1) Main objectives: This study will validate the efficacy of nVNS in the acute and preventive treatment of primary headache in children and adolescents and establish an objective evaluation system for the improvement of headache based on the electrocardiogram (ECG) and electromyography (EMG) parameters during nVNS intervention. 2) Secondary objectives: This study will further explore the role of stimulation parameters on the effect and realize the optimization of parameters.
Research hypothesis	1) Transcutaneous auricular vagus stimulation can prevent acute primary headache in adolescents; 2) Heart rate variability changes significantly during acute attack of primary headache.
Design and procedure	This study was a randomized, double-blind, single-center study. Patients will be randomly assigned to two groups by envelope drawing. The subjects will be divided into two groups: the acute intervention group and the preventive intervention group. In each group, the subjects will be randomly divided into the experimental group and the control group by means of envelope extraction. Children and adolescents (7-20 years old) with migraine who met the inclusion criteria were enrolled as subjects, and the changes in headache scores before and after intervention were compared. The intervention method was as follows: ictal intervention, in which subjects were evaluated for headache improvement after a short intervention during an acute exacerbation for acute group, and 8 weeks for prevention group. By wearing a vagus stimulator, the stimulating electrode was located in the concha region rich in vagus nerve fiber endings, and the appropriate stimulation intensity was adjusted for stimulation. Therefore, this study will verify the effect of nVNS on the acute attack and preventive treatment of primary headache in children and adolescents. Based on the electrocardiogram and electromyography indicators during the intervention process of nVNS, an objective evaluation system for the improvement of headache by nVNS is established, and the role of stimulation parameters on the effect is further explored to realize the optimization of parameters.
Sample size	The acute intervention group: A single-center, randomized, double-blind trial was conducted. Patients were randomly assigned to two groups by envelope drawing. According to the sample size estimation calculation method, $n = 2*[(Z\alpha+Z\beta)\sigma/d]2$ (sample size was estimated using the statistical effect analysis software G*Power3.1), Based on the moderate effect size (Cohend's $d = 0.5$) and $\alpha = 0.05$, $\beta = 0.80$ in Martelletti et al., (2018), the sample size was estimated to be 64 subjects per group. Among them, 128 children and adolescents (7-20 years old) were divided into experimental group (64 cases) and sham group (64 cases). The preventive intervention group: A single-center, randomized, double-blind trial was conducted. Patients were randomly assigned to two groups by envelope drawing. According to the sample size estimation calculation method, $n = 2*[(Z\alpha+Z\beta)\sigma/d]2$ (sample size was estimated using the statistical effect analysis software G*Power3.1), Based on the moderate effect size (Cohend's $d = 0.5$) and $\alpha = 0.05$, $\beta = 0.80$ in Martelletti et al., (2018), the sample size for the study was estimated to be 64 participants per group. According to the clinical sample dropout rate (20%), the sample size was adjusted to 80 subjects in each group. Among them, 160 children and adolescents (7-20 years old) were divided into experimental group (80 cases) and sham group (80 cases).

Eligibility	Inclusion Criteria: Patients with migraine, cluster headache and tension-type headache were diagnosed according to Chinese Guidelines for the diagnosis and Treatment of Migraine (2022 edition) and Chinese Guidelines for the diagnosis and treatment of cluster headache (2022 edition). Age >=7 years old, <=20 years old; Patients have experienced headache on 3-15 days per month in the past; Maintain a stable dose and frequency of medication and do not take new drugs during the course of participating in the trial; They volunteered to participate in the trial and signed informed consent. Exclusion Criteria: History of secondary headache, aneurysm, intracranial hemorrhage, brain tumor, severe head trauma, drug abuse, addiction, syncope, or seizures; prior migraine-preventive surgery, cervical vagotomy, or implantation of an electronic or neurostimulator device; Simultaneous use of other devices (e.g., TENS devices, muscle stimulators); An implantable medical device in use, such as a pacemaker, hearing aid, or any implantable electronic device; underwent head and neck nerve block within the past 2 months; Opioid use (more than 2 days per month); Use of analgesics alone or non-steroidal anti-inflammatory drugs (more than 15 days per month); Or tamoxifen, ergots or combination analgesics (more than 10 days per month); Patients who underwent cervical vagotomy (cervical vagotomy); Pediatric patients (under 6 years old); Pregnant women; Patients with clinically significant hypertension, hypotension, bradycardia or tachycardia;

	Patients with congenital heart disease; Mental/cognitive disorders, etc.
Evaluating Indicator	The primary outcome : VAS score of headache. The secondary efficacy indexes : electromyography and electrocardiogram characteristics
Statistical method	Data from all participants conforming to the protocol set were included in the statistical analysis. Paired sample t test and mixed linear model were used to analyze the primary and secondary indicators.