

Study protocol

Title	Noninvasive vagus nerve stimulation for the prevention and treatment of primary headache: a single-arm, 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 single-arm, single-center, open-label study. 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. 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.
Sample size	Sample size estimation calculation method, referring to the statistical effect size in the trial of Cao et al., (2021), according to the change in headache score before and after intervention in the experimental group was significantly greater than zero, by $n = 2 * [(Z^{\alpha} + Z^{\beta})^2 / d]^2$ (sample size was estimated using statistical effect analysis software G*Power3.1), $\alpha = 0.05$, $\beta = 0.80$, the sample size of the experimental group was 15.
Eligibility	<p>Inclusion Criteria:</p> <p>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).</p> <p>Age ≥ 7 years old, ≤ 20 years old;</p> <p>Patients have experienced headache on 3-15 days per month in the past;</p> <p>Maintain a stable dose and frequency of medication and do not take new drugs during the course of participating in the trial;</p> <p>They volunteered to participate in the trial and signed informed consent.</p> <p>Exclusion Criteria:</p> <p>History of secondary headache, aneurysm, intracranial hemorrhage, brain tumor, severe head trauma, drug abuse, addiction, syncope, or seizures;</p> <p>prior migraine-preventive surgery, cervical vagotomy, or implantation of an electronic or neurostimulator device;</p> <p>Simultaneous use of other devices (e.g., TENS devices, muscle stimulators);</p> <p>An implantable medical device in use, such as a pacemaker, hearing aid, or any implantable electronic device;</p> <p>underwent head and neck nerve block within the past 2 months;</p> <p>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);</p> <p>Patients who underwent cervical vagotomy (cervical vagotomy);</p> <p>Pediatric patients (under 6 years old); Pregnant women;</p> <p>Patients with clinically significant hypertension, hypotension, bradycardia or tachycardia;</p>

	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.