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Single-centre, randomised and double-blind clinical trial on the efficacy of transcutaneous auricular vagus nerve stimulation in preventing and treating primary headache in children and adolescents: a study protocol

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ABSTRACT

Introduction Primary headaches pose a significant burden on children and adolescents, highlighting the need for effective non-pharmacological interventions. Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive modality that has demonstrated efficacy in adult populations with primary headaches and has shown safety in adolescents with mental health disorders. However, its effectiveness in managing acute headache episodes and preventing recurrences in paediatric populations remains underexplored. This study aims to evaluate the immediate analgesic effects of taVNS during acute headache episodes and its preventive efficacy over a 4-week period. Additionally, we will investigate potential biomarkers associated with primary headaches and elucidate the underlying mechanisms of taVNS through electromyography (EMG) and electrocardiography (ECG) assessments.

Methods and analysis This study will employ a double-blind, randomised clinical trial design involving 288 children and adolescent participants diagnosed with primary headaches. The study will consist of two substudies: the acute period (AP) study and the preventive period (PP) study. Participants will be randomly allocated to receive either taVNS or sham stimulation. The primary outcome for the AP study will be the reduction of pain intensity 2 hours after treatment, as measured by the visual analogue scale, while the PP study will assess the change in the headache attack days over the treatment period. Secondary outcomes will include EMG and ECG parameters.

Ethics and dissemination The study will adhere to the principles outlined in the Declaration of Helsinki and has received ethical approval from the Medical Ethics Committee of Nanfang Hospital, Southern Medical University (NFEC-2024–057), on 2 January 2024. Informed consent will be obtained from all participants or their guardians. The findings will be disseminated through peer-reviewed journals and presented at relevant scientific conferences.

Trial registration number NCT06277063.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Double-blind, randomised methodology minimises selection and performance bias, ensuring robust and unbiased results.
⇒ The study includes both acute and preventive periods, providing a holistic understanding of the therapeutic effects of transcutaneous auricular vagus nerve stimulation (taVNS) on primary headaches.
⇒ Measuring ECG and EMG provides objective data on the autonomic and muscular responses to taVNS, helping validate its effects on headache mechanisms.
⇒ The home-based intervention in this study has high ecological validity.
⇒ The study may be limited by lacking the neural signal data such as EEG or fMRI to deepen the neural mechanisms underlying the effects of taVNS in this population.

INTRODUCTION

Headache, recognised as a prevalent neurological disorder, significantly impacts the quality of life and ranks as the second leading cause of disability worldwide.[1–4] Beyond causing pain, headaches are associated with complications such as sleep disturbances, mood disorders, gastrointestinal issues and hearing problems, with chronic migraines being especially debilitating.[5 6] While the epidemiology of primary headaches in adults is well-documented, research on minors remains relatively limited. Studies indicate that 30.3% of high school students in China experience headaches at least once a week,[7] and a European study revealed that 75.7% of 3384 students aged 10–18 reported headaches annually, with prevalence increasing with age.[8 9] A meta-analysis identified 48 studies of paediatric headaches and revealed

that the pooled prevalence of primary headaches was 11% for migraine overall and 17% for tension-type headache (TTH).[10] Recent advancements in medication, such as calcitonin gene-related peptide (CGRP) antagonists and injectable monoclonal antibodies, have demonstrated efficacy and tolerability in managing migraines.[11] However, these pharmacological treatments are not universally effective and are contraindicated for non-adults, where the risks often outweigh the benefits. This underscores the urgent need for safe, non-pharmacological and repeatable therapeutic options for managing primary headaches in children and adolescents.[12–14]

Non-invasive neurostimulation methods open a new field for the treatment of headaches in children and adolescents.[15] Transcutaneous auricular vagus nerve stimulation (taVNS) is an emerging non-invasive method that offers a promising alternative for headache management. The vagus nerve is the most extensive cranial nerve in the human body, playing a crucial role in regulating involuntary physiological functions, including heart rate, respiration, digestion and homeostasis as a key component of the parasympathetic nervous system (PNS).[16 17] taVNS works by stimulating the auricular branch of the vagus nerve (ABVN) in the ear to modulate both the autonomic and central nervous system.[18]

Early studies have demonstrated the efficacy and the safety of taVNS in alleviating primary migraine and the underlying mechanisms in adults.[19–30] An early study has shown that a 12-week taVNS regimen significantly reduced headache attack days in patients with chronic migraine compared with baseline.[20] Notably, 1 Hz taVNS has shown more pronounced preventive effects on chronic migraines than 25 Hz stimulation.[20] Another study observed decreased migraine days, pain intensity of acute attack period and attack frequency after 4 weeks of taVNS compared with sham treatment.[29] One case report suggests the potential of the auricular vagus nerve stimulation on the TTH.[19] The therapeutic mechanism of taVNS involves activating the ascending antinociceptive pathway from the periaqueductal grey (PAG) and raphe nuclei to the thalamus,[31] which is critical to migraine development and maintenance.[32–34] Additionally, taVNS has been shown to modulate key brain regions, including the nucleus of tractus solitarius (NTS), locus coeruleus (LC), raphe nuclei and insula,[21] the functional connectivity of the PAG[23] and the central vagus nerve pathway in patients with migraine.[27]

Early studies demonstrate the safety of taVNS in children and adolescents with efficacy in treating depressive and anxiety-like behaviours,[35] major depressive disorders[36] and autism spectrum disorders[37] without significant long-term adverse effects. However, its effectiveness for primary headaches in this population remains unexplored. We propose investigating the acute and preventive effects of taVNS on migraine, TTH and cluster headache (CH) in a comprehensive exploratory study among children and adults. Early studies have shown the efficacy of non-invasive VNS on these three types of headaches. These headache types share overlapping mechanisms, including trigeminovascular system dysfunction, neuroinflammation and emotional or sleep-related factors,[38 39] which align with the therapeutic scope of taVNS.[15] Including all three types is also practical, as migraine is the most common recurrent headache in children, TTH dominates in adolescents, and CH, while less frequent, is more prevalent in adolescents than younger children.[40] This inclusive approach enhances recruitment feasibility and explores taVNS's broad efficacy across primary headaches.

The visual analogue scale (VAS) is commonly used to evaluate the efficacy of migraine treatments; however, its subjective nature has led researchers to explore objective and quantitative biomarkers. Electromyography (EMG) and ECG are two promising alternatives. EMG in the trapezius muscle has shown a strong correlation with headache onset.[41] This correlation is evident within the first 10 minutes of headache onset and diminishes gradually, suggesting that EMG recordings from the neck could help differentiate between TTH and other headache types, as well as evaluate pain relief.[41] High reproductivity has been reported for EMG measurements in evaluating headaches among adolescents with migraines and TTH.[42]

Additionally, ECG offers a quantitative assessment of the autonomic nervous system through heart rate variability (HRV) analysis, which is closely linked to vagal regulation. An early study has recorded EMG and ECG signals during auricular vagus nerve stimulation treatment in a patient with primary cervical dystonia. After treatment, both the VAS score and neck muscle tone measured by EMG were significantly reduced, and the HRV increased significantly.[42] Abnormal HRV changes have been proposed as potential biomarkers for headaches, especially for CH.[43 44] By examining HRV patterns during and after taVNS, real-time changes in vagal regulation can be identified during treatment. Early studies indicate that differential autonomic regulation may underlie individual responses to taVNS, making HRV a potential predictor of treatment efficacy in primary insomnia[45] and possibly migraines.

Taken together, in this study, we aim to examine the effectiveness of taVNS as both a therapeutic acute intervention and a preventive approach for primary headaches in children and adolescents. We will investigate the EMG characteristics as potential biomarkers to identify TTH and evaluate the efficacy of taVNS. Additionally, we will analyse HRV features from ECG data to evaluate the regulatory impact of taVNS on the autonomic nervous system and its role as a biomarker for headache improvement and identification. This study aims to shed light on the relationship between the mitigation of headaches and changes in EMG and ECG features, laying the groundwork for incorporating taVNS into primary headache management strategies for children and adolescents.

METHODS AND ANALYSIS

Participants

This is a single-centre, randomised, double-blind study. The study includes two substudies: an acute period (AP) study and a preventive period (PP) study, each with a

taVNS group and a sham taVNS group. The AP study will assess the efficacy of taVNS in treating primary headaches during the acute stage, while the PP study will evaluate the preventive efficacy of taVNS on primary headaches. Participants eligible for this trial must meet several criteria, including a verified diagnosis of migraine, CH or TTH by a certified clinician. The diagnosis must adhere to the standards outlined in the 2022 editions of the Chinese Guidelines for the Diagnosis and Treatment of Migraine and Cluster Headache. Participants will undergo cranial MRI or CT scans to exclude headaches caused by organic brain lesions. Given the limited research on primary headache among the young population, as identified in a recent large meta-analysis,[10] this study appropriately broadens the age range to include patients aged 7–20 years. Therefore, this study appropriately expanded the age range to include patients aged 7–20 years. Additionally, candidates should have endured headaches for 3–15 days per month in the preceding year, adhered to a stable regimen of medication in terms of dosage and frequency and will not take new medications throughout the trial. Comprehensive information about the study will be provided, and informed consent (see online supplemental appendix 1) must be obtained from both the patients and their legal guardians.

The study will exclude individuals with conditions that may interfere with outcomes or pose risks to participants. Exclusion criteria include secondary headaches and severe medical conditions such as aneurysms, intracranial haemorrhage, brain tumours or significant head injuries. Individuals with a history of drug abuse, addiction, syncope, seizures, foramen ovale occlusion or cervical vagotomy are also ineligible. Patients using opioids more than two times per month, analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) more than 15 days per month or specific medications such as tamoxifen, ergots or combined analgesics more than 10 days per month will be excluded. Additionally, the study will not include children under 6 years of age, pregnant women or individuals with significant cardiovascular conditions, mental or cognitive disorders or contraindications to taVNS (eg, ear inflammation, brain implants or a history of epilepsy).

This study has received approval from the Medical Ethics Committee affiliated with the Nanfang Hospital of Southern Medical University for Clinical Studies (NFEC-2024–057). It has been registered on ClinicalTrials (NCT06277063) on 10 March2024.

Patient and public involvement

The parents of two children with migraine were involved in the protocol design. They provided practical advice on how to streamline the process of bringing the device home and teaching the participants and their parents to use it. Based on their feedback, several changes were made to the original study procedure, including presetting the parameters, simplifying the device return process and improving the method for recording VAS scores.

Sample size

The sample size was determined using $n=2*[(Z_{\alpha}+Z_{\beta})^{\sigma/d}]^2$ and statistical power analysis software G*Power 3.1. Since no prior studies have evaluated the effects of taVNS on paediatric populations with primary headaches, we estimated the sample size for the AP study based on data from a non-invasive VNS acute treatment study on adult primary headache by Martelletti *et al*,[46] and for the PP study, based on the preventive treatment studies of taVNS by Zhang *et al*[29] and another non-invasive VNS study by Diener *et al*.[47] The effect size is estimated to range from 0.5 to 0.65 (Cohen's d). For the AP study, we used a medium effect size (Cohen's d=0.5), calculated from the difference in pain relief between the VNS and sham groups in Martelletti *et al*'s study and applied the parameters of α=0.05 and β=0.80. Based on these calculations, the estimated sample size for each group in the AP study was 64. For the PP study, the sample size was conservatively estimated based on a medium effect size (Cohen's d=0.5) and a 20% dropout rate due to the 8-week treatment and follow-up period. A total of 160 participants will be enrolled.

Randomisation method and blinding

Patient candidates may opt to participate in either the AP or PP study after receiving a detailed briefing on the research protocol. On enrolment, participants will randomly select a sealed envelope containing a unique digital identifier associated with either the AP (1–128) or PP (1–160) study. In the AP study, participants drawing identifiers AP1–AP64 will be assigned to the taVNS group, while those with identifiers AP65–AP128 will be placed in the sham group. Similarly, in the PP study, participants drawing identifiers PP1–PP80 will be allocated to the taVNS group, and those with identifiers PP81–PP160 will be assigned to the sham group. To maintain allocation concealment, the contents of the envelopes will only be revealed after the follow-up assessments are completed. The entire randomisation process will be overseen by a research assistant who is not involved in the intervention or data analysis phases.

To maintain blinding, a certified doctor will screen eligible patients, remaining unaware of their group assignments. Second, enrolled participants will be randomly assigned to groups by a designated researcher. This researcher will receive an instruction sheet containing the digital identifier and corresponding stimulation site information without knowledge of the active or sham assignment. Using identical equipment for both groups (eg, EMG, ECG and stimulation devices), the researcher will collect biological signals and adjust stimulation intensity. Importantly, the researcher's role will be limited to assisting and instructing participants and their parents on how to place the electrodes on the ear, without knowledge of which electrode sites correspond to the active or sham group. Both groups will experience a similar sensation of electrical stimulation at the electrode site, such as maximum tolerable stimulation without painful feeling,

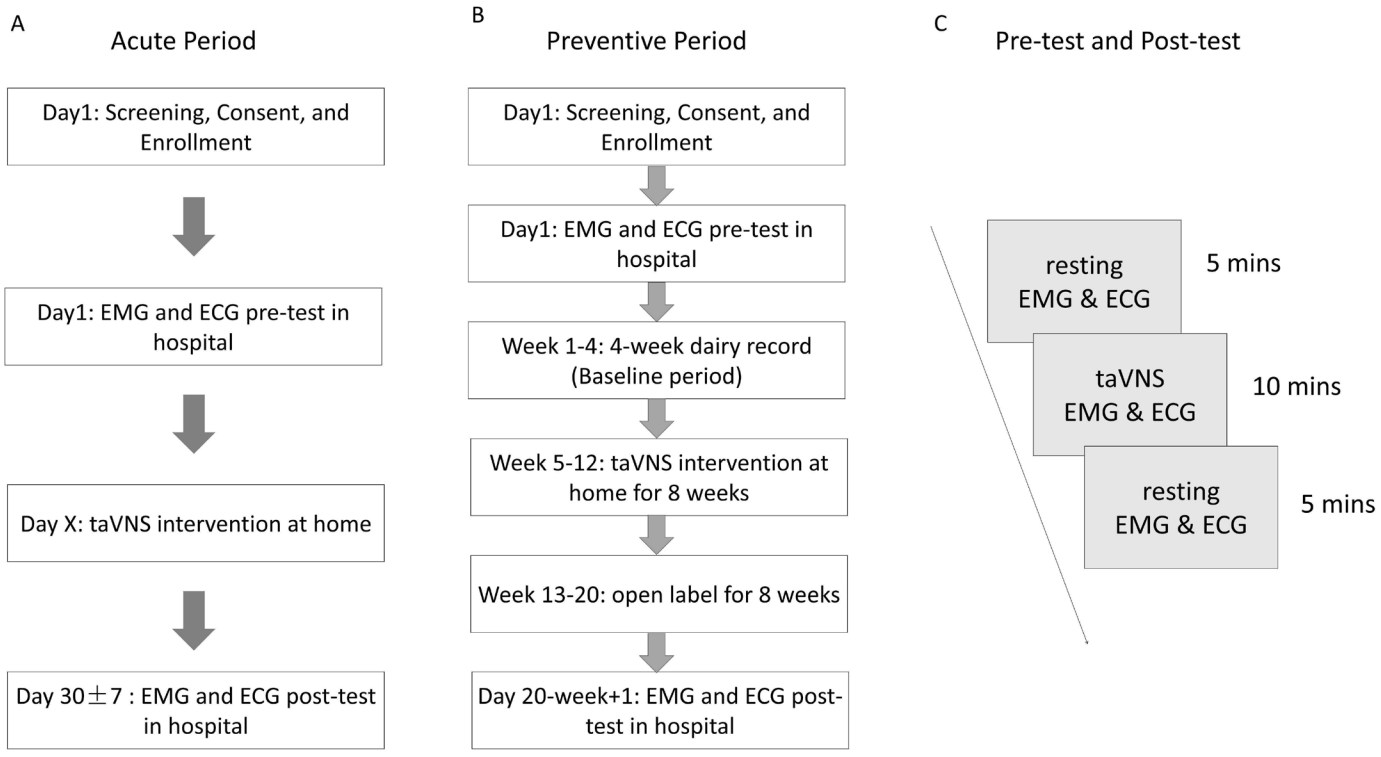

Figure 1 Study flow chart. (A) The timeline and procedures of the AP study. (B) The timeline and procedures of the PP study. (C) The 5–10–5 measurement during pretest and post-test for both AP and PP studies. AP, acute period; EMG, electromyography; PP, preventive period; taVNS, transcutaneous auricular vagus nerve stimulation.

ensuring participant blinding. Third, all collected data will be anonymised before being provided to the data analysis team. Unblinding will occur only after the completion of all data analyses for participants, and this process will be conducted by a separate set of researchers to preserve blinding throughout the trial.

Procedures

taVNS and sham group

For both AP and PP studies, the taVNS and sham groups will be different in the stimulation position of the ear electrode only. For the participants in the taVNS group, the stimulating electrodes will be placed in the cymba concha area, which is rich in ABVN fibres.[48] For the sham group, the ear electrodes will be the same but will be placed near the auricle and the earlobe. The stimulation parameters of the taVNS and sham groups will be the same (see Equipment and Parameters section).

AP study

As shown in figure 1A, the whole study process will mainly include three phases after enrolment: pretest (on Day 1), intervention (on Day X) and post-test (on Day 30±7).

Pretest period

On the first day after enrolment, participants will provide basic demographic information, including gender, age, medical history, family history of genetic conditions, current medical history, medication use and allergy history, and they will be assigned their randomisation number. Baseline data will then be collected, including VAS scores, EMG and ECG signals. EMG/ECG signals will be collected in three stages: a 5-min resting state, a 10-min taVNS/sham stimulation stage, and another 5-min resting state (5–10–5 measurement) (as shown in figure 1C). Specifically, the participant will be positioned in front of a computer, with both upper limbs comfortably placed on the table. They will then proceed to wear the ear electrodes, neck EMG sensors and the ECG sensor. Ear electrodes will be placed according to their grouping. The experimenter will disinfect the cymba concha area or the sham stimulation area of the participant's left ear (as shown in figure 2A) using an alcohol wipe. Subsequently, the electrodes will be attached to the left ear. The amplitude of the taVNS device will be adjusted to ensure it remains below the participant's pain threshold. The researcher will attach two sets of wireless EMG electrodes to the trapezius muscles on both sides of the neck to record surface EMG activity. A set of wireless ECG sensors will be placed on the chest to record ECG activity prior to the treatment sessions (as shown in figure 2B,C).

Following the baseline measurement, participants and their legal guardians will receive instructions on the proper use of the device. Once they are familiar with its operation, they will take the device home and use it at the onset of a headache attack. The stimulation parameters (except for the amplitude) of the taVNS device will be preset before it is taken home.

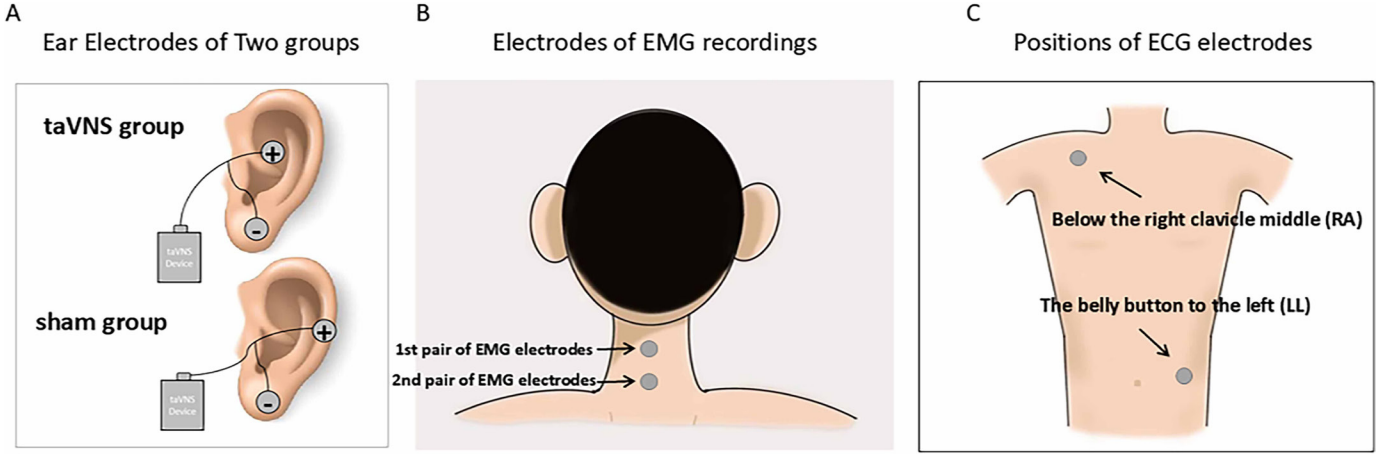

Figure 2 (A) The upper ear illustrates the electrode placement sites for participants in the taVNS group, with electrodes positioned on the cymba concha and earlobe. The lower ear depicts the electrode placement for the sham group, where electrodes are similarly positioned but placed near the auricle and earlobe. (B) Two pairs of wireless EMG electrodes will be attached to the trapezius muscles while the participant is in a supine position. (C) The positions of a pair of ECG electrodes are at RA and LL. EMG, electromyography; LL, left leg; RA, right arm; taVNS, transcutaneous auricular vagus nerve stimulation.

Period of intervention

When participants experience an acute headache, they will use the device for headache intervention according to the research staff training procedure. Simultaneously, the severity of the headache attacks will be recorded in a headache diary card by the VAS score. The heart rate and timing of the attacks will also be recorded. The treatment process involves administering stimulation within 20 min of onset, with a duration of half an hour, followed by immediate post-treatment assessments. Subsequent assessments will be conducted at 2 hours, 8–12 hours, 24 hours and 36–48 hours after the completion of the treatment.

Post-test period

The device will be returned to the hospital within 48 hours after completion of the intervention, and another 5–10–5 EMG/ECG measurement will be performed.

PP study

As shown in figure 1B, the whole study process will mainly include three phases after enrolment: pretest and baseline period, intervention and unblinding period, and post-test period.

Pretest and baseline period

The participants in the PP group will receive the same VAS, ECG and EMG measurements as the participants in the AP study. In addition, participants in the PP group will be instructed to finish 4 weeks baseline data of headache assessment using the headache diary. During the 4 weeks, they need to record the onset time, duration, pain intensity (using VAS score), accompanying symptoms and medication use. After the 4 weeks baseline, researchers will collect their diaries and evaluate whether the participant can take part in the PP study. Then, the participants who are enrolled will be assigned to the taVNS or sham group according to randomisation.

Period of intervention and unblinding

Participants and their guardians will be trained by doctors and researchers on how to use the device, ensuring their familiarity with its use. The patients will take the device home and will be instructed to use it regularly for 8 weeks, two times a day (7:00–8:00 and 19:00–20:00). The prevention effect will be evaluated during 8 weeks of home intervention and an additional 8 weeks of open-label observation postintervention. During the 16 week period, participants will be required to maintain headache diaries, with data collected every 4 weeks. The headache diary will include the time of headache onset, duration, pain intensity (VAS score), accompanying symptoms and medication use.

Post-test period

The device will be returned to the hospital within 48 hours after completion of the home intervention. After the 8 weeks of open-label observation, another 5–10–5 EMG/ECG measurement will be performed in the hospital.

Outcome measures

The primary outcome measures and secondary outcome measures of two studies are shown in table 1.

For the AP study, the primary outcome measure is reduction in pain intensity, as assessed by VAS, 2 hours after the taVNS or sham treatment at home. The VAS is a widely used assessment tool that has been applied to various pain evaluations. In addition to the primary outcome, the AP study will include several secondary measures, including the change in VAS scores at other time points and the EMG and ECG features. Specifically, the averaged signal and the power density of EMG signals and the time domain and frequency domain of HRV features will be extracted.

For the PP study, the primary outcome measure is the reduction in the headache attack days during the

Table 1 The primary and secondary outcomes

Study	Primary outcome measures	Secondary outcome measures
AP study	Reduction in pain intensity assessed by VAS 2 hours after treatment	Change in pain intensity assessed by VAS scores, half hour, 8–12 hours, 24 hours, and 36–48 hours after treatment and the EMG and ECG features.
PP study	Reduction in the headache attack days during intervention	Days of headache medication, mean headache intensity, mean headache duration, and the EMG and ECG features

AP, acute period; EMG, electromyography; PP, preventive period; VAS, visual analogue scale.

intervention period. The secondary measures include mean headache attack days during the open-label period, the days of acute headache medication, mean headache intensity, mean duration of headache and the features derived from EMG and ECG.

Equipment and parameters

The taVNS device (BC102), EMG (BC107) and ECG (BC116) used in this experiment will be provided by Shenzhen BrainClos Technology Co. The stimulation parameters of the taVNS device are as follows: a frequency of 1 Hz, a pulse width of 300 µs and a stimulation intensity adjustable between 0 and 7.2 mA. The device delivers a constant current output, with the intensity finely adjustable across 60 levels, each representing a 0.12-mA increment. The output maintains a precision margin within 20%. The stimulation intensity will be customised based on the participant's tolerance and comfort level. Both EMG and ECG have a sampling rate of 1000 Hz, and the signals are obtained through a 24-bit AD converter. The two devices are designed to use Bluetooth communication with very low noise to acquire uV-level electrophysiological signals. Bluetooth minimises signal artefacts from patient movements and avoids industrial frequency interference at 50 Hz.

EMG and ECG data processing

EMG signals filtered with a low-pass filter of 250 Hz. The filtered EMG signals were rectified and averaged in a moving window with a length of 200 samples. The power spectral density of 0–160 Hz of the signal will be extracted. Analyses were performed on representative data segments of 20-s length and the power density of representative frequency band of the EMG signals from resting stage, stimulation stage and resting stage during the EMG examinations of preintervention and postintervention, respectively.

ECG signals will be filtered with a low-pass filter of 20 Hz before identifying the R–R interval and calculating HR and HRV. HRV will be represented in both the time domain and frequency domain. The chosen index of HRV in the time domain is the root mean square of successive R–R interval differences (RMSSD), which reflects the beat-to-beat variance of HR and serves as a primary measure for estimating vagally mediated changes in HRV.[49] Spectral-domain measures of HRV are the total power (TP, 0.0033–0.4 Hz), the high-frequency power (HF, 0.15–0.4 Hz), low-frequency power to TP (LF/TP, 0.04–0.15 Hz), high-frequency power to TP (HF/TP, 0.15–0.4 Hz) and low-frequency to high-frequency power (LF/HF). The ratio may provide an estimate of the balance between sympathetic nervous system (SNS) and PNS activity.

Statistical analysis

The critical level of significance for all statistical analyses will be set to p value <0.05. The analyses will be carried out using the Matlab and R statistical software packages. Missing data will be addressed using multiple imputation methods to minimise bias, ensuring robustness of the results.

Analysis of main endpoint indicators

Prior to conducting inferential statistics, Kolmogorov-Smirnov (K-S) tests will be employed to assess the normality of the measurement data. In cases where the data deviate from a normal distribution, transformation methods will be applied. Specifically, logarithmic transformation may be employed for data exhibiting extreme skewness, while the square root transformation can be adopted for data displaying moderate or small skewness. The examination of the difference in age, headache types and gender between the active taVNS and sham group will be conducted for the AP study and the PP study, respectively.

To evaluate the primary efficacy of the AP study (eg, VAS scores), a paired samples t-test will be performed before and after the treatment sessions for both the taVNS and sham group. This analysis will determine if there is a significant improvement in relief of headache after taVNS treatment or sham intervention. The VAS scores before and after the treatment sessions will be subtracted to calculate the improvement scores, representing the treatment effect. Independent samples t-tests will be conducted between the taVNS group and the sham group to assess the potential benefits of taVNS. The effect sizes of the treatment effects (Cohen's d) will be documented.

Primary measures of the PP study between taVNS and sham groups will be examined using mixed analysis of variance (Mixed ANOVA), which is a statistical test used to analyse data that involve both between-subjects and within-subjects factors. The headache attack days of the 4 week baseline, the last 4 week of intervention and the last 4 week of open label periods of two groups will be tested by mixed ANOVA. Pairwise comparisons will be performed for three sets of data for each group, respectively. To address the risk of alpha inflation, Bonferroni

correction will be applied to counteract the problem of multiple comparisons.

Analysis of secondary endpoint indicators

Secondary outcome measures between groups will be statistically examined by mixed ANOVA, paired t-test and independent samples t-test to examine the efficacy of taVNS. The statistical results will be corrected based on Bonferroni's principle as this statistical operation requires multiple comparisons, and there will be a bias of Alpha inflation. In addition, correlation analysis will be conducted between the change in VAS scores, the change in headache attack days (ie, treatment efficacy index) and the HRV features.

For the analysis of the EMG features, the subjects in each group will be further divided into three subgroups based on their diagnosis, that is, migraine, CH and TTH. To investigate whether EMG features can be used to distinguish three types of headaches, ANOVA will be performed to test the difference in the EMG features of these three groups before the treatment in each study. For two TTH subgroups (receiving taVNS vs receiving sham), mixed ANOVAs will be performed on EMG features from pretest and post-test to examine the treatment efficacy.

Records of side effects

TaVNS does not have any known long-term risks, and no serious side effects or safety accidents have been mentioned in the existing studies. Participants in the process of using the instrument may experience some, all or none of these adverse reactions: skin pain in the ear, tinnitus, hoarse throat, nausea and vomiting. When the above symptoms occur, the subject should immediately communicate with the physician and discontinue the intervention. In most cases, the symptoms will disappear within a period of time after stopping the intervention.

ETHICS AND DISSEMINATION

This clinical trial will adhere to the Declaration of Helsinki and relevant Chinese regulations. The study has received approval from the Research Ethics Committee of the Nanfang Hospital (reference number: NFEC-2024–057) and has been registered on ClinicalTrials.gov (reference number: NCT06277063). Written informed consent will be obtained from each participant prior to the commencement of the study (see online supplemental file for the consent form and information sheet).

Throughout the study, all participant data will be meticulously recorded, stored confidentially and analysed. Relevant authorities may conduct audits to verify the authenticity and completeness of the data. Findings may be published in academic journals without disclosing participants' identities, thereby ensuring their privacy. The principal investigator is committed to upholding the dignity, privacy and health rights of participants and ensuring compliance with applicable privacy laws. Participants' anonymity will be maintained when presenting data at scientific conferences or in journal publications. Personal medical information collected during the study will remain confidential and will not be disclosed to third parties.

Additional measures will be implemented to ensure document confidentiality. However, in specific circumstances, such as medical emergencies, the sponsor, their designated physician or researchers may access a participant's identification code. Regulatory authorities may also require access to relevant documents for oversight purposes.

Contributors Conceptualisation, XX and YJ; methodology, SW, YX and XX; validation, XX and SL; resources, XX and YJ; writing—original draft preparation, SW, XY and XX; writing—review and editing, YJ and SL; visualisation, XX and SW; supervision, YJ; project administration, YJ; YJ acted as guarantor. ChatGPT was used to correct the grammatical mistakes in the article.

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Competing interests SL is the RA of BrainClos company. The other authors declare no conflict of interest.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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