Consent Form

Project Name: A Single-center, Double-blind, Randomized Clinical Trial on the Efficacy of Transcutaneous Auricular Vagus Nerve Stimulation (taVNS) in Preventing and Treating Primary Migraine

Scheme Version and Date: V6.0/2024-03-06
Informed Consent Form Version and Date: V6.0/2024-03-06

Dear Participants,

We invite you to participate in a research study that has been reviewed and approved by the Ethics Committee of Southern Medical University Southern Hospital. Before you make a decision, we hope you understand the reasons for conducting this study and what is required of you. Your participation is entirely voluntary, meaning you can choose to participate or not. The research team will explain this information sheet to you and address any questions you may have. If anything is unclear, please feel free to ask us. You are welcome to discuss this study and the information contained in this document with close relatives, family, friends, and your doctor.

After considering all information related to this study and having all your questions answered, if you agree to participate, the research team will ask you to sign the informed consent form and indicate the date (at the end of this document) before any study-related procedures take place.

I. Background of the Study

Headache is a common neurological disorder that seriously affects patients' quality of life. Headache seriously affects quality of life and has become the second leading cause of disability in the world. In recent years, non-invasive vagus nerve stimulation (nVNS), as a novel intervention method, has attracted wide attention in the field of headache treatment. nVNS is a kind of non-implantable non- invasive neuroregulation therapy, which stimulates the vagus nerve endings in the neck or ear through a weak current and percutaneous way. As an alternative and emerging therapy, it provides new ideas for improving headache.

II. Objectives of the Study

The aim of this study is to validate the efficacy of nVNS in the acute-onset and preventive treatment of primary headache in children and adolescents. Based on the electrocardiogram and electromyography indicators during the intervention of nVNS, an objective evaluation system for the improvement of headache by nVNS was established. The effect of stimulation parameters on the effect was further explored to realize the optimization of parameters.

III. Study Procedure

How many people will participate in this study?
Approximately (288) individuals will participate in this study at our institution.

Duration of the study
The study will be divided into 2 period: intervention of acute exacerbation(test 1) and intervention of prevental period(test 2). You can choose to join in one of period or both of them. In each period, you will be assigned to different groups by drawing envelopes, so you will have a 50% chance of getting into the control group and an equal chance of getting into the experimental group.

If you decide to join the test 1, the study will last for about 1 hour. If you choose to join the tset 2, the study will last for about 8 weeks. You can choose to withdraw from the study at any time without any penalties or loss of benefits. However, if you decide to withdraw during the study, we encourage you to consult with your doctor first.

Study steps
Participating in this study will not affect your existing treatment; you will continue to receive your regular treatment, and your diagnosis and treatment will be determined by the research doctor based on standard practice. Visual analogue scale (VAS) was used to assess pain intensity when headache occurred.
Test 1: Within 20 minutes of onset, patients received nVNS for half an hour, and post-treatment assessments were recorded immediately, 2 hours, 8-12 hours, 24 hours, and 36-48 hours after the end of treatment.
Test 2: Subjects will be required to keep a headache diary for 4 weeks at baseline before the intervention. After the intervention, headache diary will be still needed to fill out, and the content will be the same as above. Headache diaries will be collected at 4-week intervals from week 4 to week 20.

What tests and assessments will be conducted in this study?
After providing written informed consent, you will undergo some tests, examinations, and procedures during this study. If you have any concerns about any of the tests, please discuss them with the research doctor. Regarding the tests and procedures of this study, we would like to explain the following:
Medical history: The research doctor will ask you some questions to understand any current or past illnesses.
Demographic information: The research doctor will collect information about you, such as your date of birth and ethnic background.
Questionnaires: Including VAS scale to assess your pain level.
Electrocardiogram (EEG)& Electromyography (EMG) signals: We will collect your EEG signals, EMG signals and Heart rate variability (HRV) to study your Vagus nerve activity.

IV. Risks and/or Discomfort

The adverse reactions that may occur after receiving the non-invasive vagus nerve stimulation device in the subjects of this trial include ear skin sensitivity, tinnitus, tingling, etc. When these symptoms occur, talk to your doctor immediately and discontinue the intervention. In most cases, the symptom will resolve within a period of time after cessation of the intervention stimulus. There are no known long- term risks associated with nVNS, and no serious side effects or safety incidents have been reported.Additionally, you can take breaks at any time during the study. At any moment during the study, you can withdraw from the study.

V. Benefits of Participation

If you agree to participate in this study, you will be given nVNS corresponding to your randomization assignment. nVNS has been shown to be effective in reducing the discomfort caused by chronic headaches, but this technology is still in the stage of experimental research, so it may not be effective for you.

VI. Alternative Treatment Plans

In addition to participating in this study, you have other treatment options, including medications and nonmedications. You can always discuss your disease and its possible consequences with a study physician to determine which is the best course of treatment for you.

VII. Use of Research Results and Confidentiality of Personal Information

At the end of the study, we will analyze the data. You will have the opportunity to know the research results. You can ask your research doctor about the research results and request explanations. The results of this study may be published in journals or reported at conferences, but

they will not include any information that could identify you. To ensure privacy, records published for research purposes will not include your name or other identifying information. Instead, your information will be identified only by a code. Only the research doctor and authorized personnel will be able to connect this code to your name through a list, which will be securely stored at the research center. To ensure that the study is being conducted correctly, when necessary, sponsors, ethics review committees, and government regulatory agencies may review your data, and they are bound by confidentiality obligations and will not violate your privacy. You have the right to control the use and disclosure of your personal information. In accordance with national laws, you can request to view your medical information at any time. You have the right to view all information collected about you during the study and request corrections through the research doctor.

VIII. New Information Related to the Study

During the study, if there are changes in study procedures, newly discovered side effects, or significant situations that may affect your health or willingness to participate, the research team will notify you. The research doctor will inform you immediately and discuss with you whether you want to continue participating in the study.

IX. Study Costs, Compensation, and Compensation for Damages

Study-related examination costs and compensation
You will not be required to bear any costs for participating in this study. This study will not provide any compensation.

Compensation for damages
If you suffer any harm as a result of participating in the study, you will receive active treatment, the cost of treatment will be provided by the sponsor, Future Naolu (Hunan) Medical Technology Co., LTD., and you will be compensated according to law.

X. Rights and Responsibilities of Participant

Your rights
Throughout the entire process of participating in the study, your participation is voluntary. If you decide not to participate in this study, it will not affect other treatments you should receive. If you decide to participate, you will be asked to sign this written informed consent form. You have the right to withdraw from the trial at any stage without discrimination or unfair treatment, and your medical treatment and rights will not be affected.

Your responsibilities
When participating in the study, please adhere to the following agreements:
If you wish to terminate the clinical trial, you can inform your research doctor at any time.
Provide truthful information about your medical history and current physical condition.
Follow the instructions of the research personnel.
Inform the research doctor of any discomfort you may experience during this study.

XI. Contact Information

If you have any questions related to this study, please contact Yabin Ji at 15913186246. If you have any questions related to your rights/interests or if you want to report difficulties, dissatisfaction, and concerns encountered during your participation in this study, or if you want to provide opinions and suggestions related to this study, please contact the Ethics Committee of Southern Medical University Southern Hospital at 020-62787238 or nfyyec@163.com.