Informed Consent Form

Official name： Exploratory Study on Transcutaneous Auricular Vagus Nerve Stimulation as Adjuvant Treatment for Sepsis Patients

Acronym： TaVNS-Sepsis

Organization's Unique Protocol ID： AIIT2024050

NCT number：

Date： 2025.1.24

Informed Notification Page

Dear Study Participants,

Hello!

We invite you to participate in the clinical trial "Exploratory Study on Transcutaneous Auricular Vagus Nerve Stimulation as Adjuvant Treatment for Sepsis Patients".This study is jointly carried out by the Department of Rehabilitation and the Department of Intensive Care Medicine, and is under the responsibility of Jingming Hou, director of the Department of Rehabilitation, and will be carried out in our hospital, with an estimated 60 study participants.This study has been reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Army Medical University (Southwest Hospital).

Before you decide whether or not to participate in this study, please read the following as carefully as possible.It can help you understand the study, why you are doing it, the procedure and duration of the study, and the benefits, risks, and discomfort you may experience if you participate in the study.You can ask your doctor any questions you may have.If you wish, you can also discuss it with your relatives, friends, or ask your doctor to explain it.

This informed consent form may contain words that you are not familiar with or understand, please ask your study doctor or study group member about the meaning of these words or information.

If you decide to participate in this study, you will be asked to sign this informed consent form.You will keep a copy of this informed consent form after you have signed it.If you decide not to participate, your treatment at our hospital will not be affected in any way.

I. Background and purpose of the study

1. Background:

Sepsis is a life-threatening organ dysfunction caused by the body's dysfunctional response to infection.The 2020 Global Burden of Disease Report highlights that sepsis is common, with nearly 50 million cases worldwide each year, accounting for nearly 20% of all global deaths, and is the major global health burden.To date, more than 200 randomized controlled trials have been conducted on sepsis over a period of more than 30 years, but no single treatment has been found that can sustainably save the lives of people with sepsis.In recent years, many immunomodulatory agents have been shown

to play a role in the treatment of sepsis and immunosuppression and prognosis.Therefore, immunomodulatory therapy for sepsis has become a hot topic of current research.

The vagus nerve has received increasing attention over the past two decades for its anti-inflammatory effects.Extensive experimental work has shown that vagus nerve stimulation inhibits cytokine production and activity and ameliorates many systemic inflammations.Non-invasive transcutaneous auricular vagus nerve stimulation is a neuromodulation therapy technique that has been certified safe by the European Union.At present, some basic and clinical studies have used it for epilepsy, depression and migraine, and compared with traditional invasive vagus nerve stimulation surgery, taVNS has the advantages of safety, non-invasiveness and simple operation.A 2023 pilot trial of 5-day non-invasive euricular vagus nerve stimulation in 20 patients with sepsis showed a significant decrease in serum pro-inflammatory cytokines and an increase in serum anti-inflammatory cytokines.Through this study, the safety and anti-inflammatory efficacy of non-invasive transcutaneous auricular vagus nerve stimulation in patients with sepsis have been preliminarily confirmed, but its sample size and intervention period still need to be further improved.In this study, we planned to use non-invasive transcutaneous auricular vagus nerve stimulation to treat systemic inflammatory response in patients with sepsis under mechanical ventilation, and to explore its long-term efficacy in sepsis-related organ dysfunction, duration of mechanical ventilation and ICU stay, so as to further promote the selection of sepsis combined treatment regimens and improve efficacy and safety.

2.Objectives:

The purpose of this study is to:To investigate the efficacy of transcutaneous auricular vagus nerve stimulation combined with standard intensive care for systemic organ function and overall prognosis in patients with mechanically ventilated sepsis.

II. Who can participate in the study?

1.Inclusion Criteria:

1)Age 18-80

2)Sepsis was diagnosed per the Sepsis-3 criteria (SCCM/ESICM 2016) as infection with SOFA score ⩾ 2

3)ICU admission within 7 days after sepsis onset

4)Informed consent was obtained from patients/guardians

2. Exclusion Criteria:

1)Severe ARDS defined by PaO_2/FiO_2 ≤100 mmHg with PEEP ≥5 cm H_2O

2)HR > 120 per minute

3)Epinephrine or norepinephrine ＞1ug/kg/min

4)Severe underlying pulmonary diseases including interstitial lung disease, diffuse alveolar hemorrhage, severe asthma, or lung cancer

5)TaVNS contraindications: existing pacemakers, cochlear implants, or other active implantable electronic medical devices

6)Dermatologic or infectious disorders affecting the auricular region

7)Pregnancy or lactation

8)Participation in other clinical trials

9)Inability to remain motionless during treatment (e.g., due to epilepsy or Parkinson's disease)

3.Termination Criteria

1） Patient or his/her immediate family member is unwilling to continue to participate in the pilot study;

2） Missing number of treatments;

3） Those who have serious complications or special physiological changes and are not suitable to continue the test;

III. The content and procedure of this study

1. Before you are enrolled in the clinical study, your doctor will ask and record your medical history.If you meet the inclusion criteria, you can voluntarily participate in the clinical study and sign the informed consent form.If you do not wish to participate in the clinical study, we will treat you according to your wishes.

2. If you are willing to participate in a clinical study, you will do so as follows:

A randomized controlled design was adopted in this study.Our study was divided into two groups, and you had a 50% chance of being randomly assigned to either group (like flipping a coin), so neither you nor the study doctor could choose which group to group.

You will receive standard care from an intensive care specialist according to standard clinical guidelines, including infection management, hemodynamic management, mechanical ventilation, supportive care, etc., including vasoactive drugs, fluid resuscitation, antibiotics, enteral and parenteral nutrition, and previous cytotoxic chemotherapy, endocrine therapy, biologic therapy, or radiation therapy for any reason;At the same time, on the basis of conventional treatment, gastrointestinal nutrition was suspended for 30 minutes in the morning and afternoon, and the study participants were given true or sham taVNS treatment (2 times a day for 7 consecutive days, a total of 14 times).

(1) taVNS group:On the basis of conventional rehabilitation treatment, taVNS treatment was given, and the stimulation site was in the left ear nail area (the main distribution area of the vagus nerve), the frequency was 25Hz, the stimulation intensity was about 3mA, which was lower than the patient's pain threshold, and the stimulation time was 30 minutes.

(2) sham-taVNS group:On the basis of conventional rehabilitation, only sham taVNS stimulation was performed, and the left ear nail area (the main distribution area of the vagus nerve) at the stimulation site was only 10 seconds of current stimulation at the beginning and end of the 30-minute period, and there was no current stimulation for the rest of the time, that is, no effective stimulation was done.The rest of the stimulation regimens were the same as those in the taVNS group.

After the end of treatment, we will have a brief follow-up phone call with you or your family on days 28 and 60 to discuss your condition.

IV. Other matters that require your cooperation

During follow-up visits, your doctor may also be able to get to know you over the phone and other means.Your follow-up is very important because the doctor will tell if the treatment you are receiving is really working and guide you in a timely manner.

You cannot take any treatment other than the one labeled above during the study.If you need other treatments, please contact your doctor beforehand.

V. Possible benefits of participating in the study

There is evidence that non-invasive transcutaneous auricular vagus nerve stimulation is effective in reducing inflammation in sepsis, and participating in this study may be appropriately controlled and may be more helpful in weaning your ventilator.At the same time, the relevant data and information obtained in this study will provide a more

reliable evidence-based medical basis for the treatment of sepsis patients in the future, and benefit sepsis patients in the future.

VI. What other treatments are available if I do not participate in this study?

If you do not participate in this study, you may still receive standard care from an intensive care specialist according to standard clinical guidelines, including vasoactive drugs, fluid resuscitation, antibiotics, and enteral and parenteral nutrition, prior cytotoxic chemotherapy, endocrine therapy, biologic therapy, or radiation therapy, as well as standard rehabilitation by a rehabilitation therapist.

VII. Possible risks of participating in the study

In previous studies of non-invasive transcutaneous auricular vagus nerve stimulation, its safety has been proven, and adverse effects have been reported rarely, including mild itching and tingling sensation at the treatment site.In addition, there may be cough, voice changes, or heart rate changes caused by vagus nerve stimulation, but no serious adverse events have been reported.

If there is an aggravation of the corresponding adverse reaction, or a more serious adverse reaction, we will discuss the case and deal with it, and reduce the corresponding treatment cost.

VIII. Fees

To compensate for the inconvenience you may have suffered from participating in this study, this study will cover the cost of transcutaneous auricular vagus nerve stimulation treatment involved in your study.In addition, the cost of using the ventilator and routine blood gas tests are not included in the scope of the free fee.Follow-up visits are all telephone follow-ups, so there is no cost involved.

The treatment and tests required for other conditions that you have comorbid at the same time will not be covered by the free of charge.

IX. Injury compensation:

The physician will do his best to prevent and treat possible harm as a result of this study.If an adverse event occurs in a clinical trial, it will be determined whether it is relevant to the study.The investigator will provide treatment and compensation for the damage related to the trial in accordance with the relevant laws of China.

X. Is personal information confidential?

Your medical records will be kept intact at the hospital where you were treated.Your doctor will record the results of your lab tests on your medical record.The investigator, ethics committee, and hospital regulatory authority will be allowed access to your medical records.Any public report on the results of this study will not reveal your personal identity.We will protect the privacy of your personal medical information to the extent permitted by law.

XI. How to get more information

You can ask any questions you have about this study at any time and get them answered.

Your doctor will keep you informed if there is any important new information during the course of the study that may affect your desire to continue participating in the study.

If you have any questions about the procedure of this study, you can consult Dr. Yang Hong at the following phone:18580262250。If you have any questions about your rights to participate in this study, you can contact the Ethics Committee of the Academy at the following contact information:023-68754035。

XII. They can voluntarily choose to participate in the research and withdraw from the research halfway

Whether or not to participate in the study depends entirely on your wishes.You may refuse to participate in the study, or withdraw from the study at any time during the course of the study, without affecting your relationship with your physician or with any loss of medical or other benefits to you.

In your best interest, your doctor or investigator may discontinue your participation in this study at any time during the course of the study.

If you withdraw from the study for any reason, you may be asked about your time in the trial.You may also be asked to have lab tests and a physical exam to keep you safe if your doctor thinks so.

We will ask you to withdraw from the study if:

1）You or family members are unwilling to continue participating in the pilot study;

2）missing number of treatments;

3）Those who have serious complications or special physiological changes and are not suitable to continue the test.

XIII. What should I do now?

It's up to you (and your family) to decide whether or not to participate in this study.

Before you make a decision to participate in the study, ask your doctor as many questions as possible.

Thank you for reading the above material.If you decide to participate in this study, please tell your doctor and he/she will arrange everything for you.Please keep this information.

Informed Consent Form and Consent Signature Page

Clinical Research Project Name:Exploratory Study on Transcutaneous Auricular Vagus Nerve Stimulation as Adjuvant Treatment for Sepsis Patients

Research Affiliations: Department of Rehabilitation Medicine/Department of Critical Care Medicine, Southwest Hospital

Declaration of Consent

I have read the above presentation of this study and have had the opportunity to discuss and ask questions about this study with my doctor.All the questions I asked were answered satisfactorily.

I am aware of the risks and benefits that may arise from participating in this study.I understand that participation in the study is voluntary, I confirm that I have had sufficient time to consider this, and I understand that:

- ✧ I can always ask my doctor for more information.
- ✧ I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.
- ✧ Signing this informed consent form will not affect my rights.

I also knew that if I dropped out of the study, it would be very beneficial for the whole study if I told the doctor about the changes in my condition and completed the corresponding physical examination and physical and chemical tests.

If I need any other treatment due to changes in my condition, I will seek the doctor's advice beforehand or tell the doctor truthfully afterwards.

I consent to the hospital regulatory department, ethics committee, or investigator access to my research data.

I will be provided with a signed and dated copy of the informed consent form (both informed and signed).

I understand that the choice to participate in the study "Exploratory Study of Transcutaneous Vagus Nerve Stimulation in Patients with Sepsis" is determined by the flipping of a coin.

In the end, I decided to agree to participate in the study and promised to follow my doctor's instructions as much as possible.

Study Participant Signature: Date:_year_month_day_hour_minute

Study participant contact number (mobile):

Guardian's Signature: Date:_year_month_day_hour_minute

Guardian contact number (mobile phone):

Relationship between guardian and study participant:

Investigator's Statement

I confirm that I have explained the details of this study, in particular the possible risks and benefits of participating in this study, to the patient, and have answered all questions about the study participant, who has voluntarily consented to participate in this study.This informed consent form is in duplicate, and the investigator and the study participant each keep a signed informed consent form.

Investigator's Signature: Date:_year_month_day_hour_minute

Investigator's contact number (mobile phone):