Informed consent · Informed page

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Dear Subject:

We are going to invite you to participate in a study (Ear vagus nerve stimulator improves symptoms and gut microbiota in patients with irritable bowel). The project leader of this study is Professor xxx, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. The study protocol has been reviewed by the Medical Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, and the clinical study has been approved.

Please read the following as carefully as possible before you decide whether to participate in this study. It can help you understand the study and why it is being conducted, the procedures and duration of the study, and the benefits, risks, and discomfort that may be associated with participating in the study. If you prefer, you can also discuss it with your relatives, friends, or ask your doctor for an explanation to help you make a decision.

If you are currently participating in other clinical studies, be sure to inform your study physician or investigator. Thank you for your support of this study.

1. Why was this study conducted?

Irritable bowel syndrome (IBS) is a highly prevalent disorder of the functional digestive system characterized by chronic abdominal pain and altered bowel habits in the absence of biological or structural abnormalities. In the field of IBS, effective medical treatments are very limited, and patients are urgently looking for alternatives, including probiotics, hypnotherapy, osteopathic therapy, dietary changes, and fecal microbiota transplantation. In recent years, with the continuous elucidation of the vagus nerve mechanism, IBS patients have become more and more interested in bioelectrical modulation. These patients are usually skeptical of traditional drug treatment and believe that drugs are easy to cause side effects.

Recent studies have shown that vagus nerve stimulation (VN) has anti-inflammatory effects. This vagal function is mediated through a variety of pathways, some of which are still controversial. The first is the anti-inflammatory pathway of the hypothalamic-pituitary-adrenal

axis, stimulated by the afferent fibers of the vagus nerve, where the adrenal gland releases cortisol, providing an important first line of innate defense against inflammatory infections and helping to restore homeostasis. The second, called cholinergic anti-inflammatory pathway, releases acetylcholine (ACh) at synaptic junctions with macrophages through synaptic connections of enteric neurons mediated by vagal efferent fibers. Acetylcholine binds to the α-7-nicotinic acetylcholine receptor of macrophages and inhibits the release of tumor necrosis factor-alpha (TNF-α), a proinflammatory cytokine. The final pathway is the splenic sensitization and anti-inflammatory pathway, where stimulation of splenic sympathetic nerves by VN causes the release of acetylcholine distally from norepinephrine (noradrenaline). Finally, ACh inhibits TNFα release from splenic macrophages via α-7-nicotinic ACh receptors. For the above reasons, vagus nerve stimulation (VNS) may be a promising option for improving IBS symptoms.

Vagus nerve stimulation (VNS) is currently used as a treatment option for many clinical conditions, such as heart failure, migraine, and inflammatory bowel disease. VNS techniques are mainly divided into invasive (surgical implantation) and noninvasive (percutaneous)VNS techniques. Invasive VNS (iVNS) involves implantation of a programmable pulse generator device in the chest wall and placement of electrodes around the left (typical) cervical vagus nerve. As it stands, iVNS carries several potential risks, such as bradycardia and cardiac arrest, localized infection around the wound, etc. The transcutaneous VNS (tVNS) delivery system relies on the skin distribution of the vagal afferent nerve and intervenes in the external ear (auricular branch of the vagus nerve) or neck (cervical branch of the vagus nerve), which avoids the risk of surgical implantation of VNS delivery devices and promotes further research on the application of tVNS.

In this study, the portable conchal stimulator produced by Ruizhenan Medical can accurately stimulate the conchal boat and stimulate the auricular vagus nerve percutaneously, giving full play to its therapeutic effect. Therefore, the purpose of this clinical trial is to use the conchial stimulator in patients with irritable bowel syndrome, and to explore whether it has a therapeutic effect on patients with irritable bowel syndrome. To explore the effect of tVNS therapy on irritable bowel syndrome (IBS) compared with drug therapy, hoping that the use of TVNS therapy can reduce the use of related drugs, or even replace drugs.

The treatment method of the portable ear concha stimulator produced by Ruisenan Medical

used in the current project is to use a pulse width of 200us; The frequency of 30Hz weak electrical stimulation, the experiment is relatively safe, almost no side effects. Patients need to adjust the stimulation amplitude to feel weak stimulation.

2. Who will be invited to participate in the study?

Patients with colorectal neoplasia excluded by colonoscopy within two years, who presented clinically with irritable bowel syndrome with diarrhea, met the Rome IV diagnostic criteria.

3. Study units and estimated number of participants

The participating units were Tongji Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology and School of Life Science and Technology of Huazhong University of Science and Technology. About 40 people were enrolled in this study.

4. **What will I need to do if I participate in the study?**

1. Before you are enrolled in the study, your doctor will take your medical history, and you will be asked about IBS symptoms.

You are eligible for enrollment, and you may voluntarily participate in the study by signing an informed consent form.

If you do not wish to participate in the study, we will treat you according to your wishes.

2. If you volunteer to participate in the study, the following steps will be taken:

1. On the day of signing the informed consent form, the materials you received included a survey questionnaire (GSRS-IBS) and questionnaire two-dimensional code (IBS-QOL), a set of portable ear conchal stimulator produced by Ruisen Medical, 6 fecal sample collection boxes, and a registration form for the use of ear conchal stimulator.

2. On the day of collecting the materials, fill out a survey questionnaire and hand it to the outpatient doctor.

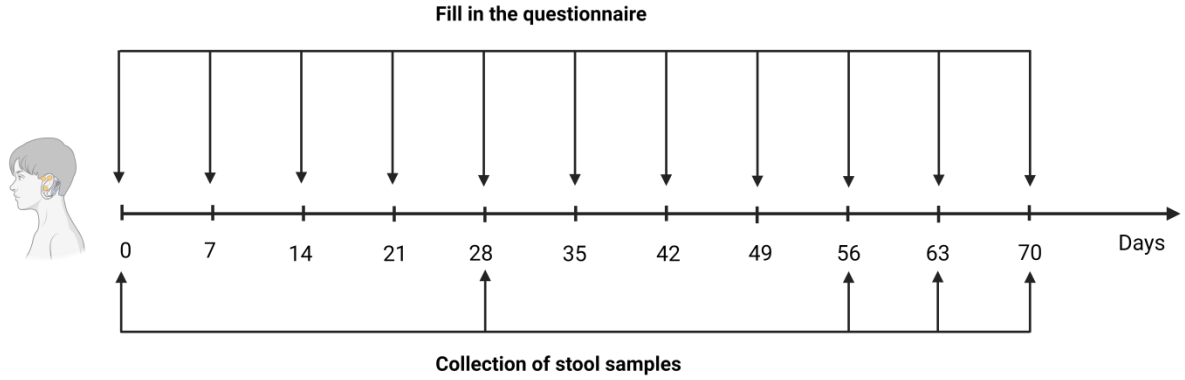
3. At the designated sampling time, before using the auricular conchal stimulator, collect a stool sample, and try to select the middle part of the stool that is not contaminated by urine. After the collection of stool samples, please contact researcher He Junqing at 13177628984, mailing

address: Building G, Wuhan Optoelectronics National Laboratory, Huazhong University of Science and Technology (East Campus), No. 1037, Hongshan District, Wuhan, Hubei, China. Freight is payable on arrival.

4. After the first collection of stool samples, the auricular concha-stimulating device can be used for 3 hours a day, and the parameters are set as 200μs pulse width and 30Hz frequency (the specific parameters should be adjusted under the guidance of the outpatient doctor). The device was used continuously for 56 days. Stool samples were collected again on days 28, 56, 63, and 70 in the same manner as the first post.

5. After using the auricular concha stimulator at the specified time points each week, the second survey questionnaire was completed by scanning the two-dimensional code.

6. On the 28th day, the collected stool samples and the auricula stimulator will be collected and replaced by mail or delivered to the hospital (the cost will be borne by this project). On the 56th day, the auricular concha stimulator was collected in the same way as the first time.



3. Other matters that need your cooperation:

Fill out the questionnaire after using the auricular concha stimulator at the designated time each week, use the auricular concha stimulator on time every day, and do not take antibiotics, probiotics, prebiotics, and other products during the study period.

5. Possible benefits of participating in research

Improvement in irritable bowel symptoms

6. Possible adverse effects, risks and discomfort, inconvenience of participating in the study

Mild pain may occur during vagus nerve stimulation. If you experience any discomfort during the study, such as bloating, stomach pain, a new change in your condition, or any unexpected situation, whether related to the study or not, you should notify your doctor immediately so that he/she can make a judgment and give appropriate medical treatment.

You will need to fill out the questionnaire and change the auricular nerve stimulator on time during the study so that the researchers can retrieve the data. Some of this time may also cause trouble or inconvenience for you.

7. Related fees

The auricula stimulators used for participation in this experiment were provided free of charge, the mailing cost of fecal samples was borne by the program, and the high-throughput testing of fecal samples was borne by the program. In this project, the symptoms of irritable bowel syndrome are identified according to the self-described situation of patients. No tests are performed and no testing costs are involved. The auricular concha-stimulating device used in this project belongs to the electrical stimulation medical device. If the patient feels uncomfortable after using it, the use can be stopped in time to stop the influence on the subject. The expenses of treatment, compensation and compensation for adverse events related to the experiment will be borne by the project group. In case of discomfort caused by other reasons or uncertain factors, the related medical expenses will not be borne by the project.

8. Confidentiality of personal information

Your medical records (study charts /CRF, lab tests, etc.) will be kept intact at the hospital you visit. Your doctor will record laboratory and other test results in your medical record. Investigators, ethics committees, and regulatory authorities will be given access to your medical records. Your personal identity will not be disclosed in any public report of the results of this study. We will make every effort to protect the privacy of your personal medical data to the extent permitted by law.

In accordance with medical research ethics, except for personal privacy information, the trial data will be available for public inquiry and sharing, and the inquiry and sharing will be limited to Web-based electronic databases, and no personal privacy information will be disclosed.

9. How can I get more information?

You can ask any questions about the study and get answers at any time.

Your doctor will notify you if any important new information becomes available during the course of the study that may affect your willingness to continue in the study.

10. There is a voluntary option to participate and drop out of the study

Whether or not to participate in the study is entirely up to your wishes. You may refuse to participate in the study, or withdraw from the study at any time during the study, without affecting your relationship with the doctor or any loss of medical or other benefits.

It is in your best interest to discontinue your participation in the study at any time during the course of the study by the physician or investigator.

If you withdraw from the study, you may be asked about your use of the study medication in the best interest of your health, and you may also be asked to undergo a physical examination and physical examination if deemed necessary by your doctor, which will be beneficial to your health.

If you need to take any other treatment due to changes in your condition, you may take other treatment at any time, and please tell your doctor the truth afterwards.

11. What should you do now?

Participation in the study is up to you (and your family). Ask your doctor as many questions as possible before you decide to participate in the study.

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

Informed consent. Consent signature page

Project Name:_____

Sponsor: Tongji Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology

Statement of Agreement

I have read the above description of the study and had the opportunity to discuss it with my physicians and ask questions about it. All of my questions were satisfactorily answered.

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

- I could always consult my doctor for more information.
- I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights and interests will not be affected.

I consent to the ethics committee or administration to access my research data.

I will be provided with a signed and dated copy of my informed consent.

In the end, I have decided to agree to participate in the study and promise to follow my doctor's advice to the best of my ability.

Signature of subject:_____ _____Year,_____Month,_____Day

Contact number: _____

I confirmed that the details of the trial, including its rights and possible benefits and risks, were explained to the patient and that I gave her a copy of her signed informed consent.

Investigator signature:_____ _____Year,_____Month,_____Day

Contact number: _____