Clinical study protocol

Protocol Title: The efficacy and mechanisms of transcutaneous auricular vagus nerve stimulation on symptoms in patients with constipation-predominant irritable bowel syndrome

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Sponsor: Shanghai East Hospital, Tongji University

Clinical study summary

Title	The efficacy and mechanisms of transcutaneous auricular vagus nerve stimulation on symptoms in patients with constipation-predominant irritable bowel syndrome
Protocol number	2020-006
Sponsor	Shanghai East Hospital, Tongji University
Indication	Constipation-predominant Irritable Bowel Syndrome (IBS-C)
Objective/Aim	This study aims to investigate the effects and possible mechanisms of transcutaneous auricular vagal nerve stimulation (taVNS) on abdominal pain and other symptoms in patients with IBS-C.
Sample size	N = 42
Case selection criteria	Inclusion criteria: 1) age 18–75 years, 2) willing to sign a written informed consent form, 3) met the Rome IV diagnostic criteria for IBS-C. Exclusion criteria: 1) had a history of previous abdominal surgery (other than appendectomy), 2) suffering from carcinoma, 3) had any organic diseases causing constipation or neurologic diseases such as multiple sclerosis, rachischisis, Parkinson's disease or spinal cord injury, 4) taking antidepressant agents including tricyclic antidepressants and selective serotonin reuptake inhibitors, 5) had a serious concomitant disease of the heart, liver, kidney, or diabetes, 6) women during pregnancy or lactation, 7) participating in another trial or enrolled in a trial during the past month, 8) allergic to surface electrodes.
Timeline	1) July 2019 - August 2019: Screen and confirm the clinical diagnosis of IBS-C patients, and estimate the sample content 2) September 2019–July 2020: Patient recruitment，and for the selected participants, signed an informed consent form, underwent percutaneous auricular vagus nerve stimulation treatment, and collected outcome measures 3) August 2020-October 2020: Data analysis
Statistical analysis	The independent sample t-test is used to assess the difference between the sham-taVNS and taVNS groups; The paired student's t-test is applied to evaluate the differences before and after the taVNS or sham-taVNS treatment. $P<0.05$ is considered statistically significant.

Background

Irritable bowel syndrome (IBS) is a clinical syndrome characterized by persistent or intermittent attacks, abdominal pain, abdominal distension, defecation habits and (or) changes in stool characteristics. According to the world-wide population survey, the global prevalence of IBS is about 11.2% (95% CI: 9.8-12.8) (1), and the prevalence of IBS in China is about 5-10% (2). According to Rome IV diagnostic criteria (3), IBS can be divided into four types: constipation type (IBS-C), diarrhea type (IBS-D), mixed type (IBS-M) and unclassified type (IBS-U). Among them, IBS-C accounted for about 27% of the total prevalence (4). The persistent or intermittent symptoms of patients bring a lot of inconvenience and pain, resulting in a significant decline in the quality of life, but also increased the burden of the social health system.

The etiology and pathogenesis of IBS have not been fully elucidated, but many factors are involved, including genetic factors, intestinal infection, mucosal immune and inflammatory response, altered gastrointestinal motility, visceral hypersensitivity, post infectious reactivity, brain-gut interactions, disturbance of intestinal flora, food sensitivity or stress(5-8), among which altered gastrointestinal motility and visceral hypersensitivity have been considered to be the main pathophysiological basis. At present, various drugs are used for pharmacologic treatment. Laxatives and prokinetics are used for constipation, while antispasmodics and antidepressants are prescribed for abdominal pain, which in turn may impair gastrointestinal motility and thus could worsen constipation (9, 10). Additionally, such medications can only relieve symptoms temporarily, and long-term medication is expensive and easy to relapse after withdrawal (11). Accordingly, patients often seek complementary and alternative therapies (12).

It is well known that the autonomic nervous system is a complex hierarchically controlled system, providing a neural link between the brain and the body that integrates the external environment with the internal milieu to maintain homeostasis. It is composed of two broadly opposing branches, the sympathetic and parasympathetic nervous system, and the vagus nerve is the main neural substrate of the parasympathetic nervous system (13). A relative paucity of vagal activity, has been implicated in the pathophysiology of a number of disorders including, but not limited to, functional dyspepsia, irritable bowel syndrome (IBS), inflammatory bowel disease, and chronic pain syndrome (14, 15). Thus, vagus nerve stimulation is of interest as a potential therapeutic intervention.

Vagus nerve stimulation (VNS), approved by FDA for epilepsy and drug-resistant depression (16), has been extended in recent years as a complementary and alternative treatment to treat other diseases, including gastrointestinal dysmotility, inflammation and pain (17-19). The classic implantable device consists of an electrode, which is wrapped around the left vagus nerve, and an implantable unit, positioned below the collarbone and containing the battery and pulse generator. However, despite being a minimally invasive procedure, the involvement of surgery, perioperative risks, and potentially significant side effects have limited its applicability.

Transcutaneous vagus nerve stimulation (tVNS) is a noninvasive method that has been developed to overcome these limitations. The rationale for using tVNS on the ear is based on anatomical studies that suggest that the ear is the only place on the surface of the human body where there is afferent vagus nerve distribution (20, 21). Thus, direct stimulation of the afferent nerve fibers on the ear should produce an effect similar to classic VNS. In recent years, transcutaneous auricular vagus nerve stimulation (taVNS)

has been reported to improve gastrointestinal disorders, including abdominal pain (22), constipation (23) and functional dyspepsia (24), but there is no study on ta VNS in the treatment of IBS-C. Based on the integrative effects of taVNS on both pain and motility we observed in the animal model of functional dyspepsia and patients with abdominal pain-related functional gastrointestinal disorders (22, 24, 25), we hypothesized that taVNS might improve symptoms in patient with IBS-C by enhancing vagal efferent activity. The aim of this study is to investigate the effects and mechanisms of taVNS on symptoms in patients with IBS-C.

Methods

Study design and plan

(1) The patients diagnosed with IBS-C are screened and the sample size is estimated;
(2) The inclusion and exclusion criteria are selected and informed consent is signed;
(3) The treatment group is treated with taVNS, while the control group is treated with sham taVNS. The blood samples are collected and outcome measures are taken;
(4) Samples are sent for inspection and the results are statistically analyzed.

Patients

Inclusion criteria:
1) age 18–75 years,
2) willing to sign a written informed consent form,
3) met the Rome IV diagnostic criteria (26) for IBS-C.
Exclusion criteria:
1) had a history of previous abdominal surgery (other than appendectomy),
2) suffering from carcinoma,
3) had any organic diseases causing constipation or neurologic diseases such as multiple sclerosis, rachischisis, Parkinson's disease or spinal cord injury,
4) taking antidepressant agents including tricyclic antidepressants and selective serotonin reuptake inhibitors,
5) had a serious concomitant disease of the heart, liver, kidney, or diabetes,
6) women during pregnancy or lactation,
7) participating in another trial or enrolled in a trial during the past month,
8) allergic to surface electrodes.
Withdrawal criteria:
1) The subject or his legal guardian voluntarily requests to withdraw;
2) Violation of inclusion / exclusion criteria;
3) Withdraw when other unexplained serious complications occur;
4) If pregnancy occurs during treatment, withdraw from the study;
5) For safety reasons, the study sponsor proposed to stop the study;
6) Subjects whose ethics committee decided to stop the study;
7) Subjects who are considered unsuitable for further study.
The reason and date of withdrawal are recorded, and the withdrawal rate is counted at the end of the study.

The subjects who withdraw from the study will take appropriate treatment measures according to the judgment of the researchers.

Trial interventions

Enrolled patients will be randomized to undergo either taVNS or sham-taVNS. The taVNS treatment is performed at auricular cymba concha, while Sham-taVNS is performed at a sham point (elbow area).

Study Design and Protocol

Enrolled patients are randomly divided into two groups (taVNS and sham-taVNS) with a ratio of 1:1 according to a computer-generated random digital table. The sample size is calculated by G*power analyses based on our preliminary study. One week before the start of the study, patients are asked to stop all constipation and IBS medications, including laxatives, prokinetic agents, probiotics, and antispasmodics. After one-week run-in period, patients in each group are requested to complete the following questionnaires once a week: the visual analog scale (VAS) for abdominal pain, IBS symptom severity score (IBS-SSS) for the overall IBS symptoms, IBS quality of life questionnaire (IBS-QOL) for patient's quality of life, Bristol Stool Form Scale (BSFS) for the stool type, Self-Rating Anxiety Scale (SAS) for anxiety, Self-Rating Depression Scale (SDS) for depression, and the bowel diary for the number of complete spontaneous bowel movements per week. Autonomic function is assessed at the baseline and after 4 weeks of treatment. by the spectral parameters of heart rate variability (HRV), calculated using spectral analysis of R-R intervals in electrocardiogram (ECG). A blood sample is taken at 8 a.m. at baseline and after 4 weeks treatment, Serum and plasma are separated and frozen at - 80 ℃. The chronic taVNS and sham-taVNS intervention is performed twice a day (8am and 8pm) for half an hour each time, lasting for four weeks. During the run-in and treatment periods, only Macrogol 4000 and pinaverium are permitted for use, when the patient could not tolerate symptoms of constipation and abdominal pain. The flowchart is shown in Figure 1, and the study schedule is detailed in Table 1.

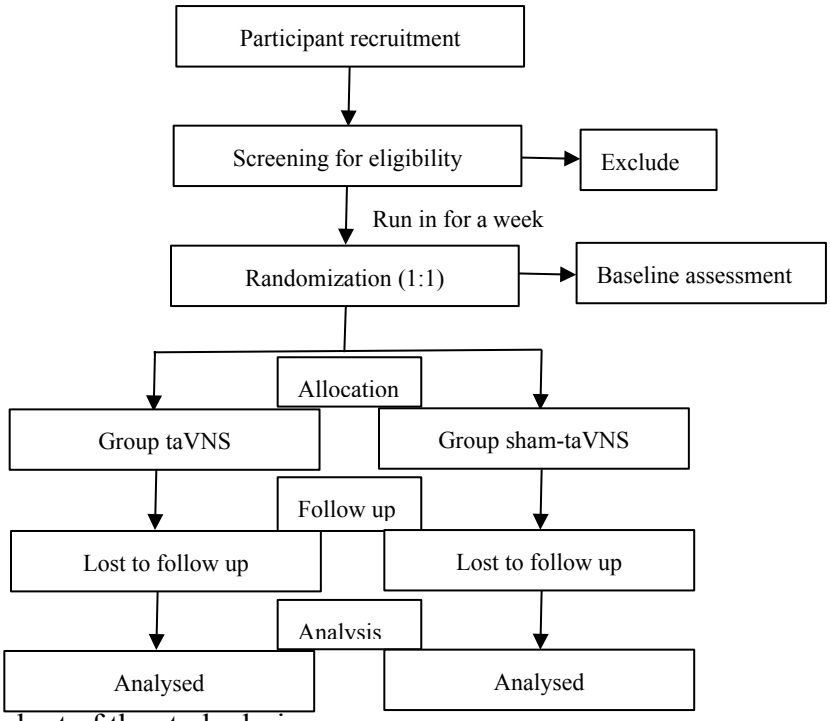

Figure 1. Flowchart of the study design.

	Baseline	Week 1	Week 2	Week 3	Week 4
Consent	×				
VAS	×	×	×	×	×
IBS-SSS, IBS-QOL	×	×	×	×	×
SAS, SDS, BSFS	×	×	×	×	×
HRV	×				×
Blood	×				×

Table 1. Study schedule. A bowel diary is recorded during the treatment.
VAS, visual analog scale; IBS-SSS, IBS symptom severity score; IBS-QOL, IBS quality of life questionnaire; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; BSFS, Bristol stool form scale; HRV, heart rate variability.

Randomization

Enrolled patients are randomly divided into two groups (taVNS and sham-taVNS) with a ratio of 1:1 according to a computer-generated random digital table, which contains 21 odd numbers and 21 even numbers. Odd numbers represent taVNS, while even numbers represent sham-taVNS, and enter corresponding groups according to the sequence of patients.

Blinding

The patients are blinded to the type of treatment.

Serious adverse events (SAEs)

Pain at the stimulation site and allergy to the electrode are adverse events. Lowering the intensity of stimulation can relieve or eliminate pain. If the patient is allergic to the electrode, we will terminate the treatment and let the patient withdraw from the study.

Statistics

Quantitative variables are reported as means ± standard deviations (SD), while categorical data qualitative variables are presented as absolute values and percentages. Categorical data are compared using the chi-squared test. The independent sample t-test is used to assess the difference between the sham-taVNS and taVNS groups; The paired student's t-test is applied to evaluate the differences before and after the taVNS or sham-taVNS treatment. $P<0.05$ is considered statistically significant.

Sample size estimation

G-Power software is used for calculation, and the steps are as follows:

1. T test, mean difference between two dependent means (two groups)
2. A priori: compute required sample size, given α, power, and effect size
3. Tails：One
4. Effect size: In the previous study, the number of spontaneous defecation was: 2.3 ± 2.1 (SD) in sham stimulation group; 3.7 ± 1.4 (SD) in true stimulation group. Therefore, the effect size dz=0.784.
5. α=0.05； β=0.2， 1-β=0.8；

Based on the above data, G-Power software calculated total sample size: n = 42

Ethics committee review

The protocol, written informed consent, and information directly related to the subjects will be submitted to the Ethics Committee for written approval before the study can be formally carried out. The researcher must submit an annual report of the study to the ethics committee at least annually (if applicable). When the study is terminated and / or completed, the researcher must inform the ethics committee in writing; the researcher must timely report to the ethics committee all changes in the research work (such as the revision of protocol and / or informed consent number), and shall not implement these changes without the approval of the ethics committee, unless it is made to eliminate obvious and direct risks to the subjects Changes to the contract. When this happens, the ethics committee will be informed.

Informed consent

The researcher must provide the subject or his legal representative with the informed consent which is easy to understand and approved by the ethics committee, and give the subject or his legal representative sufficient time to consider the study. The subject shall not be enrolled until the written informed consent is obtained from the subject. All updated versions of informed consent and written information will be provided to the subjects during their participation. Informed consent should be kept as an important document of clinical trials for future reference.

Confidentiality measures

Subject's medical records (research medical records, examination reports, etc.) will be kept in the hospital, and the doctor will record the examination results in outpatient medical records. Researchers, sponsor representatives and ethics committee will be allowed to access subject's medical records. Any public report on the results of this study will not disclose subject's personal identity. We will make every effort to protect the privacy of subject's personal medical data within the scope permitted by law.

Subject's medical records will not be used for any purposes other than this study.

Timeline

1) July 2019 - August 2019: Screen and confirm the clinical diagnosis of IBS-C patients, and estimate the sample content

2) September 2019–July 2020: Patient recruitment, and for the selected participants, signed an informed consent form, underwent percutaneous auricular vagus nerve stimulation treatment, and collected the outcome measures

3) August 2020-October 2020: Data analysis

References

1. Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. Nat Rev Dis Primers. 2016;2:16014.
2. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol. 2012;10(7):712-721 e714.
3. Drossman DA, Hasler WL. Rome IV-Functional GI Disorders: Disorders of Gut-Brain Interaction. Gastroenterology. 2016;150(6):1257-1261.
4. Hungin AP, Whorwell PJ, Tack J, et al. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther. 2003;17(5):643-650.
5. Spiller R, Aziz Q, Creed F, et al. Guidelines on the irritable bowel syndrome: mechanisms and practical management. Gut. 2007;56(12):1770-1798.
6. Gupta A. Peripheral mechanisms in irritable bowel syndrome. N Engl J Med. 2013;368(6):578.
7. Fukudo S, Kaneko H, Akiho H, et al. Evidence-based clinical practice guidelines for irritable bowel syndrome. J Gastroenterol. 2015;50(1):11-30.
8. Zhong L, Hou X. Pathophysiologic findings of irritable bowel syndrome in china. J Neurogastroenterol Motil. 2012;18(1):19-33.
9. Khan S, Chang L. Diagnosis and management of IBS. Nat Rev Gastroenterol Hepatol. 2010;7(10):565-581.
10. Camilleri M. Management Options for Irritable Bowel Syndrome. Mayo Clin Proc. 2018;93(12):1858-1872.
11. Triantafillidis JK, Malgarinos G. Long-term efficacy and safety of otilonium bromide in the management of irritable bowel syndrome: a literature review. Clin Exp Gastroenterol. 2014;7:75-82.
12. Tillisch K. Complementary and alternative medicine for functional gastrointestinal disorders. Gut. 2006;55(5):593-596.
13. Tak LM, Riese H, de Bock GH, et al. As good as it gets? A meta-analysis and systematic review of methodological quality of heart rate variability studies in functional somatic disorders. Biol Psychol. 2009;82(2):101-110.
14. Pellissier S, Dantzer C, Canini F, et al. Psychological adjustment and autonomic disturbances in inflammatory bowel diseases and irritable bowel syndrome. Psychoneuroendocrinology. 2010;35(5):653-662.
15. Farmer AD, Coen SJ, Kano M, et al. Psychophysiological responses to visceral and somatic pain in functional chest pain identify clinically relevant pain clusters. Neurogastroenterol Motil. 2014;26(1):139-148.
16. George MS, Nahas Z, Borckardt JJ, et al. Vagus nerve stimulation for the treatment of depression and other neuropsychiatric disorders. Expert Rev Neurother. 2007;7(1):63-74.
17. Bonaz B, Sinniger V, Pellissier S. Vagal tone: effects on sensitivity, motility, and inflammation. Neurogastroenterol Motil. 2016;28(4):455-462.
18. Matteoli G, Gomez-Pinilla PJ, Nemethova A, et al. A distinct vagal anti-inflammatory pathway modulates intestinal muscularis resident macrophages independent of the spleen. Gut. 2014;63(6):938-948.
19. Multon S, Schoenen J. Pain control by vagus nerve stimulation: from animal to man…and back. Acta Neurol Belg. 2005;105(2): 62–67.
20. Henry TR. Therapeutic mechanisms of vagus nerve stimulation. Neurology. 2002;59(6 Suppl 4):S3-14.
21. Peuker ET, Filler TJ. The nerve supply of the human auricle. Clin Anat. 2002;15(1):35-37.
22. Kovacic K, Hainsworth K, Sood M, et al. Neurostimulation for abdominal pain-related functional gastrointestinal disorders in adolescents: a randomised, double-blind, sham-controlled trial. Lancet Gastroenterol Hepatol. 2017;2(10):727-737.
23. Zhang Y, Lin X, Meng Y, et al. Invasive and noninvisive vagal nerve stimulation for opioid-induced constipation (OIC) in rats. AGA ABSTRACT. 2019;156(6):S-589.
24. Zhou J, Li S, Wang Y, et al. Effects and mechanisms of auricular electroacupuncture on gastric hypersensitivity in a rodent model of functional dyspepsia. PLoS One. 2017;12(3):e0174568.
25. Li H, Yin J, Zhang Z, et al. Auricular vagal nerve stimulation ameliorates burn-induced gastric dysmotility via sympathetic-COX-2 pathways in rats. Neurogastroenterol Motil. 2016;28(1):36-42.
26. Mearin F, Lacy BE, Chang L, et al. Bowel Disorders. Gastroenterology. 2016.