Study PROTOCOL

(Effect of auricular vagus nerve stimulator on symptom improvement and gut microbiota in patients with irritable bowel)

Version number: V3.0

Version date: 2024.2.7

Principal Investigator:

Setting: Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

1. Research Background

The human gut microbiota is one of the most abundant microbial communities on earth, containing highly diverse microbial communities that provide metabolic, immune, and protective functions and play a critical role[1-3] in human health. The gastrointestinal microbiome is influenced by a variety of factors, including neural stress, genetics, host physiology (host age, disease, etc.), and environmental factors such as living conditions and drug use. At the same time, the vagus nerve (VN) is considered to be a key component of the autonomic nervous system (ANS), which innervates most of the digestive tract and many GI organs such as esophagus, stomach, small intestine, and colon. It also innervates important organs[6] in the digestive system such as liver, pancreas, and gallbladder. The vagus nerve transmits excitation to the corresponding brain regions by sensing stimulation in the intestine, and regulates[5] the gut and brain bi-directionally through the "gut-brain axis".

Recent studies have shown that 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 home[7]ostasis. 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[8] of tumor necrosis (TNF)α, a proinflammatory cytokine. The last pathway is the splenic sympathetic anti-inflammatory pathway, where stimulation of splenic sympathetic nerves by VN leads to the distal release of acetylcholine by norepinephrine (noradrenaline). Finally, ACh inhibits TNFα release from splenic macrophages via α-7-nicotinic ACh receptors[9].

Irritable bowel syndrome (IBS) is a highly prevalent functional digestive disorder characterized[10] 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[27], and

patients are urgently looking for alternatives, including probiotics, hypnotherapy, osteopathic therapy, dietary changes, and fecal microbiota transplantation[11-14]. 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. For the above reasons, vagus nerve stimulation (VNS) may be a promising option[15] for improving IBS symptoms.

In fact, the interaction between the gut and nervous system seems to be one of the links of the brain-gut axis, which is mainly regulated by the autonomic nervous system. The anti-inflammatory effect of VNS has been demonstrated in previous studies, while low-grade intestinal mucosal inflammation[16,17] has been reported in IBS. In the gut, the vagus nerve is also the interface for the interaction between the microbiota and the mucointestinal tract, suggesting that there may be dys[18,19]biosis in VN in IBS.

Vagus nerve stimulation (VNS) is currently used as a treatment option for many clinical conditions, such as heart failure[20], migraine[21], and inflammatory bowel disease[22]. 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[23] arrest, localized infection[24] 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.

Ruisen auricular concha vagus nerve stimulator can be used directly without installation. It is easy to carry and can be turned on at any time, without affecting daily work and life (as shown below). The current approved indications are as follows: for sleep disorders, anxiety, loss of appetite, fatigue as an adjunct treatment, and diabetes as an adjunct treatment. In foreign countries, concha vagus nerve stimulation has been approved for the adjuvant treatment of epilepsy and depression. At present, some hospitals in China have introduced new technologies for the treatment of disorders of consciousness, stroke rehabilitation, migraine, epilepsy, pain intervention and so on.

Schematic illustration of the actual use of the auricular concha stimulator by the participants

According to Mion, F et al. (2020), transcutaneous auricular stimulation of the left vagus nerve (taVNS) has been shown to improve symptoms of irritable bowel syndrome (IBS). In 12 patients with IBS, taVNS was applied for 6 months for at least 3 hours per day (preferably before bedtime), 5 days per week, with continuous stimulation at a pulse width of 250 μs and a frequency of 30 Hz. Results Effective data were obtained in 9 patients (4 with diarrhea type and 5 with constipation type). IBS-SSS was significantly decreased at 3 and 6 months (baseline: 336, 3 months: 231[p = 0.0084]; The IBS-SSS decreased from 336 at baseline to 231 at 3 months [p = 0.0084], and 246 at 6 months [p = 0.0209][28].

According to the above research results, combined with the characteristics of the auricular

conchae stimulator that is portable and does not affect daily life and work, this study aims to use auricular conchae stimulation with pulse width of 200μs, frequency of 30Hz, 3 hours a day for 8 weeks to improve the clinical symptoms of patients with irritable bowel syndrome.

2. Objectives of the study

This study aimed to recruit a group of patients with irritable bowel syndrome (IBS) to use the Ruisenan portable auricular conic stimulator. (1) To observe the improvement of symptoms in patients with IBS; (2) To analyze the changes of gut microbiota in patients with irritable bowel syndrome; (3) verify whether the level of intestinal inflammation is reduced and find metabolic markers in the gut.

3. Study design

This was a randomized, double-blind study without placebo. Forty patients with physician-diagnosed IBS-D were recruited. The recruited patients were randomly assigned to undergo either real tVNS (transcutaneous vagus nerve stimulation) or sham TVNS (using the same device but without vagus nerve stimulation) at different times.

4.Selection of subjects

1、Eligibility Criteria

1.1 Patients with colorectal cancer were excluded by colonoscopy within two years, and the clinical manifestations were diarrhea predominant irritable bowel syndrome, which met the Rome IV diagnostic criteria[25]. That is, recurrent abdominal pain or discomfort, occurring at least 3 days per month in the past 3 months, and meeting the following two or more points:

(1) Improvement after defecation;

(2) the change of the frequency of defecation;

(3) The onset of the disease accompanied by changes in stool character (appearance).

* Symptoms have been present for at least 6 months before diagnosis, and symptoms have met the above criteria for the past 3 months

* Discomfort refers to non-painful discomfort. For pathophysiological studies and clinical trials, the frequency of pain/discomfort used for screening assessment is at least two days per week when selecting subjects for research.

1.2 Patients with diarrhea and irritable bowel were mainly selected for enrollment.

1.3 The enrolled patients with IBS were between 18 and 65 years of age and had a normal electrocardiogram before enrollment.

1.4 Subjects were excluded from the study if they did not meet the requirements by having them fill out the questionnaire to assess the health status of the intestinal health-related questionnaire.

2、Exclusion criteria

(a) patients with other gastrointestinal diseases; (b) patients with a history of previous abdominal surgery, cardiovascular disease or serious illness; (c) in the past month, the participant has used medications that could affect the outcome of the study (e.g., probiotics, prebiotics, antibiotics, laxatives, prokinetic drugs); (d) pregnant women; And (e) patients enrolled in other clinical studies.

5. Estimation of sample size

Forty patients with diarrhea-predominant irritable bowel syndrome

6.Study PROCEDURE

Stool samples were collected from patients with diarrhea-type irritable bowel syndrome. The auricular concha-stimulator was used for 3 hours per day with a pulse width of 200μs and a frequency of 30Hz. Each patient was randomly selected for true stimulation or sham stimulation every 4 weeks for 8[28] weeks, resulting in a total of 4 groups, namely, true-true, true-false, false-true, and false-false (FIG. 2). Stool samples were collected on day 0, day 28 and day 56. Stool samples were collected two weeks after the end of the treatment. Patients completed questionnaires on day 0 and every other 7 days thereafter, for a total of 11 questionnaire collections (Figure 1); the questionnaires are shown in Table 2.

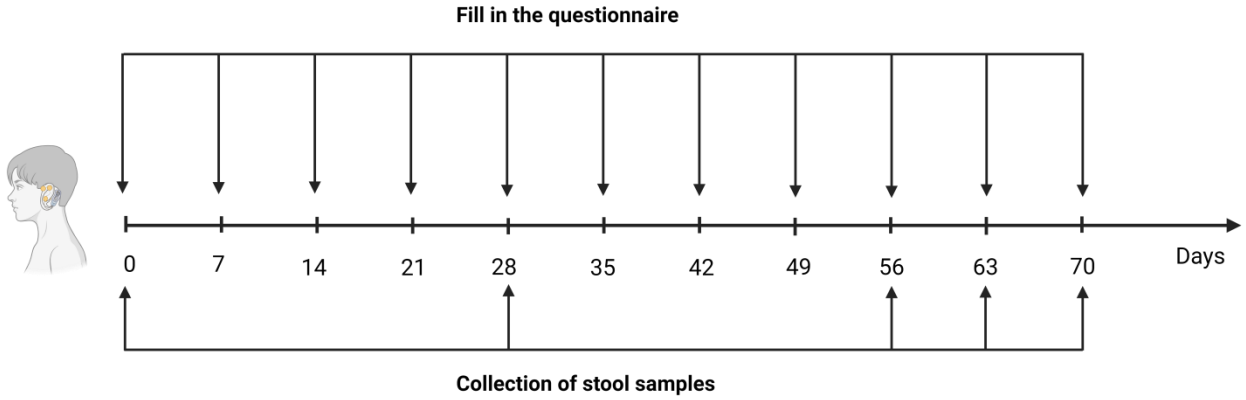


FIG. 1 Experimental design time schedule

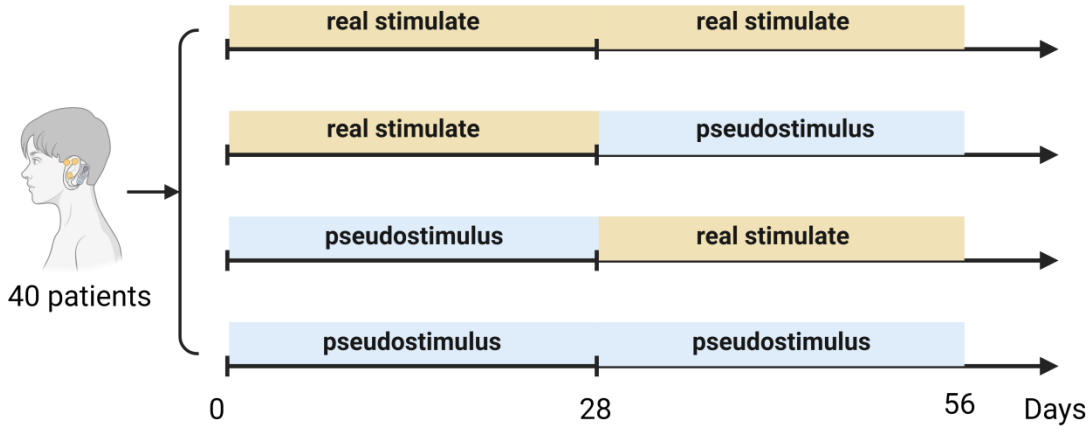


Figure 2 Schematic representation of patient randomization

A questionnaire was used to determine whether the symptoms of patients with irritable bowel syndrome improved, and stool samples were collected on days 0, 28, 56, 63, and 70 for 16s sequencing analysis. To study the changes in intestinal microbial composition and intestinal marker metabolites in patients before and after the intervention of ear conchal stimulator. Continuous sampling survey was conducted 2 weeks after treatment to observe the long-term effect of tVNS treatment, and to explore whether the irritable bowel level of patients would return to the level before treatment or could be improved after stopping the stimulation.

The study did not require recruitment advertisement, and the recruitment of subjects was completely voluntary. The possible risks in the process of the study were explained to the subjects, and the subjects signed the informed consent form after they agreed to participate in the study. A questionnaire survey was conducted on the volunteers who agreed to participate in the study to

obtain their intestinal health and other health status. The subjects were screened according to the above selection criteria and exclusion criteria. The collected samples were named by number, and no personal information of the subjects was disclosed. The identity of the subjects was kept confidential throughout the study, only the number and disease phenotype were visible. Subjects may withdraw from the study at any time stage.

The composition and structure of gut microbiota of the subjects will be analyzed. Subjects can keep informed of the progress of the experiment and analysis and obtain their own relevant data at any time.

The auricular conchal stimulator used in this study was manufactured by Ruisenan Medical Company. The portable conchal stimulator used in this study was in the form of earphones, which was well accepted by patients. It is easy to use and can be used at night before going to bed without affecting the normal life of the participants. The contact point of the earphone was closely fitted to the left ear conchial boat, which precisely stimulated the conchial boat and gave full play to the therapeutic effect. The instrument has three optional modes to meet the needs of personalized treatment.

The medical device registration certificate number of Ruisenan portable ear conchial stimulator is 20212090050, which meets the national standards for medical devices. The range (level) of Ruisenan portable auricular concha stimulator is 1-60; Frequency (Hz) range: 1-120; Pulse width (μs) range: 100, 200; Pulse on (off) time (s) range: 10-200. A variety of diseases can be treated by parameter adjustment, such as: sleep disorders, anxiety, depression, fatigue, pain, tinnitus, rehabilitation and so on.

Product design diagram:

The product inspection certificate is shown in Annex 1.

7.Description of concha vagus nerve stimulator

1、brand: Ruishan

2、Model: tVNS501

3、Core technical indicators:

(1) The stimulation location should be the concha boat, which is enriched in the vagus nerve.

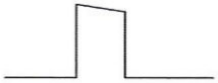
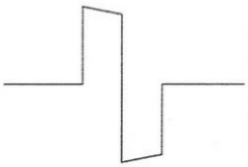
(2) Built-in rechargeable lithium battery.

(3) It has three output modes: ① Mode 1: randomly transform between pulse amplitude 0 level and set level, pulse width 200μs, pulse frequency in the range of 1-120Hz; ② Mode 2: pulse width 200μs; The pulse frequency is 20Hz for 7s and 4Hz for 3s, alternating between the two. ③ Custom mode programmable: pulse width (100-2000μs), pulse frequency (1-120Hz), pulse on time (10-200s), pulse off time (10-200s).

(4) The duration of stimulation can be set to 0-480min

(5) The stimulation output amplitude can be set to 0-60 levels, and the current can be adjusted to 0-50mA. The current increases linearly with the increase of the output amplitude and can be adjusted freely.

4、output waveform:

Patterns	Monopulse schematic	Parameters	Programmable range
A mode		Pulse amplitude	Change randomly between level 0 and set level
		Pulse width (μs)	200, error ±10%
		Pulse frequency (Hz)	Vary randomly in the range 1-120
B mode		Pulse width (μs)	200, error ±10%
		Pulse frequency (Hz)	20Hz run 7s, 4Hz run 3s, alternating between the two, error ±25%
Custom Modes		Pulse width (μs)	100, 200, error ±10%
		Pulse frequency (Hz)	Range 1-120, error ±10%
		Pulse on time (s)	Range 10-200, error ±10%
		Pulse closing time (s)	Range 10-200, error ±10%

5、Functions

The current approved indications for concha-vagus nerve stimulation are as following: for the adjunctive treatment of sleep disorders, anxiety, loss of appetite, fatigue, and diabetes. In foreign countries, concha vagus nerve stimulation has been approved for the adjuvant treatment of epilepsy and depression. At present, some hospitals in China have introduced new technologies for the treatment of disorders of consciousness, stroke rehabilitation, migraine, epilepsy, pain intervention and so on. At the same time, a number of scientific research papers using the device are published every year, including the journal Brain Stimulation has also included research papers on the device.

6、configuration requirements: no installation, direct use. It is convenient to carry, can be opened at any time to stimulate, and does not affect daily work and life.

7、consumables: no consumables

8、 Hospitals currently using the equipment of the same brand and model:

General Hospital of the People's Liberation Army

Sichuan West China Hospital

Beijing Xuanwu Hospital

Beijing Tiantan Hospital

Shanghai Mental Health Center

The First Affiliated Hospital of Zhejiang University School of Medicine

Jiangsu Provincial People's Hospital

Fujian Medical University Union Hospital

The First Affiliated Hospital of Sun Yat-sen University

Beijing Aviation General Hospital

Xijing Hospital of Air Force Medical University

The First Affiliated Hospital of Army Medical University

Xiangya Boai Rehabilitation Hospital, Hunan Province

People of Henan Province

Anhui Provincial Hospital

8. Possible risks and preventive measures

1、Possible risks:

① During the study period, if the patient's skin is allergic to the ear electrode, the use of the ear electrode can be immediately suspended, and the stopping date and time can be recorded.

② If the current density of the electrode exceeds 2mA(r.m. s)/cm2, special attention should be paid to the use of the electrode. In case of discomfort, please stop using the electrode immediately or reduce the pulse amplitude.

2、Preventive measures:

If the symptoms of patients are not improved significantly after receiving otovagus nerve stimulation, the researchers of this experiment, as digestive specialists, will give further professional guidance, including drugs, psychological counseling, traditional Chinese medicine and other comprehensive programs, in order to improve the symptoms of patients.

9. Data collection and statistical analysis

The degree of pain, the frequency of diarrhea, and the degree of abdominal distension were used to evaluate the changes in the patient's irritable bowel status. The degree of pain refers to the use of psychometric practices to evaluate the patient's subjective feeling, which is also considered to be the main factor to evaluate the poor health-related quality of life (HRQL). The severity of

irritable bowel syndrome was measured according to the Gastrointestinal Symptom Rating Scale for Irritable Bowel Syndrome (GSRS-IBS)[26]. On the GSRS-IBS scale, a score of 1 to 3 is defined as mild symptoms, a score of 4 or 5 as more severe, and a score of 6 or 7 as extremely severe[26].

Two-way analysis of variance (ANOVA) was used for statistical analysis. Two-sided t test was used for pairwise comparison, and p value was corrected for multiple comparisons. Kruskal-Wallis test was used for multiple group comparison. Spearman correlation analysis was used to determine the correlation between gut microbiota alterations and biological and pathological parameters related to constipation, with p values corrected by Benjamini-Hochberg method (Benjamini and Hochberg, 1995). A False Discovery Rate (FDR) threshold of 0.1 was used to consider the p value statistically significant. $p < 0.05$ or $p < 0.01$ was considered statistically significant. All rule plots were generated using GraphPad Prism version 8.0 (La Jolla, CA, United States). All statistical analyses were performed using GraphPad prismore and R(version 4.1.2,https://www.r-project.org/)

10. References

[1] R. Jumpertz, D. S. Le, P. J. Turnbaugh, C. Trinidad, C. Bogardus, J. I. Gordon, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. Am J Clin Nutr, 2011, 94(1): 58-65

[2] Z. Wang, E. Klipfell, B. J. Bennett, R. Koeth, B. S. Levison, B. Dugar, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature, 2011, 472(7341): 57-63

[3] J. R. Goldsmith, R. B. Sartor. The role of diet on intestinal microbiota metabolism: downstream impacts on host immune function and health, and therapeutic implications. J Gastroenterol, 2014, 49(5): 785-798.

[4] Bonaz B, Sinniger V, Pellissier S. Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation. J Physiol. 2016; 594(20):5781-5790. doi:10.1113/JP271539

[5] Yu CD, Xu QJ, Chang RB. Vagal sensory neurons and gut-brain signaling. Curr Opin Neurobiol. 2020; 62:133-140. Doi: 10.1016 / j.carol carroll onb. 2020.03.006

[6] Chen Chen, JIN Yinchuan, Zhang Liang et al. [6] Chen C, Jin Y C, Zhang L, et al. Research progress of transcutaneous vagus nerve stimulation in the treatment of neurological and psychological diseases [J]. Stroke and neurological diseases, 2021, 38 (11) : 1043-1046. The DOI: 10.19845 / j.carol carroll nki zfysjjbzz. 2021.02619.

[7] Johnston GR, Webster NR. Cytokines and the immunomodulatory function of the vagus nerve. Br J Anaesth. 2009; 102(4):453-462. doi:10.1093/bja/aep037

[8] Pavlov VA, Wang H, Czura CJ, Friedman SG, Tracey KJ. The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation. Mol Med. 2003; 9 (5 to 8) : 125-134.

[9] 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. doi:10.1136/gutjnl-2013-304676

[11] Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology130(5), 1480–1491 (2006).
[12] Wang Y, Zheng F, Liu S, Luo H. Research progress in fecal microbiota transplantation as treatment for irritable bowel syndrome.Gastroenterol. Res. Pract. 2019, 9759138 (2019).
[13] Shah K, Ramos-Garcia M, Bhavsar J, Lehrer P. Mind-body treatments of irritable bowel syndrome symptoms: an updated metaanalysis. Behav. Res. Ther. 128, 103462 (2019).
[14] Muller A, Franke H, Resch KL, Fryer G. Effectiveness of osteopathic manipulative therapy for managing symptoms of irritablebowel syndrome: a systematic review. J. Am. Osteopath. Assoc. 114(6), 470–479 (2014).
[15] Ford AC, Harris LA, Lacy BE, Quigley EMM, Moayyedi P. Systematic review with meta-analysis: the efficacy of prebiotics,probiotics, synbiotics and antibiotics in irritable bowel syndrome. Aliment. Pharmacol. Ther. 48(10), 1044–1060 (2018).
[16] Bonaz B, Picq C, Sinniger V, Mayol JF, Clarencon D. Vagus nerve stimulation: from epilepsy to the cholinergic anti-inflammatorypathway. Neurogastroenterol. Motil. 25(3), 208–221 (2013).
[17] Borovikova LV, Ivanova S, Zhang M et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin.Nature 405(6785), 458-462 (2000).
[18] Bonaz B, Bazin T, Pellissier S. The vagus nerve at the interface of the microbiota–gut–brain axis. Front. Neurosci. 12, 49(2018).
[19] Foster JA, Rinaman L, Cryan JF. Stress & the gut–brain axis: regulation by the microbiome. Neurobiol. Stress 7, 124–136(2017).
[20] De Ferrari GM, Crijns HJ, Borggrefe M, et al. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. Eur Heart J. 2011; 32 (7) : 847-855. The doi: 10.1093 / eurheartj/ehq391
[21] Botha C, Farmer AD, Nilsson M, et al. Preliminary report: modulation of parasympathetic nervous system tone influences oesophageal pain hypersensitivity. Gut. 2015; 64(4):611-617. doi:10.1136/gutjnl-2013-306698
[22] Ghia JE, Blennerhassett P, Kumar-Ondiveeran H, Verdu EF, Collins SM. The vagus nerve: a tonic inhibitory influence associated with inflammatory bowel disease in a murine model. Gastroenterology. 2006; 131 (4) : 1122-1130. The doi: 10.1053 / j.g astro. 2006.08.016
[23] Asconape JJ, Moore DD, Zipes DP, Hartman LM, Duffell WH Jr. Bradycardia and asystole with the use of vagus nerve stimulation for the treatment of epilepsy: a rare complication of intraoperative device testing. Epilepsia. 1999; 40(10):1452-1454. doi:10.1111/j.1528-1157.1999.tb02019.x
[24] Fahy BG. Intraoperative and perioperative complications with a vagus nerve stimulation device. J Clin Anesth. 2010; 22 (3) : 213-222. The doi: 10.1016 / j.j clinane. 2009.10.002
[25] Lacy BE, Patel NK. Rome Criteria and a Diagnostic Approach to Irritable Bowel Syndrome. J Clin Med. 2017; 6(11):99. Published 2017 Oct 26. doi:10.3390/jcm6110099
[26] Wiklund IK, Fullerton S, Hawkey CJ, et al. An irritable bowel syndrome-specific symptom questionnaire: development and validation. Scand J Gastroenterol. 2003; 38 (9) : 947-954. The doi: 10.1080/00365520310004209
[27] Travers P, Lacy BE, Cangemi DJ. Irritable bowel syndrome - less irritable, or better treatments? . Curr Opin Gastroenterol. 2024; 27-40 (1) : 33. Doi: 10.1097 / MOG. 0000000000000987
[28] Mion, F., et al., Transcutaneous auricular vagus nerve stimulation for the treatment of irritable bowel syndrome: a pilot, open-label study. Bioelectronics in Medicine, 2020. 3(1): p. 5-12.

Table 1. Gastrointestinal Symptom Rating Scale for Irritable Bowel Syndrome (GSRS-IBS).

The following questions relate to the symptoms of irritable bowel syndrome. The severity or intensity of the following symptoms during the past 2 weeks	No discomfort at all	Slight discomfort	Mild discomfort	Moderate discomfort	Moderate to severe discomfort	Severe discomfort	Very severe discomfort
	1	2	3	4	5	6	7
1. Are you bothered by abdominal pain?							
2. Have you							

ever felt pain or discomfort in your abdomen that relieved with bowel movements?							
3. Have you been bothered by feelings of bloating?							
4. Are you bothered by gas?							
5. Do you suffer from constipation (difficulty defecating)?							
6. Do you suffer from diarrhea (frequent bowel movements)?							
7. Do you have trouble having loose bowel movements?							
8. Do you have difficulty bowel movements because your stools are dry?							
9. Have you ever been bothered by							

the urgent need to defecate (the need to go to the toilet to defecate)?							
10. Do you have the feeling that your bowel movements are incomplete?							
11. Do you feel full soon after you start a meal?							
12. Do you still feel full long after you stop eating?							
13. Do you have significant abdominal swelling?							

Table 2. Irritable Bowel Syndrome-Quality of Life Instrument (IBS-QOL)

The following questions relate to the symptoms of irritable bowel syndrome.	no	A little bit	More	Quite a lot	Totally so
The severity or intensity of the following symptoms during the past week	0	1	2	3	4
1. I feel helpless because of my bowel movements					
2. The smell caused by my stool makes me feel embarrassed					
3. I worry about how much time I spend in the bathroom					
4. Because of my defecation problems, I feel vulnerable to other diseases					
5. I feel like I'm putting on weight because of my bowel problems					
6. I feel unable to organize my life because of my bowel problems					
7. I feel unhappy with my life because of my bowel problems					
8. I feel uncomfortable whenever I talk about my bowel problems					
9. I feel frustrated about having problems with my bowel movements					
10. I feel disconnected from those around me because of my bowel problems					
11. I have to watch how much I eat because of my bowel problems					
12. My sex life is not working because of my bowel movements					
13. I feel angry about my bowel movements					
14.1. I feel prone to irritating others because of my bowel problems					
15. I'm worried that my bowel problems are going to get worse					
16. I feel irritable and irritable because of my bowel movements					
17. I'm worried that people think I'm exaggerating my bowel problems					
18. Do I feel like I can't get anything done because of my bowel movements					
19. I have to avoid stressful situations because of my bowel problems					
20. My bowel problems have reduced my libido					

21. My bowel problems limit what I wear					
22. Because of my defecation problems, I have to avoid strenuous exercise					
23. Because of my defecation problems, I have to watch what kind of food I eat					
24. I have trouble getting along with unfamiliar people because of my bowel movements					
25. I feel slow to respond because of my bowel movements					
26. I feel unclean because of my defecation problems					
27.. It is difficult for me to travel long distances because I have problems with my bowel movements					
28. I feel frustrated that I can't eat what I want because of my defecation problems					
29. Being close to the bathroom is necessary because of my defecation problems					
30. My daily life revolves around my bowel problems.					
31. I worry about not being able to control my bowel movements					
32. I'm afraid I won't be able to defecate properly					
33. My bowel problems are affecting my relationships with those closest to me					
34. I feel like no one understands my bowel movements					

Attachment 1:

中华人民共和国医疗器械注册证

注册证编号：苏械注准20212090050

注册人名称	常州瑞神安医疗器械有限公司
注册人住所	常州市新北区华山中路26号D3006-D3008
生产地址	常州市新北区华山中路26号D3006-D3008
代理人名称	不适用
代理人住所	不适用
产品名称	耳甲迷走神经刺激器
型号、规格	tVNS501
结构及组成	产品由刺激器主机和电极导线组成。
适用范围	适用于睡眠障碍、乏力、食欲减退、焦虑症状的辅助治疗；配合药物，适用于糖尿病的辅助治疗。
附　件	产品技术要求
其他内容	
备　注	

审批部门：江苏省药品监督管理局　　批准日期：2021年02月03日

有效期至：2026年02月02日

Annex 2:

检 验 报 告

Test Report

(2020) QW 类第 [illegible]704 号

样 品 名 称 Product Name 耳甲迷走神经刺激器

规 格 型 号 Specifications tVNS501

检 验 类 别 Test Category 委托检验

委 托 单 位 Entrusting Unit 常州瑞神安医疗器械有限公司

江苏省医疗器械检验所
Jiangsu Testing and Inspection Institute for Medical Devices

江苏省医疗器械检验所
检 验 报 告 首 页

报告编号：2020QW4704　　首页 1 页 D 59 页 Z 3 页 共63 页

样品名称	耳甲迷走神经刺激器		样品编号	SLQW2006319*
	送样（√）	抽样（）		
商　　标	/		型号规格	tVNS501
委 托 方	常州瑞神安医疗器械有限公司		检验类别	委托检验
委托方通讯地址	常州市新北区华山中路 26 号 D3006-D3008		产品编号/批号	产品编号：50102000218 生产批号：50102001
标示生产单位	常州瑞神安医疗器械有限公司		抽样单编号	/
受检单位	常州瑞神安医疗器械有限公司		生产日期	2020-05-15
抽样单位	/		样品数量	3台
抽样地点	/		抽样基数	/
抽样日期	/		检验地点	本检验所试验室
收样日期	2020 年 6 月 18 日		检验日期	2020 年 7 月 6 日～11 月 26 日
检验项目	全项目（不含生物相容性）			
检验依据	GB 9706.1-2007《医用电气设备 第 1 部分：安全通用要求》 YY 0607-2007《医用电气设备 第 2 部分：神经和肌肉刺激器安全专用要求》 YY 0868-2011《神经和肌肉刺激器用电极》 常州瑞神安医疗器械有限公司产品技术要求《耳甲迷走神经刺激器》			
检验结论	被检样品符合 GB 9706.1-2007《医用电气设备 第 1 部分：安全通用要求》、YY 0607-2007《医用电气设备 第 2 部分：神经和肌肉刺激器安全专用要求》、YY 0868-2011《神经和肌肉刺激器用电极》、常州瑞神安医疗器械有限公司产品技术要求《耳甲迷走神经刺激器》规定的要求。 （检验报告专用章或检验单位公章） 签发日期 2020 年 12 月 14 日			
备注	1） 本医疗器械产品技术要求不能直接作为资质认定许可的方法。本实验室对报告涉及的检验项目具备相应的承检能力； 2） 报告中的“——”表示此项不适用，报告中“/”表示此项空白； 3） 加“*”的为整改后合格项； 4） 电磁兼容性报告见 2020QW4704-EMC 检验报告； 5） 报告页眉中的“D”表示电气安全及性能，“Z”表示照片。			

批 准：

职 务：

160015143853

中国认可
国际互认
检测
TESTING
CNAS L2058

仅复

检 验 报 告

Test Report

(2020) QW 类第4404-EMC 号

样品名称 Product Name：经颅迷走神经刺激器

规格型号 Specifications：tVNS501

检验类别 Test Category：委托检验

委托单位 Entrusting Unit：常州瑞神安医疗器械有限公司

江苏省医疗器械检验所

Jiangsu Testing and Inspection Institute for Medical Devices

江苏省医疗器械检验所

检 验 报 告 首 页

报告编号：2020QW4704-EMC　　首页 1 页 E 32 页 Z 2 页 共 35 页

样品名称	耳甲迷走神经刺激器 送样（√）　抽样（）	样品编号	SLQW2006319*
商　　标	/	型号规格	tVNS501
委 托 方	常州瑞神安医疗器械有限公司	检验类别	委托检验
委托方通讯地址	常州市新北区华山中路 36 号 D3006-D3008	产品编号/批号	50102000218
标示生产单位	常州瑞神安医疗器械有限公司	抽样单编号	/
受检单位	常州瑞神安医疗器械有限公司	生产日期	2020-06-18
抽样单位	/	样品数量	1 台
抽样地点	/	抽样基数	/
抽样日期	/	检验地点	本检验所试验室
收样日期	2020 年 6 月 18 日	检验日期	2020 年 7 月 9 日~11 月 13 日
检验项目	电磁兼容 YY 0505-2012 全项目及 YY 0607-2007 第 36 章，具体内容见“3 试验结果概述”		
检验依据	YY 0505-2012《医用电气设备 第 1-2 部分：安全通用要求 并列标准：电磁兼容 要求和试验》 YY 0607-2007《医用电气设备 第 2 部分： 神经和肌肉刺激器安全专用要求》		
检验结论	被检样品符合 YY 0505-2012《医用电气设备 第 1-2 部分：安全通用要求 并列标准：电磁兼容 要求和试验》及 YY 0607-2007《医用电气设备 第 2 部分： 神经和肌肉刺激器安全专用要求》第 36 章规定的要求。 （检验报告专用章或检验单位公章） 签发日期 2020 年 11 月 26 日		
备注	1、 报告中“/”表示此项空白，“——”表示不适用； 2、 其中带“*”的项目是整改后合格项目； 3、 报告页眉中的“E”表示电磁兼容，“Z”表示照片。		

批 准：

职 务：