Protocol | Open Access

Transcutaneous Vagus Nerve Stimulation for the Treatment of Insomnia Disorder: A Study Protocol for a Double Blinded Randomized Clinical Trial

Li Shao-Yuan[1], Jiao Yue[1], Rong Pei-Jing[1*], Li Su-Xia[2*], Yu Yu-Tian[1], Lu Lin[3] and Tang Xiang-Dong[4]

[1]Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, Beijing, P.R. China

[2]National Institute on Drug Dependence, Peking University, P.R. China

[3]Peking University Sixth Hospital/Institute of Mental Health/National Clinical Research Center for Mental Disorder, Peking University, P.R. China

[4]Sleep Medicine Center, Translational Neuroscience Center, West China Hospital, Sichuan University, Chengdu 610041, P.R. China

*Corresponding author: Rong Pei-Jing, Institute of Acupuncture and Moxibustion, China Academy of Chinese Medical Sciences, P.R. China, Tel: +86-10-64089302; E-mail: rongpj@hotmail.com

Abstract

Background: Insomnia disorder (ID) is a prevalent and costly health condition. Pharmacological treatment, one of the most common treatments provided by primary caregivers, which is far from optimal and has not been recommended since a 2005 consensus report of the National Institutes of Health. Cognitive Behavioral Therapy for Insomnia is recommended. Effectiveness, however, is still limited. Another opportunity for optimization of treatment is based on the idea that the people suffering from insomnia most is seen as an organic unity, with acupuncture, a typical traditional Chinese medicine, can provide expected treatment responses. This double-blind controlled randomized multicenter clinical trial aims to examine whether noninvasive transcutaneous vagus nerve stimulation (taVNS) is a safe and tolerable alternative treatment option for insomnia disorder.

Design: A random sample of seventy - four participants with insomnia disorder will receive transcutaneous vagus nerve simulation (taVNS) or transcutaneous non-vagus nerve simulation (tnVNS) for 4 weeks and for 2 weeks follow-up afterwards. The primary outcomes are PSG parameter, Pittsburgh Sleep Quality Index (PSQI) score, and the concentration of melatonin in plasma. The secondary outcomes are Epworth, Flinders, Hamilton Depression Rating Scale (HDRS; 17 items), Hamilton Anxiety Scale (HAMA;14 items), the MOS item short from health survey (SF-36), Heart Rate Viability (HRV) and functional magnetic resonance imaging (fMRI). PSQI, Epworth and Flinders are to be assessed at baseline and on the 7th, 14th, 21th, and 28th day of treatment and the 14th day of follow-up afterwards. PSG, melatonin, HRV and fMRI are to be detected measured at baseline and on the 28th day of treatment. 17 HDRS, 14HAMA and SF-36 are to be assessed at baseline and on the 28th day of treatment and the 14th day of follow-up afterwards.

Discussion: This study evaluates the effects of taVNS on insomnia disorder and on the quality of life of patients.

Keywords: Insomnia disorder; Vagus nerve stimulation; Transcutaneous vagus nerve stimulation; PSG; Melatonin

Background

Studies in the general population indicate that one-third of adults in Western countries experience difficulty with sleep initiation or maintenance at least once a week and 6–15% are thought to meet criteria of insomnia in that they report sleep disturbance as well as significant daytime dysfunction [1,2]. The prevalence is even higher in older people and twice as high in women as in men [3,4]. Daytime complaints of people with insomnia concern cognitive functioning [5], depressed mood [6] and fatigue [6]. Additionally, people reporting insomnia or low sleep quality have higher risks of depression [7], anxiety and irritation [8,9], metabolic diseases and cardiovascular problems [10]. Though it is not a life threatening disorder, these daytime consequences and comorbidities lead to a reduction in work productivity, to increased sick leave and healthcare consumption and consequently to high economic costs.

Acupuncture has been practiced in China for more than 3,000 years [11]. The rapid development of acupuncture over the last few decades has itself led to great innovations in practice. Auricular acupuncture, an important branch of acupuncture, has been widely used in a variety of disorders. Previous studies have exhibited that taVNS is an effective treatment for some diseases, like depression [12], epilepsy [13] and diabetes [14]. Moreover, stimulation at the auricular branch of vagus nerve can trigger melatonin secretion [15], which may improve the symptoms of insomnia.

Melatonin is a hormone secreted by the pineal gland and is important in sleep regulation [16]. Melatonin can help sleep and regulate the circadian rhythm by transforming photoperiodic signals. Previous studies indicate that melatonin can regulate sleep-wake rhythm [17] and ameliorate the sleep quality by normalizing sleep-wake cycle [18]. It also can be used to treat periodic insomnia, such as those caused by jet lag or shift work [19,20]. Here melatonin is as a biomarker to evaluate the effects of taVNS on insomnia disorder.

The present study aims to evaluate the effects of taVNS on insomnia disorder. The findings of this study will offer a treatment option for insomnia disorder.

Methods and Design

Study design

This is a multicenter, randomized, double-blind controlled prospective study. A random sample of one hundred and twenty participants with insomnia disorder will be assigned to taVNS group and tnVNS group for 4 weeks and 2 weeks' follow-up afterwards (Figure 1).

Eligibility

Participants meeting the following criteria are included:

1. Participants meet the diagnostic criteria for insomnia disorder as defined in the DSM-5.

2. Patients have to be between 18 and 70 years old.

3. Patients must understand the content of scales and cooperate with their doctors.

Participants meeting one or more of the following criteria are excluded:

1. Pregnant women;

2. Patients with unstable heart condition, liver, kidney, and hematopoietic system diseases, or other disease, such as contagious diseases and malignancies;

3. Patients with insomnia disorders secondary to environmental factors or comorbidities that prohibit sleep;

4. Patients who use sleep medication regularly, unless they are willing and able to restrict their usage to a maximum use of twice a week, at least 1 month prior to enrolment.

Figure 1: Flow chart of the clinical trial.

Withdrawal criteria and management

Withdrawal or dropout criteria:

1. At the participants' own request or that of the legal representative;

2. Participants who develop a serious disease, such as heart disease or pneumonia and, in the investigator's opinion, it is not suitable to continue;

3. The participant's compliance is poor, in the investigators' opinion, and it is not suitable that they should keep taking part in the research;

4. The participants have an adverse reaction related with transcutaneous VNS (tVNS) treatment.

Withdrawn subjects or dropouts should be managed as follows. Details of the withdrawn patients should be documented in the 'clinical trial performance forms' in the case report files (CRF) of the patients. Details of patients who have withdrawn as a result of an adverse event or reaction should be recorded in the CRF. If the patients who have been determined as dropout or withdrawn cases require further treatment, the investigators should provide the treatments; however, their data will be treated as missing data. Details of all withdrawn patients will reported in the final results, to guarantee maximum transparency.

Ethics

The study is conducted in collaboration with the Clinical Evaluation Center at the China Academy of Chinese Medical Sciences (CACMS) in Beijing, China. Ethical approval and scientific review of this study were obtained from the Ethics Committee of the Institute of Acupuncture and Moxibustion, CACMS.

Setting

Patients will be recruited from three hospitals in China: Sleep Medicine Center, West China Hospital, Sichuan University, Chengdu, China; Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China; and Acupuncture Hospital, China Academy of Chinese Medical Sciences. Beijing, China.

Randomization

Participants who meet the criteria and sign informed consent will be randomly assigned to taVNS group or to tnVNS group. The stratified block randomization will be used and the center will be taken as the stratification factor. The central randomization table will be performed and encoded by a special statistician beforehand and then kept in envelops.

Blinding

All eligible participants take part in a double-blind study. Both investigators/ physicians and patients are blinded to treatment group (taVNS vs tnVNS). Two carbons - impregnated silicone electrodes are fixed to one ear clamp (Figure 2). Only one of the electrodes however, is connected to the electrical lead (wire) imbedded in the clamp in order to keep the operation of the study double blind. In the taVNS group, the upper electrode is wired to the transcutaneous electrical nerve stimulator (TENS) while in the tnVNS group, the lower electrode is inactively wired to the TENS.

The primary outcomes are the PSQI score, PSG parameter, and the concentration of melatonin in plasma. The secondary outcomes are Epworth, Flinders, 17HAMD, 14HAMA, SF-36, HRV and fMRI scores. PSQI, Epworth and Flinders are to be assessed at baseline and on the the 7th, 14th, 21th, and 28th day of treatment and the 14th day of follow-up afterwards. PSG, melatonin, HRV and fMRI are to be detected
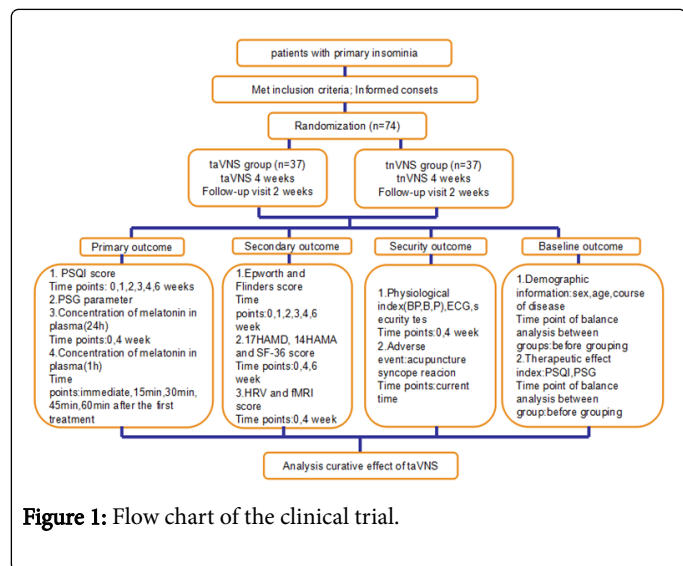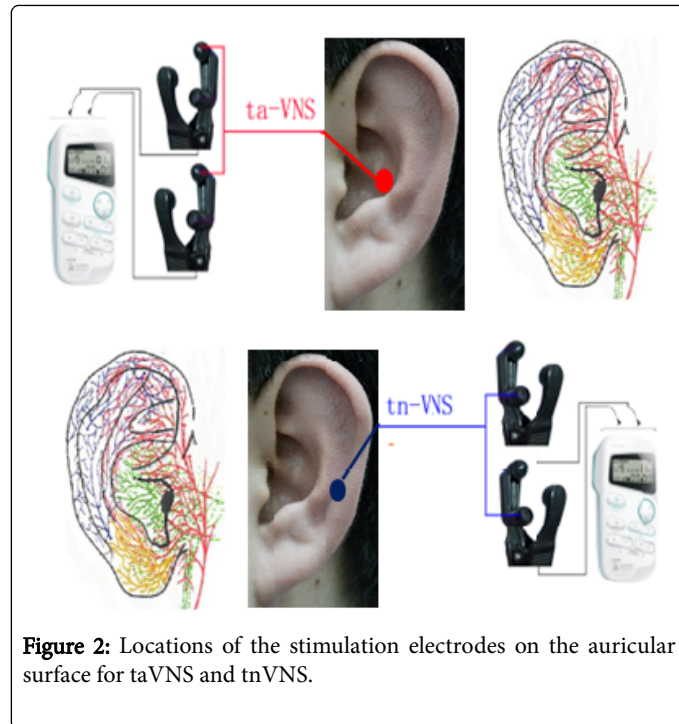
measured at baseline and on the 28th day of treatment. 17 HDRS, 14HAMA and SF-36 are to be assessed at baseline and on the 28th day of treatment and the 14th day of follow-up afterwards. The study design is detailed in Figure 1.

Figure 2: Locations of the stimulation electrodes on the auricular surface for taVNS and tnVNS.

Showing the location of taVNS (A) and tnVNS (B). The red round spot indicates the location for transcutaneous auricular vagus nerve stimulation (taVNS) and the blue one indicates the location for tnVNS. The green area indicates the innervation area of the auricular branch of vagus nerve. The upper electrode is wired to the machine in taVNS group, while the lower one is wired to the machine in tnVNS group.

Recruitment procedures

Participants will be recruited via advertisements and flyers in the three hospitals. Prior to the study, patients will be informed the procedures of the study and will provide their written consent.

Intervention and Comparison

taVNS treatment

Location

The points for taVNS are located in the auricular concha area where there is rich vagus nerve branch distribution (Figure 2).

Intervention procedure

Patients take a seated position or lay on their side. After the stimulation points are disinfected according to standard practice, ear clips are attached to the ear area (auricular concha) that will be stimulated. The SDZ-IIB electronic needling stimulator (Suzhou Medical Application Factory, 12-14 West Qilin Lane, 215005, Suzhou, China) will be used with the following parameters: 1) wave form: dilatational wave, 20 Hz for 7 seconds and 4 Hz for 3 seconds alternately; 2) wave width: 0.2 ms ± 30%; 3) intensity: selected individually by patients according to their tolerance; 4) time of treatment: treatment lasts for 30 min in the morning, and 30 min before going to bed; 5) course of treatment: 5 consecutive days per week for the duration of the treatment period (4 weeks).

tnVNS treatment

Location

The stimulation points for sham tVNS are located at the superior scapha (outer ear margin midpoint), where there is no vagus nerve distribution (Figure 2).

Intervention procedure

All procedures performed in the tnVNS treatment group are identical to the procedures for the taVNS group.

Outcome measures

Participant demographics and general status

Demographic information such as sex, age, nationality, occupation, marital status and educational background will be extracted at baseline.

Primary outcomes

Pittsburgh sleep quality index, PSQI

The PSQI is an effective self-report questionnaire used to assess the quality of sleep and sleep disturbances. The score of PSQI is highly relevant to the results of polysomnography [13]. PSQI can not only be used for the analysis of sleep behaviors of general population, but also for a comprehensive evaluation of clinical patients [14]. The changes in the PSQI between the baseline and post-treatment assessment, 2-week follow-up are used as one of the primary outcomes of this study. PSGI will be assessed at the baseline, the end of the 1st, 2nd, 3rd, 4th week of the treatment and the end of the 2nd week of follow-up afterwards.

Polysomnography (PSG) recording

Currently, PSG is regarded as a gold standard for the diagnosis of a variety of sleep disorders. Alice* 5 diagnostic equipment from Respironics/HealthDyne, Pittsburgh, PA, USA is used for data acquisition. During PSG, we monitor brain activity using six electroencephalographic (EEG) placements (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1), muscle tone by chin electromyography (EMG), eye movements by electrooculography (EOG), heart rate by electrocardiography (EKG), oxygen saturation by finger pulse oximeter, chest and abdominal wall movements by thoracic and abdominal belts, air flow by thermistor and nasal prong pressure, sleep position by position sensor, and snoring by microphone. PLMs are detected by surface EMG of both anterior tibialis muscles.

A page-by-page analysis and scoring of the electronic raw data are performed manually. This analysis is used to determine lights out, lights on, total time in bed

(TIB), total sleep time (TST), sleep period time (SPT), sleep latency, sleep efficiency [(TST/TIB) x 100], wake after sleep onset (WASO) (total duration in minutes of pages scored as WAKE from sleep onset

to the last sleep page) and stage shifts (total number of changes in sleep state from lights out to lights on). Scoring include the sleep stages and the percentage of the TST corresponding to each sleep stage, REM latency, number of REM sleep cycles, and number of arousals. Reports are generated using the Alice[*] 5 software.

PSG record will be conducted at the baseline and at the end of the 4th week of treatment. The changes of the TST, SPT, sleep latency, sleep efficiency, WASO between the baseline and the post-treatment assessment are used as one of the primary outcomes of this study.

The plasma concentration of melatonin

Melatonin, a peptide hormone secreted rhythmically by the pineal gland, has an obvious regulative effect on body rhythm [21]. Rhythmic disturbance induced by various reasons, such as diseases and jet lags, leads to changes of the melatonin level and even body function decline [22]. Melatonin plays an important role in the regulation of the circadian rhythm, especially the sleep-waking cycle [23]. The diurnal rhythm of plasma melatonin will be examined at the baseline and at the end of the 4th week of treatment. A total of seven blood samples are collected at the two timepoints. Collection occurs every 4 h at 0400 h, 0800 h, 1200 h, 1600 h, 2000 h and 2400 h over a 24 h period. The lights are turned off at 2230 h, and the participants are awakened at 0700-0730 h. The tubing system is kept patent by continuously infusing heparinized isotonic saline between blood samplings. The levels of plasma melatonin will be increased after the stimulation at the auricular branch of vagus nerve. We also detect the levels of plasma melatonin within 1 h after the first treatment. A total of five blood samples are collected at the 0 min, 15 min, 30 min, 45 min and 60 min after the first treatment.

The changes of diurnal rhythm, amplitude, mesor and peak phase of melatonin secretion and the levels of plasma melatonin within 1 h after the first treatment between the baseline and the post-treatment assessment are used as one of the primary outcomes of this study.

Secondary outcomes

The secondary outcomes include Epworth, Flinders, 17 HDRS, 14 HAMA, SF-36, HRV, fMRI and the weekly average of the components in the sleep logs during the 4-week period,. Epworth and Flinders will be assessed at the baseline, the end of the 1st, 2nd, 3rd, 4th week of the treatment and the end of the 2nd week of follow-up afterwards. 17 HDRS, 14 HAMA and SF-36 will be assessed at the baseline, the end of the 4th week of the treatment and the end of the 2nd week of follow-up afterwards. HRV and fMRI will be detected at the baseline and the end of the 4th week of the treatment.

Follow-up

The follow-up procedure is designed to evaluate the time of duration of the effect of the taVNS treatment.

Study Organization

Statistical analysis will be carried out by the Design, Measurement and Evaluation in Clinical Research (DME) professionals in Clinical Evaluation Center, CACMS, Beijing, China, after approval of the protocol by the Ethics Committee of the Institute of Acupuncture and Moxibustion, CACMS (201403152, March 15, 2014). The trial is internationally registered at Chinese Clinical Trial Register http://www.chictr.org.cn (ChiCTR-TRC-13003519). A training working team

will be established, consisting of DME professionals of Clinical Evaluation Center, CACMS, staff of the scientific research department and staff of the General Acupuncture Department. The principle institution is Institute of Acupuncture and Moxibustion, CACMS, and the cooperative institutions are the Sleep Medicine Center, West China Hospital, Sichuan University; Department of Neurology, Xuanwu Hospital, Capital Medical University; and Acupuncture Hospital, CACMS. Data management and statistical analysis will be carried out under the guidance of DME professionals according to a pre specified statistical analysis plan. The clinical trial quality control group will be established, and the investigator in each branch center will be responsible for quality control.

Sample Size Calculation

The sample size is calculated based on the equation (1) on page 165 of Clinical Epidemiology published by Shanghai Scientific and Technological Publishing House in 2009.

$$n=(Z\alpha+Z\beta)^2 \times (1+1/k) \times p(1-p)/(p1-p2)^2 \text{ (1)}$$

It is known that the effectiveness of transcutaneous vagus nerve stimulation for the treatment of primary insomnia for 4 weeks is 80.40% [24]. The effectiveness of TaVNS at the control group is 44.20%. The value of α is set to 0.05 and the value of β is set to 0.1. The ratio is equal and the value of k is set to 1. The value of p (0.6230) can be calculated by equation (2).

$$p=(p1+kp2) / (1+k) \text{ (2)}$$

Sample size is calculated as follows:

$$n=(1.64 + 1.28)^2 \times 2 \times 0.6230 \times (1 - 0.6230) / (0.8040 - 0.4420)^2$$

The sample size n is 30.56384, i.e. there will be 31 samples in each group and the total sample size is 62. Taking into account a lost rate of 20%, the total sample size will be increased to 74. That is, a sample size of 74 will be able to ensure that the better effectiveness of the treatment group than that of the control group is reliable.

Statistical analysis

The primary outcomes for efficacy analysis are the PSQI, PSG and melatonin. The secondary outcomes are the Epworth, Flinders, 17 HDRS, 14 HAMA, SF-36, HRV and fMRI. Demographics, sleep logs, PSQI, PSG, melatonin, Epworth, Flinders, 17 HDRS, 14 HAMA, SF-36, HRV and fMRI will be analyzed using independent sample t-tests at baseline to determine equality of the two groups. A chi-square test will be used to assess sex differences. A repeated-measures analysis of variance (ANOVA) will be used to assess melatonin secretion differences. The factors are time (7 levels: 0800, 1200, 1600, 2000, 2400, 0400, and 0800) and groups (2 levels: taVNS and tnVNS) and their interaction. An efficacy analysis will be done using both per-protocol and intention - to - treat analyses. Data from participants who do not violate the treatment protocols will be included in the per-protocol analysis. Missing data are dealt with using the 'last value carried forward' method.

Independent t-tests between the two groups and a repeated-measures analysis of variance (ANOVA) will be used to determine and compare the effect of tVNS. The factors are treatment (3 levels: pre-, post - taVNS and 2-week follow-up) and groups (2 levels: taVNS and tnVNS) and their interaction. As for the diurnal rhythm of melatonin secretion, the factors are treatment (3 levels: pre-, post - taVNS and 2-week follow-up), time (7 levels: 0800, 1200, 1600, 2000, 2400, 0400,

and 0800) and groups (2 levels: taVNS and tnVNS). As for the acute effect of tVNS on melatonin secretion, factors are time (7 levels: 0800, 1200, 1600, 2000, 2400, 0400, and 0800) and groups (2 levels: taVNS and tnVNS). The significance level was set at $P<0.05$ and post - hoc analyses were performed where appropriate.

Safety assessment

The experiment will ask subjects to report adverse events (AEs), such as unexpected physical changes or side effects, in person when they visit and/or by telephone at other times during the study. Every adverse event reported by subjects will be described in the case report form (CRF). If the adverse event is severe and associated with the trial, the participant will be withdrawn from the study and given appropriate medical care.

Data Safety Monitoring

Independent data safety monitoring board members will meet every 6 months or as be needed. Participants who show persistent worsening symptoms during the course of the clinical trial or develop unstable psychiatric or physical symptoms will be withdrawn from the study and will be referred for appropriate treatment immediately. According to the following classifications, a safety monitoring board will review and rate adverse events to determine whether to suspend the test condition.

Level 1: Security, without any adverse reactions.

Level 2: Safe, and have mild adverse reaction, do not need any treatment can continue to treatment.

Level 3: There are security issues; there is a moderate adverse reaction, after treatment may continue to treatment.

Level 4: Because of adverse reactions, terminate this research.

All adverse events will be reported to the Human Research Committee promptly in accordance with guidelines.

Discussions

VNS is a relatively new FDA - approved somatic treatment for depressive disorders [25,26] and may provide long-term sustained benefits [25,27]. However, the limitations and adverse events related to VNS are quite obvious, including the involvement of surgery, the high cost, perioperative risks, and potentially significant side effects such as hoarseness, throat pain, coughing, dyspnea, and paresthesil. Recently, a novel method of stimulating superficial branches of the vagus nerve to treat depressive disorder was introduced in order to overcome these limitations by our team. tVNS has the advantage of being low cost, safe and noninvasive. We found that tVNS could improve patients sleep during our previous studies with tVNS in depressed patients [12,28] and in epilepsy patients [29], These accidentally findings and our knowledge that traditional acupuncture is more effective for treating insomnia inspire a hypothesis occurrence. Our hypothesis is that stimulating auricular branch of vagus nerve can be used as a method to treat insomnia disorder.

Insomnia disorder is a series of sleep disorders excluding those caused by psychiatric and physical diseases and drug abuses, and other sleep disorders such as psychogenic insomnia, psychophysiological insomnia, sleep bad perception and idiopathic insomnia [30]. People with mild insomnia feel difficulty falling asleep, or frequent awakenings or early morning awakenings [31]. A sleep disorder is not only a risk factor for subsequent development of certain mental conditions but also a potential warning sign for serious mental or medical issues.

In the trial, we will test the taVNS has an obvious effectiveness for treating insomnia. The auricular branch of vagus nerve is stimulated 5 days per week by subjects applying it continuously on their own at home.

The design of the control group in studies verifying the effect of acupuncture treatment is always an issue. For this blind - controlled study, the stimulation points for sham tVNS are located at the superior scapha (outer ear margin midpoint), where there is no vagus nerve distribution. The present proposed trial can really test whether stimulating auricular branch of vagus nerve can treat insomnia. To blind both the investigator and patient, we applied two pairs of carbon - impregnated silicone electrodes, only one of which was wired to give electrical output; thus, neither patients nor physicians know whether they received real or sham tVNS. This double blinded design can significantly improve the quality of the trial and will shed new light on the development of methodologies in clinical trials of acupuncture treatment.

In the present trial, we also design to detect both the changes of diurnal rhythm of melatonin after 4 weeks' treatment and the acute changes of plasma concentration of melatonin within 1 h after the first taVNS treatment. The resting state changes of the brain function are also designed to be detected by fMRI. The underlying mechanism of the therapeutic effects of VNS for insomnia will be explored in this trial.

In summary, in this clinical trial, we are evaluating the efficacy of tVNS in patients with insomnia using a randomized and double - blinded design. The success of the trial will significantly provide a new choice of this promising new method to treat insomnia.

Trial Status

This clinical trial is currently recruiting participants. Trials registration- Clinical Trials. ChiCTR-TRC-13003519, http://www.acmctr.org

Competing Interests

All authors claim no conflict of interest.

Authors' Contributions

PJR, designed the trail and was responsible for obtaining approval by the Institutional Ethics Committee of the China Academy of Chinese Medical Sciences.

Acknowledgements

References

1. LeBlanc M, Mérette C, Savard J, Ivers H, Baillargeon L, et al. (2009) Incidence and risk factors of insomnia in a population-based sample. Sleep 32: 1027-1037.

2. Sivertsen B, Krokstad S, Mykletun A, Overland S (2009) Insomnia symptoms and use of health care services and medications: the HUNT-2 study. Behav Sleep Med 7: 210-222.

3. Sivertsen B, Krokstad S, Mykletun A, Overland S (2009) Insomnia symptoms and use of health care services and medications: the HUNT-2 study. Behav Sleep Med 7: 210-222.

4. Ohayon MM (2002) Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 6: 97-111.

5. Fortier-Brochu E, Beaulieu-Bonneau S, Ivers H, Morin CM (2012) Insomnia and daytime cognitive performance: a meta-analysis. Sleep Med Rev 16: 83-94.

6. Buysse DJ, Thompson W, Scott J, Franzen PL, Germain A, et al. (2007) Daytime symptoms in primary insomnia: a prospective analysis using ecological momentary assessment. Sleep Med 8: 198-208.

7. Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, et al. (2011) Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord 135: 10-19.

8. Roth T, Roehrs T, Pies R (2007) Insomnia: pathophysiology and implications for treatment. Sleep Med Rev 11: 71-79.

9. Sateia MJ, Nowell PD (2004) Insomnia. Lancet 364: 1959-1973.

10. Schwartz S, McDowell Anderson W, Cole SR, Cornoni-Huntley J, Hays JC, et al. (1999) Insomnia and heart disease: a review of epidemiologic studies. J Psychosom Res 47: 313-333.

11. Wang YS, Wang LL, Zhang JB, Chen RS (2009) [Ancient understanding and the method analysis of combined acupuncture and medication]. Zhongguo Zhen Jiu 29: 235-238.

12. Fang J, Rong P, Hong Y, Fan Y, Liu J, et al. (2016). Transcutaneous Vagus Nerve Stimulation Modulates Default Mode Network in Major Depressive Disorder. Biol Psychiatry 79: 266-273.

13. Rong P, Liu A, Zhang J, Wang Y, He W, et al. (2014) Transcutaneous vagus nerve stimulation for refractory epilepsy: a randomized controlled trial. Clin Sci (Lond).

14. Huang F, Dong J, Kong J, Wang H, Meng H, et al. (2014) Effect of transcutaneous auricular vagus nerve stimulation on impaired glucose tolerance: a pilot randomized study. BMC Complement Altern Med 14: 203.

15. Li S, Zhai X, Rong P, McCabe MF, Wang X, et al. (2014) Therapeutic effect of vagus nerve stimulation on depressive-like behavior, hyperglycemia and insulin receptor expression in Zucker fatty rats. PLoS One 9: e112066.

16. Brzezinski A (1997) Melatonin in humans. N Engl J Med 336: 186-195.

17. Sack RL, Lewy AJ, Hughes RJ (1998) Use of melatonin for sleep and circadian rhythm disorders. Ann Med 30: 115-121.

18. Finati E, Mistraletti G, Iapichino G, Fraschini F, Paroni R (2013) Melatonin: positive effects on high-risk patients with desynchronized sleep-wake rhythm. BiochimClin 37: 296-296.

19. Madrid-Navarro CJ, Sanchez-Galvez R, Martinez-Nicolas A, Marina R, Garcia JA, et al. (2015) Disruption of Circadian Rhythms and Delirium, Sleep Impairment and Sepsis in Critically ill Patients. Potential Therapeutic Implications for Increased Light-Dark Contrast and Melatonin Therapy in an ICU Environment. Curr Pharm Des 21: 3453-3468.

20. Yiallourou SR, Wallace EM, Miller SL, Horne RS (2016) Effects of intrauterine growth restriction on sleep and the cardiovascular system: The use of melatonin as a potential therapy? Sleep Med Rev 26: 64-73.

21. Gillette MU, Tischkau SA (1999) Suprachiasmatic nucleus: the brain's circadian clock. Recent Prog Horm Res 54: 33-58.

22. Kostenko EV, Petrova LV, Eneeva MA, Kamchatnov PR (2015) [Sleep disorders and circadian rhythms in diseases of the cardiovascular system]. Zh Nevrol Psikhiatr Im S S Korsakova 115: 30-36.

23. Crowley SJ, Eastman CI (2015) Phase advancing human circadian rhythms with morning bright light, afternoon melatonin, and gradually shifted sleep: can we reduce morning bright-light duration? Sleep Med 16: 288-297.

24. Lan Ying (2013) Evaluation System of Auricular Plaster Therapy in the Treatment of Insomnia [D]. Chengdu University of TCM.

25. Nemeroff CB, Mayberg HS, Krahl SE, McNamara J, Frazer A, et al. (2006) VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. Neuropsychopharmacology 31: 1345-1355.

26. Daban C, Martinez-Aran A, Cruz N, Vieta E (2008) Safety and efficacy of Vagus Nerve Stimulation in treatment-resistant depression. A systematic review. J Affect Disord 110: 1-15.

27. Sperling W, Reulbach U, Kornhuber J (2009) Clinical benefits and cost effectiveness of vagus nerve stimulation in a long-term treatment of patients with major depression. Pharmacopsychiatry 42: 85-88.

28. Xu WW, Li JX, Cai Y, Wang QS (2009) Study of vagus nerve in ear electronic acupuncture stimulation for senior patients with treatment-resistant major depressive. J Clin Psych, 19: 189-200.

29. Stefan H, Kreiselmeyer G, Kerling F, Kurzbuch K, Rauch C, et al. (2012) Transcutaneous vagus nerve stimulation (t-VNS) in pharmacoresistant epilepsies: a proof of concept trial. Epilepsia 53: e115-118.

30. American Academy of Sleep Medicine 2005. The International Classification of Sleep Disorders: Diagnostic and Coding Manual. (2nd edn) Westchester.

31. Richardson CE, Gradisar M, Barbero SC (2016) Are cognitive "insomnia" processes involved in the development and maintenance of delayed sleep wake phase disorder? Sleep Med Rev 26: 1-8.