Efficacy and brain mechanism of transcutaneous auricular vagus nerve stimulation for adolescents with mild to moderate depression: Study protocol for a randomized controlled trial

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Received: 4 April, 2020
Accepted: 4 June, 2020

ABSTRACT
Background: Depression is a common mental illness in childhood and adolescence, with an incidence of 4%–5%; it can lead to impairments in learning and social functioning. Transcutaneous auricular vagus nerve stimulation (taVNS) is a commonly used method of auricular acupuncture point stimulation, which is regarded as an effective treatment for adults with depression. The aim of this study was to investigate the efficacy and mechanism of taVNS for adolescents with mild to moderate depression.

Methods: This randomized controlled clinical trial will include 120 patients aged 12–16 years, all of whom are diagnosed with mild to moderate depression. Patients will be randomly assigned to a taVNS group and a drug control group (sertraline hydrochloride) at a ratio of 1:1. Patients will be evaluated using the 17-item Hamilton Depression Scale, Hamilton Anxiety Rating Scale, Self-Rating Depression Scale, Self-Rating Anxiety Scale, and Pittsburgh Sleep Quality Index scores at baseline, as well as at the 2nd, 4th, 6th, 8th, and 12th weeks. To investigate the underlying neural mechanisms of taVNS treatment from the perspective of the default mode network, multimodal magnetic resonance imaging (MRI; i.e., structural MRI [sMRI], resting state MRI [rsMRI], and pseudocontinuous arterial spin-labeled [pcASL] MRI) will be used to compare cerebral images among groups. MRI data will also be collected from 40 healthy volunteers to assess whether the participants exhibit normal development of structural and functional components.

Discussion: Depression is the most common mental disorder in adolescence. Drug treatment can improve depression symptoms; however, the side effects of drug treatments are often severe. This study proposes a simple physiotherapy that aims to treat adolescents with mild to moderate depression. The mechanism of taVNS in the treatment of depression will also be investigated. The results of this study will provide evidence to guide the application of taVNS in adolescents with depression.

KEYWORDS
Depression, Adolescent, Transcutaneous auricular vagus nerve stimulation (taVNS)
INTRODUCTION

Depression is a common mental illness characterized by low mood, loss of interest and energy decline, and these symptoms have high rates of disability, suicide and recurrence. The Global Burden of Disease Study 2013 reported that depression ranks first in the global burden of mental illness. At present, depression is primarily treated with antidepressants, which have long been criticized for their strong side effects and long treatment cycle. Physiotherapy has several advantages, including high levels of safety, cost-effectiveness, compliance, and acceptance by patients, as well as research value and a range of potentially useful applications. Among physiotherapy methods for treating depression, vagus nerve stimulation (VNS) has been demonstrated to be an effective treatment. Previous studies have confirmed that this technique can significantly improve depression, postpartum depression, post-stroke depression, and depression accompanying body pain. In VNS, transcutaneous auricular vagus nerve stimulation (taVNS) is a commonly used auricular acupoint stimulation method. Unlike traditional acupuncture therapy, taVNS requires no insertion of needles into the skin, and is conducted by placing an electrode on the corresponding auricular acupoint, avoiding trauma pain and fear of acupuncture. Compared with traditional acupuncture, this method is more easily accepted by patients and has been applied clinically. Based on ancient and modern texts from China and elsewhere, combined with the knowledge of experienced doctors of traditional Chinese medicine, the 2014 “Evidence-based Guidelines of Clinical Practice with Acupuncture and Moxibustion: Depression” also recommended electro-acupuncture treatment and auricular acupuncture for the treatment of depression. The results of a series of previous clinical studies with small samples in our laboratory and other studies revealed that taVNS effectively improved the mental symptoms and accompanying symptoms in adults with mild to moderate depression.

Depression is a serious mental disorder of considerable sociological and clinical importance. The development of neuroscience and genetics, as well as the discovery of new antidepressant drugs, have revolutionized our understanding for the mechanisms of depression. The monoaminergic system is an important mechanism, but multiple interactions with other brain systems and the regulation of central nervous system functions also play important roles in the onset of depression.

However, the mechanisms of taVNS in the treatment of depression remain unclear. In neuroscience, the default mode network (DMN) is a large-scale brain network of interacting brain regions with activities that are strongly interconnected with each other; this network is distinct from other networks in the brain. A recent imaging study with a large sample reported abnormalities in the DMN of patients with depression. The DMN is known to exhibit activity that is highly correlated, including the posterior cingulate gyrus/anterior cuneiform lobe, medial prefrontalis, bilateral angular gyrus, bilateral temporal lobe and bilateral hippocampus. Previous studies in our laboratory suggested that the DMN plays an important role in the treatment of depression with taVNS; for example, we found that the functional connections of bilateral medial temporal lobe cortex, bilateral subparietal cortex and other brain areas changed. However, the relationship between other brain areas in the DMN and the link between their functional connections and improvement of depression symptoms remains unclear. We speculate that changes in brain functional connections in the DMN are closely associated with a decrease in the key symptoms of depression, such as affective disorder and cognitive functional impairment, and that the decrease of functional connections in the DMN is positively correlated with the severity of these key symptoms. Among these symptoms, with the aggravation of depression, inhibition of ventromedial pre-frontal cortex on the left medial temporal cortex was found to decrease gradually, whereas the activation of left medial cortex by the thalamus exhibited no significant changes; thus, the overall manifestation was a decrease in negative emotion regulation, which eventually led to the aggravation of depression symptoms.

Importantly, taVNS has mainly been used in adults with depression, and there is currently no evidence of its efficacy in adolescents. Adolescent depression and adult depression have similar pathophysiological mechanisms, but due to the sensitive period of physical and mental development of adolescents, depression in children and adolescents exhibits different clinical characteristics. The incidence of depression in childhood and adolescence is 4%-5%. Depression in children and adolescents can cause impaired learning and social functioning in patients, potentially leading to adverse events such as obesity, smoking and substance abuse. The clinical symptoms of depression in childhood and adolescence are complex and often complicated with other psychological and mental disorders, such as anxiety disorder, alcohol and substance abuse, conduct disorder and oppositional defiant disorder. Compared with adult depression, depression in children and adolescents is often more severe, and the course of disease can be prolonged, leading to the persistence of symptoms of depression into adulthood, with a severe psychological burden for patients and their families. Moreover, depression in children and adolescents is often accompanied by suicidal ideas and behaviors, and is the third leading cause of death in this age group. Therefore, it is important to explore the efficacy of this technique in young people.

The brain has a complex network structure, and different
brain regions have different information processing functions. However, these brain regions interact extensively through network connections to fulfill their functions, following the two basic principles of functional separation and functional integration. Abnormal function and structure of a single brain region cannot provide an adequate explanation for the diverse clinical manifestations of depression, and researching the abnormal integration of multiple brain regions may be more effective for elucidating the characteristics of depression. The occurrence of depression involves many aspects of brain function, as does the treatment of depression. Therefore, both diagnosis and treatment should be considered comprehensively. Many previous studies have paid attention to single aspects of the brain, producing data that are not sufficiently comprehensive; multimodal magnetic resonance imaging (MRI) has advantages in information collection, analysis and cross-verification. Various magnetic resonance techniques can provide different information about the brain, including the specific characteristics of brain structure, patterns of brain function activity, changes in cerebral blood flow, and the mode of brain functional networks, which can elucidate the characteristics of diseases and the underlying neural mechanisms of treatment methods from multiple perspectives.

Overall, the proposed study will investigate the efficacy and mechanisms of taVNS on adolescent depression. In addition, this study will explore the underlying neural mechanisms of this treatment method from the perspective of brain functional networks (such as the DMN), aiming to provide evidence to inform its design, applications and future development.

METHODS

Ethical approval

This study has been approved by the Ethics Committee of the Beijing First Hospital of Integrated Chinese and Western Medicine. Informed consent form will be obtained from all the participants and their guardians before enrollment.

Study design

This randomized controlled, noninferiority clinical trial will enroll 120 patients; these patients will be randomized into two groups, at a ratio of 1:1. Patients in the taVNS group will be treated with taVNS for 8 weeks and followed up for 4 weeks, while patients in the drug control group will be treated continually with sertraline hydrochloride. To assess whether the participants exhibit normal development of structural and functional components, 40 healthy volunteers will be recruited as a reference group for MRI (Figure 1).

Inclusion and exclusion criteria

The patients must meet the following inclusion and exclusion criteria.

Inclusion criteria: (1) meeting the diagnostic criteria of mild to moderate depression in the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V); (2) 17-item Hamilton Depression Scale (HAM-D-17) scores between 12 and 24 points; (3) Han nationality; (4) right-handed; (5) 12–16 years old; (6) no previous depression or manic episode; (7) no sleeping, analgesia, or anesthetic drugs administered within 1 month.

Exclusion criteria: (1) family history of mental illness or other family genetic diseases; (2) history of drug dependence or abuse of antipsychotic drugs; (3) history of severe physical and nervous system diseases; (4) equipped with metal devices that are not suitable for magnetic resonance scanning, such as insulin pumps and pacemakers; (5) unable to cooperate with the study protocols.

To assess whether the participants exhibit normal development of structural and functional components, healthy control volunteers will also participate in this study. Volunteers with matched with patients in terms of age, gender and years of education will be selected from schools and communities close to the hospitals. Inclusion criteria: (1) not meeting the diagnostic criteria of depression or any other mental diseases in the DSM-V, HAMD-17 score < 12 points; (2) Han nationality; (3) right-handed; (4) 12–16 years old; (5) no sleeping, anesthetic and analgesic drugs administered within 1 month. Exclusion criteria: (1) family history of mental illness or other familial genetic diseases; (2) history of drug dependence or abuse of antipsychotic drugs; (3) history of severe physical or nervous system diseases; (4) equipped with metal devices that are not suitable for magnetic resonance scanning, such as insulin pumps and pacemakers; (5) unable to cooperate with the study protocols. Furthermore, any participant can withdraw from the study at any time, if they wish to do so.

Sample size

The effect size previously reported by this group in adults was 0.57. Based on a modest power (1− beta = 0.8) and the standard alpha level (0.05, two-tailed), we calculated that at least 50 subjects per group will be required in this comparative study. We will recruit 120 patients with mild to moderate juvenile depression; all patients will be diagnosed and treated in the Xiaozhuang, Dongba, and Traditional Chinese Medicine Branches of Beijing First Hospital of Integrated Chinese and Western Medicine from January 2020 to December 2021. The recruited patients will be randomly divided into an intervention group (n
Adolescents with mild to moderate depression diagnosed in our hospital

120 patients who met the inclusion and exclusion criteria

Random grouping (1:1)

TaVNS group

Drug control group

40 healthy participants

Scale evaluation:
1. HAMD-17
2. HAMA
3. SDS
4. SAS
5. PSQI
6. TCM syndrome collection form
7. Safety

Multimodal functional magnetic resonance:
1. sMRI: brain structure
2. rs-fMRI: brain function
3. pcASL MRI: brain blood flow

Correlation analysis

Modulation of default brain network by taVNS therapy

Clinical efficacy and brain mechanism of taVNS therapy in the treatment of mild to moderate depression in adolescents

FIGURE 1 Study flow chart. taVNS, transcutaneous auricular vagus nerve stimulation; HAMD-17, 7-item Hamilton Depression Scale; HAMA, Hamilton Anxiety Rating Scale; SDS, Self-rating Depression Scale; SAS, Self-rating Anxiety Scale; PSQI, Pittsburgh Sleep Quality Index; TCM, traditional Chinese medicine; sMRI, structural magnetic resonance imaging; rs-fMRI, resting-state functional magnetic resonance imaging; pcASL MRI, pseudo-continuous arterial spin labeling magnetic resonance imaging.

= 60) and a drug control group (n = 60); 40 additional healthy controls will be recruited as a reference group for MRI.

Interventions

Eligible patients will be randomized into a TaVNS group and a drug control group.

TaVNS group: Operation and treatment

TaVNS equipment: this instrument is composed of four parts: a main engine (electric pulse instrument), an auricular stimulation electrode, a power adapter, and an output conductor. These parameters can be displayed on the screen of the electric pulse instrument, and the output can be accurately controlled using a keyboard.

Stimulation site: the main distribution area of the auricular vagus nerve branches for anatomical localization is the cavity and cymba of the auricular concha (Figure 2).

Operation: (1) The patient assumes a supine position or sitting position; (2) the auricular electrodes are fixed on the vagus nerve distribution areas of the bilateral cavity and cymba of the auricular concha, respectively, and the power supply is connected; (3) a dilatational wave with a frequency of 4/20 Hz (alternative 4 Hz for 5 seconds and 20 Hz for 10 seconds) is set, and the output is adjusted according to the degree of pain tolerance from lower to higher, to prevent pain, discomfort, or fainting during
acupuncture; (4) patients can be treated twice a day at home, for 30 minutes each session, in the morning and evening, 7 days a week. The treatment course is 8 weeks, and the patient will be followed up at the 4th week after treatment; (5) attention is paid to the pain of the patient at all times, as well as all of the stimulation parameters displayed on the screen, after treatment, the instrument will automatically turn off the power supply, and the parameters shall be reset when used again.

Notes: (1) The instrument is not suitable for use in patients with implantable medical devices such as pacemakers; (2) the instrument should not be used on scars, bruises, new scars, scratches and inflamed skin; (3) the instrument should not be used when driving or operating machinery; (4) the instrument should not contact with metal objects when operated; (5) when the device is turned on, the two electrodes should not be connected to avoid short circuiting and damage to the instrument; (6) the instrument should not be used when bathing or sweating excessively; (7) the instrument should not be used in the presence of flammable or explosive gases; (8) an adequate distance should be maintained from televisions, radios and other electrical equipment, to avoid possible electromagnetic interference.

Drug control group

Sertraline hydrochloride will be used as the intervention drug in routine antidepressant treatment. Beginning at 25 mg/day, the dose will be increased to the target dose, according to each patient’s tolerance, within 2 weeks. The maximum dose will be 200 mg/day. All patients in the drug control group will receive the drug treatment daily.

Safety assessment

Indexes of safety evaluation will be recorded, including physiological indexes (blood pressure, electrocardiography, respiration and pulse) before and after treatment, and the adverse event recording form (e.g. chronic spasms of the neck).

Primary outcome measure

HAMD-17 scores will be evaluated at baseline, as well as at the 2nd, 4th, 6th, 8th, and 12th weeks.

Brain imaging data will be collected from 40 patients in the taVNS group and 40 patients in the drug control group before treatment and at the 8th week of treatment. The 40 healthy volunteers will undergo MRI at the time of their enrollment. Multimodal MRI (structural MRI [sMRI], resting-state functional MRI [rs-fMRI] and pseudo-continuous arterial spin labeling MRI [pcASL MRI]) will be used to compare the cerebral image differences in the groups in terms of brain structure, brain function and cerebral blood flow perfusion. After confirming the absence of metal devices, a GE 3.0T magnetic resonance instrument with a standard 20-channel head and neck coil will be used for scanning. First, a standard MRI scan collecting conventional structural images will be conducted to exclude patients with organic brain lesions.

(1) sMRI: Three-dimension brain volume imaging (3D-BRAVO) will be used to obtain whole brain structural images, particularly the 12 TMN brain areas, including bilateral medial temporal cortex, bilateral inferior parietal cortex, dorsomedial prefrontalis, ventromedial prefrontalis, bilateral thalamus, bilateral frontalis cortex and the cerebellar tonsil. Repetition time/echo time (TR/TE) = 8.2 ms/3.2 ms, T1 = 380 ms, turning angle = 12°, field of view (FOV) = 240 mm × 240 mm, matrix = 256 × 256, slice thickness/spacing = 3.0/1.0 mm, NEX = 1, scanning time 4 min.

(2) rs-fMRI: A blood oxygenation level dependent gradient echo echo-planar imaging (BOLD GRE-EPI) sequence will be used to scan the whole brain, TR/TE = 2500 ms/25 ms, turning angle = 90°, FOV = 240 mm × 240 mm, matrix = 64 × 64, slice thickness/spacing = 3.0/1.0 mm, layer number = 43, NEX = 1, scanning time 7 min.
Scans will be conducted while the subject is lying flat on the scanning bed with their eyes closed, and without performing any tasks.

(3) pcASL MRI: An ASL pulse sequence will be used to label the cerebral inflow artery blood continuously, to obtain weighted images of cerebral blood perfusion. TR/TE= 4 s/7 ms, FOV = 220 mm × 220 mm, matrix = 64 × 64, slice thickness spacing = 4.0 × 1.0 mm, marking time = 1.77 s, delay time = 1.0 s, number of layers = 25. The scanning field will cover the whole brain, with continuous scanning for a total of 180 time points.

Secondary outcome measure

Hamilton Anxiety Rating Scale (HAMA), Self-Rating Depression Scale (SDS), Self-Rating Anxiety Scale (SAS), and Pittsburgh Sleep Quality Index (PSQI) scores will be evaluated at the 0, 2nd, 4th, 6th, 8th, and 12th week. Traditional Chinese Medicine syndrome will be collected at the 0, 4th, 6th, 8th, and 12th week.

Dropout

A patient will be regarded as a dropout if the following criteria are met: (1) their depression changes to bipolar disorder or another mental disorder; (2) they receive a diagnosis of other serious concurrent diseases or deterioration during the course of the clinical study; (3) they experience serious adverse events or adverse reactions; (4) they violate the study protocol (e.g., they are unable to discontinue taking the relevant drugs as required during the treatment period, they cannot fill in the efficacy evaluation scale as required, and/or they cannot cooperate with researchers to collect relevant test samples as necessary); (5) they are lost to follow-up.

Randomization and blinding

A central randomization system will be used to randomize eligible patients into two groups at a 1:1 ratio. Each participant will be assigned a unique identification number. Researchers and patients will not be blinded to the treatment, but the raters of assessments will be blinded.

Statistical analysis

The evaluation indexes of clinical efficacy will include: (1) clinical cure rate (HAMD-17 < seven points, primary outcome measure); (2) clinical response rate (reduction in HAMD-17 scores by at least 50% from baseline level); (3) all indexes and incidences of adverse events will be compared between the two groups by statistical analysis.

We consider that the taVNS was noninferior to sertraline. The noninferiority margin was set as 50% of standard deviation of the change of the HAMD-17 score of the sertraline control group. The null hypothesis was that the mean change of the HAMD-17 score of the taVNS group would be equal to or more than the noninferiority margin.

SAS statistical software will be used for the above statistical analysis, with \( P < 0.05 \) as the significance level of tests, and data analysis will be conducted by a third party statistician. (1) Data management: all data will be entered into the Epidata database by a designated researcher via double input, with timely data verification and error correction. At the end of the study, after data cleaning is completed, the data will be finalized and statistical analysis will be carried out. (2) Statistical description: demographic data, clinical baseline, treatment and clinical outcomes of subjects will be statistically examined. The normally distributed measurement data will be represented by mean ± standard deviation, the non-normally distributed measurement data will be represented by median and inter-quartile range, and the count data will be represented by percentages (%). (3) Analysis and comparison: the clinical characteristics and prognosis of patients with depression treated with taVNS will be compared using intention-to-treat analysis. Independent samples \( t \)-tests will be used to compare normally distributed measurement data, non-parametric comparison will be used to compare the non-normally distributed measurement data, and \( \chi^2 \) tests will be used to compare the count data. Univariate and multivariate logistic regression will be used to evaluate the risk factors affecting the main efficacy measure. Repeated measures analysis of variance (ANOVA) will be used for comparison of the MRI data among three groups. The significance level was set at \( P < 0.05 \) and post-hoc analyses were performed where appropriate.

DISCUSSION

To the best of our knowledge, this study protocol is the first to explore the efficacy of taVNS in adolescent patients with depression, and the delivery of taVNS for 8 weeks is a highly novel aspect of this study. Our previous studies revealed that taVNS was able to down-regulate the activation of left medial temporal cortex by the thalamus, increase the functional connections of the posterior brain area, left middle frontalis and anterior cingulate, and thus improve depression symptoms.\(^{36,37}\) PcASL is a novel and promising imaging technique for quantitatively measuring cerebral blood flow, which has low intersubject variability, no requirement for contrast agents, and no risk of radiation injury. In depression-related studies, researchers have applied ASL to detect abnormal changes in cerebral blood flow associated with symptoms of depression. For example, some previous studies demonstrated a decrease in cerebral frontalis perfusion in patients with depression, and increased cerebral blood perfusion with auricular vagus nerve stimulation, although the specific area and degree have not yet been determined.\(^{38,42}\) Therefore, the proposed study will focus on the evaluation of cerebral perfusion changes in the anti-depressive effects of taVNS, to provide new imaging evidence for the treatment of depression with taVNS.
Moreover, a previous study reported that, compared with a healthy control group, the functional connections in brain networks in children and adolescents with first-episode depression exhibited a relatively chaotic state, in which the characteristics of network activity and the overall operation efficiency of the neural network were decreased, suggesting abnormal functional connections in multiple brain areas of children and adolescents with depression.43,44 Depression affects the normal neural development of the brain network in children and adolescents, and abnormal neural network may be a potential biological indicator of the susceptibility to depression in adolescents.45,46 Zhang et al. used independent component analysis to analyze the characteristics of functional connections in the DMN of adolescents with depression, revealing that, compared with a healthy control group, the DMN of patients exhibited extensive functional connection enhancement. In addition, the study also reported that the characteristics of functional connections in the DMN of depressive patients with or without suicidal tendencies were different, suggesting that abnormal connections between the posterior cingulate gyrus/ anterior cuneiform lobe and left cerebellum may be an indicator of suicidal behavior in adolescents with depression.

The course of depression can extend beyond adolescence, requiring long-term medication; although drug treatment can improve the symptoms of depression, the side effects of drug treatments are often severe, including irritability, gastrointestinal side effects, and weight gain.48 tA VNS may overcome some of these limitations, particularly for adolescents with mild to moderate depression. The tA VNS equipment is easy to carry and easy to operate. This equipment involves two pairs of auricular electrodes, which act on the two main distribution areas of the auricular vagus nerve branches (i.e., bilateral cavity and cymba of the auricular concha); the pulse frequency can be adjusted to 4 Hz (alternating between 4 Hz for 5 seconds and 20 Hz for 10 seconds), and the intensity can be adjusted to a tolerable degree. Overall, tA VNS has a broad range of potential applications for the treatment of depression: ease of use and transport, ability to reduce or avoid the side effects of long-term administration of antidepressants, and reduction of medical expenses.49 Additional research is underway to investigate the effects of tA VNS in other conditions, such as post-traumatic stress disorder and anxiety.

Depression is the most common mental disorder in adolescents. The therapeutic effectiveness of tA VNS for the treatment of depression in adolescents requires further study, including standardization of technical operations and treatment schemes. The profile of treatment can be gradually expanded, thereby increasing awareness and implementation of tA VNS treatment.

**CONFLICT OF INTEREST**

None.

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