Title: Auricular Acupuncture Stimulation for Chronic Pain

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Specific Aim

Low back pain (LBP) is one of the most common reasons for physician visits in the USA [1] and the leading cause of disability globally [2, 3]. Current treatments for chronic LBP (cLBP) are often unsatisfactory. Opioids are the most commonly prescribed class of drugs for back pain [4, 5]. However, an increase in misuse and complications has emerged as a serious national crisis that affects public health, as well as social and economic welfare [6, 7]. Meanwhile, few new non-opioid and non-addictive pain medications have been developed in over five decades [8]. Thus, the development of new treatments for cLBP is urgently needed.

Combining multiple brain imaging modalities (resting state fMRI, fMRI signal change evoked by pressure pain, and cerebral blood flow (CBF)), Quantitative Sensory Testing, and blood inflammation markers, this application aims to investigate the therapeutic effect of tVNS on cLBP and its underlying biological substrates. Specifically, 70 chronic low back pain patients will be randomized to real or sham tVNS treatment for one month with a three-month follow up. Clinical assessment, blood inflammation markers, Quantitative Sensory Testing, and brain imaging measurements will be applied before and after treatments.

Aim 1: Characterize the therapeutic effect of transcutaneous vagus nerve stimulation (tVNS) on chronic low back pain (cLBP)

Aim 2: Characterize the tVNS modulation effect on resting state functional connectivity (rsFC) of the periaqueductal grey (PAG)

Research strategy

Significance

1. Potential high clinical impact: developing new treatment for chronic low back pain and reducing the prescription of opioid medications Low back pain (LBP) is the fifth most common reason for all physician visits in the USA [1]. LBP was the leading cause of total years lived with disability (YLDs), contributing to 10.7% of total YLDs [2], and 6th in terms of global Disability-Adjusted Life Years in 2010 [9]. The expense associated with the care of LBP is staggering [10]. Non-specific low back pain is the most common subtype of LBP [11, 12], which affects people of all ages and is a leading contributor to the global disease burden [12]. Literature suggests that transcutaneous vagus nerve stimulation (tVNS) at the ear can regulate pain, mood, and the neuro-endocrine-immune axis [13-15]. Studies have shown that tVNS can be applied to treat both chronic pain, such as migraine [16-21], as well as common comorbidities of chronic pain disorders, such as depression and anxiety [22-24]. Thus, tVNS may be a promising method for treating cLBP. Investigating the treatment effects of tVNS on chronic low back pain and exploring its underlying mechanism will extend the application of this promising method and offer a new, non-opioid, and cost-effective pain management treatment.

2. Enhance our understanding of peripheral neuromodulation on chronic low back pain Accumulating evidence suggests that peripheral nerves can significantly influence the function of organs in the body [23, 25, 26]. The newly emerging field of Stimulating Peripheral Activity to Relieve Conditions (SPARC) aims to understand the mechanisms that underlie electrical control of organ systems and how to stimulate the body's peripheral nerves to treat various disorders, including pain disorders [25, 26].

The vagus nerve (VN) is the longest cranial nerve in the human body and is involved in the regulation of multiple systems and functions in the human body [14]. Due to its important role in maintaining homeostasis, it has become a promising target of peripheral neuromodulation. By investigating the modulation effect of tVNS on chronic low back pain and comparing its effect and mechanism in patients with chronic low back pain, we will significantly enhance our understanding of peripheral neuromodulation and the function of the vagus nerve.

Experimental Design and Methods

Overview of Experimental Design

In this study, we will recruit 70 non-specific cLBP patients based on a recent publication in Lancet [12] using the diagnostic triage as recommended by the American Physical Therapy Association Guidelines [27]. Participants who pass the screening will be randomized to one of two groups: 1) real tVNS or 2) sham tVNS. All subjects will participate in nine sessions plus self-administration of tVNS at home.

Detailed Experimental Procedure

Subject recruitment & screening: Non-specific cLBP patients will be recruited (see Protection of Human Subjects and Human Subject and Clinical Trial section for details on recruitment and inclusion and exclusion criteria) through the phone and on-site screening.

Randomization and blinding: cLBP patients will be randomized to real or sham tVNS using a permuted-block randomization with variable-sized blocks. During data acquisition, all study personnel, except the clinician who trains the patients on how to apply the real/sham tVNS, will be blinded with respect to the treatment group. All investigators will be blinded during data analysis, and coded identifiers will designate patient data.

Endpoints: The *primary clinical endpoint* is the LBP intensity score, as measured by the pain severity scale. The *primary brain imaging endpoint* is the resting state functional connectivity changes of the PAG.

Experimental procedure

Session 1 is a screening, clinical assessments, and treatment (tVNS or sham tVNS) exposure session. All subjects who pass the screening will be exposed to six minutes of real or sham tVNS based on their randomization assignment to ensure they can tolerate the tVNS in the study. Five minutes of ECG will be collected before and after real or sham tVNS treatment.

Interventions

tVNS treatment Identical to previous studies [22, 23], the tVNS points will be placed in the bilateral auricular concha area, where there is rich vagus nerve branch distribution.

Sham tVNS treatment Identical to previous studies [22, 23], the stimulation points for sham tVNS will be placed at the bilateral earlobe.

Session 2 is the baseline MRI session.

MRI data acquisition The MRI scan will be performed using a 3 Tesla Siemens MRI System equipped for Echo Planar Imaging (EPI) with a 32-channel head coil. Resting state fMRI data will be acquired using a gradient echo T2*-weighted sequence (TR/TE=2000/30 msec, flip angle=90º, slice thickness=3 mm). Arterial spin labeling (ASL) images will be acquired using a pseudo-continuous ASL (pCASL) perfusion imaging sequence [28]. Twenty-four slices will be acquired in ascending order, with the slice thickness/gap=5/1.5mm, labeling duration=1500ms, post labeling delay=1200ms, TR=3870ms, TE=12ms, and gradient-echo echo-planar readout.

Sessions 3-4 are two consecutive on-site tVNS sessions after session 2 in week 1. Participants will be trained to 1) apply real or sham tVNS with the assistance of the research investigator, and 2) fill in the tVNS diary. In these sessions, patients will also receive full tVNS treatment. These sessions will be used to detect and discuss any issues patients might experience during treatment.

Sessions 5-7 are on-site treatment sessions that oocur once a week during Weeks 2-4. The research staff will check the patients' tVNS diaries of the previous week to increase compliance.

Self-administration of tVNS: After Sessions 3-4, similar to a previous study [22], patients will be required to apply the treatments at home by themselves one time / day to reach the total treatment target of five times / week for one month (three times / week in week 1, four times / week in week 2-4).

Session 8 is the post-treatment assessment session that will take place one month after the first treatment. The procedure of this session is identical to Session 2, except only the following scans will be applied: resting state, ASL, fMRI during application of calibrated pressure pain, and brain structure.

Session 9 is a follow-up session. All participants will be invited for a follow-up session three months after last treatment. All clinical assessments except the MRI will be repeated to test the long-term effects of tVNS.

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