The effectiveness and safety of auricular acupoint therapy for patients with chronic insomnia: study protocol for a randomized controlled trial

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Study protocol

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Abstract

Background: Chronic insomnia (CI) is the most common subtype of insomnia. Auricular acupoint therapy (auricular acupoint bloodletting plus auricular acupressure) is a common treatment for CI, but its efficacy is uncertain due to the poor quality of previous studies. The purpose of this study is to evaluate the efficacy and safety of auricular acupoints in the treatment of CI by comparing with sham auricular acupoint therapy.

Methods: This is a multicenter, randomized, two-arm interventional clinical trial. Participants will participate in the study for a total of 18 weeks, consisting of three phases: 2 weeks of screening, 4 weeks of treatment, and 12 weeks of follow-up. Based on the response rate of the primary outcome in our previous study, 156 randomly allocated participants are planned. Eligible participants will be randomly assigned to the auricular acupoint therapy group and sham auricular acupoint therapy group according to a ratio of 1:1. A total of 8 sessions in 4-week treatment period will be carried out. The primary outcome is a response rate at week 4, and the responder is defined as the percentage of those having at least 3 points reduction in insomnia symptoms from baseline as measured via the Pittsburgh Sleep Quality Index (PSQI). Furthermore, response rates at other weeks, PSQI, Insomnia Severity Index (ISI), Self-Rating Depression Scale (SDS), Self-Rating Anxiety Scale (SAS), World Health Organization Quality of Life Scale-Abbreviated Form (WHOQOL-BREF), as well as sleep efficiency (SE), sleep arousal frequency (SA) and total sleep time (TST) recorded by actigraphy are chosen as secondary outcomes.


Background

Insomnia, a common psychological disease in clinic, refers to a subjective experience that patients are not satisfied with their sleep time and (or) quality which affecting social function during the day time, including insufficient sleep time and (or) depth caused by various factors, or difficulty in falling asleep, or easy to wake up when sleeping, or difficulty in falling asleep after waking up, or early awakening, or even sleepless all night. According to the survey by the World Health Organization, about 1/3 of the people in the world have sleep disorders, and more than 300 million people in China are suffering from insomnia. At present, psychotherapy, drug therapy, physical therapy and Chinese medicine (CM) are the main methods employed in treating insomnia. Cognitive behavioral therapy for insomnia (CBT-I) is the preferred treatment for insomnia, but it costs a lot, has a long course of treatment, and requires the guidance of professional therapists. Usually combined with more than 3 psychotherapies as a combination of programs, the implementation is difficult. Drugs mainly include benzodiazepine receptor agonists, melatonin receptor agonists, orexin receptor antagonists and antidepressants with hypnotic effect, but long-term use brings about potential risks such as adverse drug reactions and addiction. Physical therapies like transcranial magnetic stimulation, biofeedback therapy, diet therapy, aromatherapy and massage, lack reliable evidence-based basis. A large number of studies on the treatment of insomnia by auricular acupoint therapy have been carried out at home and abroad. The results of several systematic reviews show that auricular acupuncture and auricular acupressure can significantly relieve the symptoms of insomnia, and the efficacy is better than placebo.

Our previous study found that using auricular acupoint therapy, auricular acupoint bloodletting plus auricular acupressure (AB + AA), can improve insomnia symptom of college students. AB + AA had a stronger cumulative effect and long-term efficacy and the clinical effective rate of reached 86.1% after 4 weeks treatment. In the follow-up, it was better than AA in improving the curative effect score of CM syndromes. However, there is still a lack of high-quality clinical evidence. Thus, this study takes this therapy as the main treatment measure and placebo as the control to evaluate its effectiveness and safety.

Methods/design

Study design
In this multi-center randomized controlled trial, patients with CI are selected as the research object. The intervention method includes AB + AA (the treatment group) and sham AA (the control group). Both groups are treated twice a week for 4 consecutive weeks. After the 4-week treatment, the patients are followed up by telephone or in the outpatient department at the end of the 8th, 12th and 16th weeks respectively (Fig. 1). During the trial, we will follow the used the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guidelines.

**Participants**

Patients who meet the diagnostic criteria of sleep disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) are recruited from 3 clinical research sub-centers: Outpatient Department of Hebei University of Chinese Medicine, Hebei Provincial Hospital of Traditional Chinese Medicine, and Shijiazhuang Hospital of Traditional Chinese Medicine. Participants will be recruited by the clinical recruiters using advertisements, like leaflets, articles of WeChat official accounts.

**Diagnostic Criteria**

It is formulated by referring to DSM-5. (1) Unhappiness with the quality or quantity of sleep, which can include trouble falling asleep, staying asleep or waking up early and being unable to get back to sleep. (2) The problem occurs despite ample opportunity to sleep. (3) The difficulty cannot be better explained by other physical, mental or sleep-wake disorders. (4) The problem cannot be attributed to substance use or medication. (5) 3 nights a week for at least 3 months. (6) The sleep disturbance causes significant distress or impairment in functioning, such as within the individual's working or personal life, behaviourally or emotionally.

**Inclusion Criteria**

(1) Meets the diagnostic criteria for the DSM-5; (2) Aged 18–65 years, regardless of gender; (3) PSQI total score is more than 7 points and the ISI score is more than 8 points but less than 21 points; (4) No sedative-hypnotic drug therapy, psychotherapy, or auricular therapy are received within 2 weeks before enrollment; (5) The patients are informed of the study and sign the informed consent, as well as they are willing to accept follow-up after the end of the study.

**Exclusion Criteria**

(1) Patients with a history of psychiatric or bipolar disorder and those with the following major sleep disorders: sleep apnea (apnea/hypopnea index > 15), restless leg syndrome, periodic limb movement during sleep (PLMS with arousal > 15 per hour), circadian rhythm disorder, and parasomnias; (2) The SDS score is greater than 72 (including 72), and the SAS score is greater than 69 (including 69); (3) Pregnant or lactating women; (4) Patients with red swelling, ulcerations, or scars on their ears, or allergy to the sticking and pressing materials; (5) Patients with hemorrhagic diseases, coagulation disorders, hyperglycemia and anemia; (6) Patients are unwilling to take the actigraphy and (7) Other clinical investigators are intended to be included or have been included.

**Interventions**

The location of auricular acupoints (Table 1, Fig. 2) is determined according to the Nomenclature and Location of Auricular Points (GB/T 13734 – 2008). In the treatment group (TG), ear apex, the vena of the auricular back (the intersection of the heart, liver and antihypertensive sulcus of auricular back), are pricked to bleeding as well as sympathetic, shenmen, subcortex, kidney, heart and occiput are pressed by auricular acupressure, while in the control group (CG), the above auricular acupoints are pressed by placebo auricular acupressure.
<table>
<thead>
<tr>
<th>Time Points (week)</th>
<th>Baseline</th>
<th>Treatment Phase</th>
<th>Follow-up Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week−2</td>
<td>Week−1</td>
<td>Week 0</td>
<td>Week 1</td>
</tr>
<tr>
<td>Eligibility Screen</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Informed consent</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Randomization</td>
<td>×</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Interventions**

- **TG**
- **CG**

**Assessment**

- The response rate × × × × × × × × 
- PSQI × × × × × × × × 
- ISI × × × × × × × × 
- SAS × × × × × × × × 
- SDS × × × × × × × × 
- WHOQOL-BREF × × × × × × × × 
- SE × × × × 
- SA × × × × 
- TST × × × × 
- Credibility and expectancy × 
- Adverse events × × × × × × 

The procedure of auricular acupoint therapy is performed according to the previously published literature. The procedure of placebo auricular acupressure is as follows: When the patient is seated, the operator wipes the patient's ear with a 75% ethanol cotton ball, and applies the disposable auricular acupoint paster (replacing the seeds with a sponge ball of the same size) to the auricular acupoints. After fixation, the patient is instructed not to press until the next treatment.

Each treatment of ipsilateral auricular points, alternating application of both ears. Before the treatment, the sleep hygiene education will be carried out, and the sleep diary of the patients in the previous week is collected, which is operated by a licensed doctor with more than 3 years of clinical experience. Ask the patient to adhere to the treatment, press when not rubbing, in order to prevent ear skin damage. If it falls off, replace it in time. During the trial, patients will not be allowed to use other therapies or medications that have a therapeutic effect on insomnia, such as Chinese herbal medicine or Chinese patent
medicine, sedative hypnotics, antidepressants, anti-anxiety drugs, and so on. Estazolam (Changzhou Siyao Pharmaceutical Co., LTD., Chinese Medicine approval word H32020699, 1 mg) will be used as rescue medication under the guidance of sleep physicians whenever necessary. The medication status and other non-sedative hypnotics drug applications of patients will be strictly recorded during the trial.

**Outcome Measures**

General information such as age, sex, course of disease, education, and baseline data will be collected before the first treatment (Table 2).

<table>
<thead>
<tr>
<th>acupoints</th>
<th>location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear apex (HX_{6,7})</td>
<td>At the upper tip of the auricle folded forward, that is, the junction of the helix 6 and 7 areas.</td>
</tr>
<tr>
<td>the vena of the auricular back</td>
<td>In the upper part of the posterior, the intersection of the heart, liver and antihypertesive sulcus.</td>
</tr>
<tr>
<td>Shenmen (TF_{4})</td>
<td>In the posterior 1/3 of the upper part of the triangular fossa, namely, triangular fossa area 4.</td>
</tr>
<tr>
<td>Kidney (CO_{10})</td>
<td>It is located below and behind the foot of the antihelix, that is, area 10 of the auricular concha.</td>
</tr>
<tr>
<td>Stomach (CO_{4})</td>
<td>Where the foot of the ear wheel disappears, that is, in area 4 of the auricular concha.</td>
</tr>
<tr>
<td>Liver (CO_{12})</td>
<td>On the lower back of the cymba concha, in area 12 of the auricular concha.</td>
</tr>
<tr>
<td>Spleen (CO_{13})</td>
<td>Below the BD line, the posterior upper part of the cavum concha, that is, in area 13 of the auricular concha.</td>
</tr>
<tr>
<td>Heart (CO_{15})</td>
<td>In the middle depression of the cavum conchae, that is, area 15 of the auricular concha.</td>
</tr>
<tr>
<td>Subcortex (AT_{4})</td>
<td>On the medial side of the antitragus, that is, the antitragus area 4.</td>
</tr>
<tr>
<td>Occiput (AT_{3})</td>
<td>It is located behind the lateral side of the antitragus, that is, the antitragus area 3.</td>
</tr>
</tbody>
</table>

The primary outcome measure is the response rate at week 4 after randomization. In this trial, the response rate is defined as the percentage of those having at least 3 points reduction in insomnia symptoms from baseline as measured via the PSQI. Secondary outcomes include subjective and objective indexes. The subjective indexes are PSQI score, ISI score, SDS score, SAS score and WHOQOL-BREF score, which are evaluated before treatment (week 0 of treatment), mid-treatment (week 2 of treatment), end-treatment (week 4 of treatment) and during follow-up. The objective indexes are SE, SA and TST recorded by actigraphy (ActiGraph wGT3X-BT, USA), which are evaluated before treatment (week 0 of treatment), mid-treatment (week 2 of treatment), and end-treatment (week 4 of treatment).

PSQI includes 7 factors, including sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. The score of each factor ranges from 0 to 3 points, and the sum of the scores of each factor is the total score of PSQI, which ranges from 0 to 21 points. The higher the score, the higher the severity of insomnia.

ISI is a brief self-report instrument measuring the patient’s perception of his or her insomnia. It contains 7 questions that target the participants’ symptoms and consequences of insomnia, and the level of distress they experience in relation to these difficulties. Each item is rated on a Likert scale of 0 to 4, hence the composite scores range from 0 to 28, where higher scores suggest more severe insomnia. The ISI has demonstrated adequate sensitivity to changes in response to treatment,
where participants are considered responders to treatment if the ISI score decreases by 8 or more points. ISI score of less than 8 is the most widely used remission criterion.\textsuperscript{24}

SDS is used to evaluate the degree of depression in the two groups. A score greater than 53 indicates that the patients have depressive symptoms. A score between 54 and 62 is classified as mild depression. A score between 63 and 72 is rated as moderate depression and score greater than 72 indicates major depression. The higher the score, the more severe the depressive symptoms.\textsuperscript{25}

There are 20 items in the SAS, 15 of which are negative statements, and the score is 1–4; 5 items are positive statements (5, 9, 13, 17, 19) and are scored in a 4–1 order. Take the total score as the main index. The exact score is obtained by adding the scores of the 20 items and multiplying them by 1.25. A score of 50 or greater indicates that the patient has anxiety symptoms. A score between 51 and 59 is classified as mild anxiety. A score between 60 and 69 is classified as moderate anxiety, and A score of 70 or greater is classified as severe anxiety. The higher the score is, the more serious the anxiety symptoms are.\textsuperscript{26}

The WHOQOL-BREF scale has 26 items, which can be divided into 4 fields, including physiological field (7 questions in total), psychological field (6 questions in total), social relationship field (3 questions in total), environmental field (8 questions in total) and 2 independent questions related to overall health and overall quality of life. The highest score is 20 points in each area and the lowest score is 4 points. The higher the score, the better the quality of life.\textsuperscript{27}

wGT3X-BT Wireless Sleep monitor can be worn to monitor the SE, SA and TST of patients with CI.\textsuperscript{28}

**Sample Size**

According to the results of literature\textsuperscript{29}, the PSQI response rate of the CG after treatment was 36%, while the TG was 61% in the preliminary trial. The sample size is estimated using the formula\textsuperscript{30}:

\[
n = \frac{(u_\alpha + u_\beta)^2(1 + 1/k)p(1-p)}{\rho_e \rho_c - \rho_e - \rho_c} + 15\%
\]

Where, test efficacy $\beta = 0.1$, test level $\alpha = 0.05$, $u_\alpha$ and $u_\beta$ are 1.64 and 1.28, respectively, $\rho_e$ represents the proportion of the TG, and $\rho_c$ represents the proportion of the CG. According to the 1:1 ratio setting, the result was about 68, plus 15% loss rate, no less than 78 cases in each group. Thus, the total sample size should be 156 cases.

**Randomization Method**

Randomization is stratified by center, and dynamic block design is adopted. Randomized grouping is undertaken by Hebei International Joint Center for Acupuncture and Moxibustion of Chinese Medicine. An independent statistician who is not involved in the implementation of this trial will generate the blocked randomization sequence by using the software SPSS 27.0. Eligible participants will be randomly assigned to either TG or CG by using a telephone procedure. The recruiters, assessors, data managers and statisticians are blinded to the treatment grouping.

**Single-blind Method**

None of the patients enrolled in the study are aware of the grouping of the treatment they received. During the experiment, the physicians, the record takers and the statisticians are separated. Except for the physicians, the others do not completely know the grouping of the patients.

**Adverse Events And Safety Evaluation**

Adverse events related to auricular acupoint therapy: fainting, local infection, hematoma, discomfort after pricking, like fatigue, palpitation, dizziness, headache, pain at the pricking site and other related symptoms.
Adverse reaction report form will be used. When adverse events and adverse reactions occur, the date of occurrence, date of disappearance, outcome, degree and result of the events should be recorded in the form. Whether treatment measures have been taken for adverse events and their specific contents should be recorded in detail. According to the adverse event table, the safety of auricular point therapy is evaluated.

**Credibility And Blind Evaluation**

The reliability is evaluated after the first treatment. Blind evaluation is performed at the end of the first treatment. The researchers asks the patients, "Do you think you received auricular stimulation?" □ Yes □ No □ I don`t know

**Clinical Quality Control**

Experts in acupuncture, sleep physician, statistics, and methodology review and revise the trial protocol. Prespecified standard operating procedures, like intervention, details in filling case record form (CRF) and sleep diary card, outcome evaluation, data management will be used for the training of related staff. All data modifications can be tracked through CRF. Appropriate communication will be maintained with the patients to strengthen their compliance.

A three-level supervision system is adopted, in which the person in charge of the research center designates a person in the project team to take charge of the first-level quality control. The person must be familiar with the plan and key points, and urge the project team members to implement the plan strictly. At the end of the project, the first-level quality control task of the person will be removed. Second-level quality control is the clinical quality supervisor of each center to control the quality of research tasks undertaken by each center. Third-level quality control by the office of the full-time quality control staff. Furthermore, the clinical quality supervisor will monitor the trial process and data of each branch research center, when 10% and 90% of patients are included, respectively. If problems are found, the branch research center will be rectified and assessed in strict accordance with the relevant standard operating requirements of this trial. The trial will continue after the branch research center passes the assessment.

**Data Management**

Data management is undertaken by School of Acupuncture-Moxibustion and Tuina, Beijing University of Chinese Medicine. Excel and SPSS software are used to establish the corresponding input procedures according to the set plan and observation items specified in the protocol, and the database is run on a trial basis, and then a special database system is established for this study. Carefully record the patient's case, sometimes detection leakage or other conditions should be recorded and explained in detail. As the original records, the CRF should not be omitted or changed at will. The significant deviation or the data outside the clinically acceptable range should be verified, and the consultant should make necessary explanations. The data input is operated by two researchers. If there is any question, the data manager shall modify, confirm and input the data according to the researcher's reply.

**Statistical analysis**

SPSS 27.0 software (IBM Corp., USA) will be used for statistical analysis. Measurement data that are normally distributed are expressed as mean ± standard deviation (x ± sd), and those that are not normally distributed are expressed as median (interquartile range) [M(IQR)]. For comparison between two groups, independent sample t test is used if normal distribution is found; otherwise, Mann-Whitney test will be used. The two groups are compared before and after. If normal distribution is found, paired sample t test is used; otherwise, Mann-Whitney test is used. The counting categorical data are expressed as frequency (n) or percentage (%), and χ² test is used for comparison between groups. A p-value < 0.05 is considered statistically significant.
Patient And Public Involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Ethics And Dissemination

The study protocol has been approved by the Medical Ethics Committee of Hebei University of Chinese Medicine. The trial protocol has obtained the trial registration number (ChiCTR2200065187) and will be conducted in accordance with the rules of the Declaration of Helsinki. The recruiter in each branch center will be responsible for obtaining the informed consent of patients. Patients will be included only after the details of the study are explained to them and signing informed consent forms. The results will be published in peer-reviewed academic journals.

Discussion

CM believes that the generation of sleep-wake cycle is the result of the harmony of yin and yang\textsuperscript{28} If yin is insufficient but yang is too abundant, people will suffer from sleep disorder. However, auricular acupoint therapy, one of the alternative therapies, has become the non-drug treatment of choice for patients with CI\textsuperscript{31} Auricular acupoint bloodletting is a bloodletting therapy\textsuperscript{32} that releases an appropriate amount of blood by puncturing the acupoints with bloodletting needles, aiming at eliminating evil qi in the human body. Similarly, auricular acupressure is to apply the plaster to the acupoints for continuous stimulation, with the purpose of supporting the healthy qi of the human body.\textsuperscript{33} From the point of view of CM, the combination of the two can strengthen healthy qi to eliminate pathogenic factors, reconcile the yin and yang and treat both the symptoms and root causes of CI. The stimulation mode and acupoints of this therapy are selected according to the disease's characters and location, which is a model of integrated traditional Chinese and western medicine therapy.\textsuperscript{34}

In this protocol, we will try to study the placebo effect of auricular acupoint therapy, so sham auricular acupoint therapy is used in the study. It primarily included non-invasive acupressure for the special sticking and pressing material (placebo acupuncture)\textsuperscript{35}. In addition, in order to avoid using only subjective outcome indicators that may affect the accuracy of the results, we also use a wearable wrist watch to record the sleep parameters of patients with CI, hoping to analyze the efficacy and safety of this therapy more reasonably.

Trial Status

The trial is due to start patient recruitment in January 2023. Recruitment will be for 10 months until October 2023, with final outcome data collected by January 2024. A trial paper detailing the outcomes should be submitted for publication around June 2024.

Abbreviations


Declarations

Acknowledgements
The authors would like to thank professor Shiyan Yan, from the International Acupuncture and Moxibustion Innovation Institute, School of Acupuncture-Moxibustion and Tuina, Beijing University of Chinese Medicine, for her guidance on the protocol.

**Authors’ Contributors**

YS is the main researcher who provided idea, design of the study. HC is involved in study design and writing the manuscript. XS helps to polish the manuscript. XZ and JZ are responsible for recruiting patients. XW and YG contribute to study operation. XL is responsible for the evaluation of outcome. All authors read and approved the final manuscript.

**Funding**

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**Availability of data and materials**

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

**Ethics approval**

The trial protocol was approved by the Ethics Committee of Hebei University of Chinese Medicine, Shijiazhuang, China (YXLL202208001).

**Ethics approval and consent to participate**

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**Patient consent for publication**

Not Applicable.

**Conflict of Interests**

The authors declare that they have no conflict of interests.

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Figures
Figure 1

The flow diagram of this trial
Figure 2

Auricular acupoints in the trial