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Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in patients with insomnia: study protocol for a randomized controlled trial

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Abstract

Introduction

Insomnia affects physical and mental health due to the lack of continuous and complete sleep architecture. Polysomnograms (PSGs) are used to record electrical information to perform sleep architecture using deep learning. Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) could not only improve sleep quality, solve anxiety, depression but also ameliorate poor sleep habits and detrimental cognition. However, the clinical mechanism of this process remain unclear.

Methods and analysis

This randomized controlled trial will evaluate the efficacy and effectiveness of electroacupuncture combined with CBT-I in patients with insomnia. Participants will be randomized to receive either electroacupuncture combined with CBT-I or sham acupuncture combined with CBT-I and followed up for four weeks. The primary outcome is sleep quality, which is evaluated by the Pittsburgh sleep quality index(PSQI). The secondary outcome measures include a measurement of depression severity, anxiety, maladaptive cognitions associated with sleep, and adverse events. Sleep architecture will be assessed using deep learning on PSGs.

Ethics and dissemination

This trial has been approved by the institutional review boards and ethics committees of the First Affiliated Hospital of Sun Yat-sun University (2021763). The results will be disseminated through peer-reviewed journals.

Trial registration number

CTR2100052502

Keywords: insomnia, cognitive behavioral therapy for insomnia, electroacupuncture, randomized controlled trial

Strengths and limitations of this study

- This study will investigate the efficacy and effectiveness of electroacupuncture combined with CBT-I.
- We will observe the effects of electroacupuncture combined with CBT-I on sleep quality and sleep beliefs and attitudes of patients with insomnia.
- We will use deep learning to observe the effects of electroacupuncture combined with CBT-I on sleep architecture in different dimensions.

Introduction

Insomnia is characterized by difficulties in initiating or maintaining sleep or impaired daytime functioning, which impact both physical and mental health[1-3]. The lack of continuous and complete sleep architecture due to long-term fragmented and light sleep in patients with insomnia causes a decrease in sleep quality, which affects daily functions, and even induces anxiety, depression, and other mental symptoms[4-6]. With the increasing pressures in daily life and work, insomnia is becoming a public health problem that needs to be solved urgently as it worsens the quality of life of patients, burdens caregivers, and increases social and economic costs[7-9].

Cognitive-behavioral therapy for insomnia (CBT-I) is recommended as first-line treatment for insomnia and may improve sleep quality and alleviate poor sleep cognition in patients with insomnia[10-12]. During the early stage of treatment, the sleep quality of patients with severe anxiety were improved slowly and the compliance of these patients were poor. Thus, as confirmed in previous studies, acupuncture combined with CBT-I could not only solve anxiety, depression, and other emotions caused by insomnia but also ameliorate poor sleep habits and detrimental cognition[13-16].

However, there is a lack of rigorous clinical evidence on the treatment of insomnia with acupuncture combined with CBT-I; moreover, the clinical mechanism is unclear. In previous studies, we found that by analyzing polysomnograms (PSGs), electroacupuncture improves sleep architecture and prolongs the duration of slow-wave and rapid-eye-movement (REM) sleep[17,18]. But whether acupuncture combined with CBT-I improves sleep architecture requires futher research.

During the past decade, the application of deep learning to automatic sleep staging using PSGs has shown promise for understanding the macrostructure of sleep. Deep learning allows the automatic extraction of features from data related to classification tasks, and the performance of deep neural networks continues to improve as the size of the dataset increases[19-21].

Using a high-performance automatic sleep staging algorithm to analyze PSGs recordings via deep learning, this study will focus on the effects of electroacupuncture combined with CBT-I on sleep architecture, sleep quality, and sleep attitudes and beliefs in patients with insomnia. Furthermore, this research will provide guidance for electroacupuncture combined with CBT-I using artificial intelligence.

Methods

Study design

The study will be an assessor-blinded, randomized controlled trial. The protocol was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sun University (2021763). We will follow the Consolidated Standards of Reporting Trials and Standards for Reporting Interventions in Clinical Trials of Acupuncture guidelines for the design and reporting of the trial[22, 23]. The flowchart of the trial is presented in Figure 1, and the schedule of enrolment, interventions, and outcome assessments are presented in Table 1.

Sample size calculations: Referring to the previous litetature[24], we assume that the expected PSQI value of the observation group is 9.45 ± 1.84 and the control 6.43 ± 2.10. We determine that a sample size of 11 per group would provide a power of 90% and an alpha level of 0.05, which would allow us to detect a difference in PSQI score between the two groups. Allowing for a 20% dropout rate, a sample size of 30 in each group is sufficient to meet statistical requirements.

Randomization, allocation, and blinding

Patients who are interested in participating in the trial will initially be screened by phone and then asked to participate in a face-to-face interview to conduct further surveys. After recruiting all participants, random numbers will be generated and assigned by a central randomization system of the Clinical Research and Data Center of Guangzhou University of Chinese Medicine. The researcher who will screen the eligible patients after baseline

Table 1 Research flow chart

Project	Screening	Observation phase			Follow-up phase	
	assession 0 pre-treament	Assession 1 pre-treament	Assession 2 Week 2±1day	Assession 3 Week 4±2day	Assession 4 Week 8±1day	Unplanned follow-up
Medical history collection	√	-	-	-	-	
Sign the informed consent form	√	-	-	-	-	
Inclusion criteria	√	-	-	-	-	
Exclusion criteria	√	-	-	-	-	
Basic Information	√	-	-	-	-	
Vital signs	√	√	√	√	√	※
Index of laboratory inspection	※	※	※	※	※	
PSG	-	√	-	√	-	
Pittsburgh sleep quality index(PSQI)	-	√	√	√	√	
Beck depression inventory(BDI)	-	√	√	√	√	
Beck anxiety inventory(BAI)		√	√	√	√	
DBAS-16	-	√	√	√	-√	
Adverse Events	-	※	※	※	※	※
Medication records	-	√	√	√	√	
Terminate test evaluation	-	※	※	※	※	

Notes: **"※"**Record when necessary**;** PSG: Long-term scalp electroencephalogram recording; DBAS-16: Dysfunctional Beliefs and Attitudes about Sleep Scale 16 versio

will assign patients to either the treatment or control group. Researchers, which include statisticians, outcome assessors, and data analysts, will all be blinded to patients' group assignments. Although acupuncturists will be not blinded to group assignment, they will not be involved in outcome assessments or data analyses. In addition, all researchers will undergo training for specific procedures before the trial begins.

Participants and recruitment

Patients will be recruited using hospital-based advertisements in the Department of Acupuncture and Department of Neurology of the First Affiliated Hospital of Sun Yat-sen University from January 2022 to December 2025.

The inclusion criteria will be as follows: (1) meets diagnostic criteria for insomnia based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition[25] and the International Classification of Sleep Disorders, Third Edition[26], (2) aged 18–65 years, (3) experienced insomnia for more than 1 month but less than 2 years before the start of the trial, (4) voluntarily agrees to participate in the investigation and provides written informed consent before the clinical trial starts.

The exclusion criteria will be as follows: (1) serious cardiovascular, liver, kidney, or hematopoietic system disease, (2) insomnia was caused by a nervous system disease (e.g., stroke or Parkinson's disease), (3) insomnia was caused by a mental disorder, such as depression or anxiety, (4) history of sleep apnea, (5) pregnant or lactating women, (6) have received or currently receiving CBT-I.

Withdrawal criteria will be as follows: (1) patient withdrawal from the trial because of personal reasons, (2) patient has an adverse reaction related to acupuncture and refuses to continue treatment, (3) during the follow-up period, the patient cannot be contacted because of change of address and telephone number.

Intervention

The intervention will begin the day following randomization. All participants will receive 20 treatments (five times per week for 4 weeks).

Observation group

Acupuncture treatment

Patients' skin will be disinfected with 75% alcohol, and patients will be asked to lie supine and wear eye masks for a better curative effect. Each participant will receive acupuncture treatment from the same acupuncturist who has more than 5 years of clinical experience in acupuncture therapy. The temperature of the treatment room will not be lower than 25°C. Each treatment will last for 30 min.

Patients in the acupuncture group will receive electroacupuncture treatment on Sishenchong (EX-HN1), bilateral Neiguan (PC6), bilateral Taixi (KI3), bilateral Shenmen (HT7), and bilateral Sanyinjiao (SP6). Tube-guided acupuncture needles will be inserted to a depth of 17-25 mm at each acupoint (acupuncture location and method for each acupoint are provided in Table 2). A low-frequency electronic pulse therapy instrument (G6805-2A, Shanghai Huayi Medical Instrument Co., Shanghai, China) will be used between the two sets of acupoints.

CBT-I treatment

CBT-I will be given while acupuncture treatment is in progress. The intervention will consist of behavioral components (e.g. sleep restriction and stimulus control), cognitive components (e.g., cognitive restructuring and paradoxical intention), progressive muscle relaxation, and sleep hygiene[27].

Control group

The procedure for the control group will be the same as that for the observation group, with the major difference in interventions between the two groups being the tube needling method, in which no needle will be inserted through the tube for patients in the control group. To mimic the sensation of a real needle being inserted into the body, the acupuncturist will place the tube close to the skin at the acupoint and tap the top of the tube.

Quality control

Table 2 Acupuncture location and method for each acupoint

Acupoint	Location	Needling method
Sishenchong (EX-HN1)	On the parietal region, 1 cun anterior ,posterior and lateral to Baihui, 4 acpoints totally.	The angle between the needle tip and the scalp is 30。. Move the needle tip backward along the anterioreposterior midline, and then insert the needle 0.5 cun.
Neiguan(PC6)	On the line joining Daling and Quze, between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist.	Puncture perpendicularly 1-1.5 cun.
Taixi (KI3)	In the depression between the tip of the medial malleolus and the Achilles tendon.	Puncture perpendicularly 0.5-1 cun.
Shenmen (HT7)	On the palmar ulnar end of the transverse crease of the wrist,and on the radial aspect of the tendon of the ulnar flexor m. of the wrist.	Puncture perpendicularly 0.5-1 cun.
Sanyinjiao (SP6)	Posterior to the mesial border of the tibia,and 3 cun above the tip of the medial malleolus	Puncture perpendicularly 1-1.5 cun.

The trial will be conducted under the supervision of the First Affiliated Hospital of Sun Yat-sun University. A qualified clinical trial expert will be invited to monitor the study to identify problems during the trial, examine collected data, and control bias.

Outcome measures

Primary outcome

Pittsburgh sleep quality index

The Pittsburgh sleep quality index (PSQI) is an internationally established tool that is used to evaluate sleep quality. The scale includes seven dimensions that consist of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleeping medication, and daytime dysfunction. The score correlates adversely with sleep quality which a higher score means the sleep quality is worse, and each factor has a score of 0 to 3 to provide a total score of 21 points[28, 29].

Secondary outcomes

The Beck depression inventory

The Beck depression inventory (BDI) is a valid self-assessment index to measure depression severity and consists of 13 items. Each item is scored from 0 to 3 (0 to 4 indicates no depression, 5 to 7 indicates mild depression, 8 to 15 indicates moderate depression), with a score of 16 points or more considered as severe depression[30-32].

The Beck anxiety inventory

The Beck anxiety inventory (BAI) is used to assess the degree of anxiety and consists of 21 items scored from 1 to 4 (15 to 25 points indicates mild anxiety, 26 to 35 points indicates moderate anxiety, and 36 points is considered severe anxiety)[33, 34].

The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version

The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version (DBAS-16) is used to evaluate maladaptive cognitions associated with sleep. There are 16 items in the index, which are divided into four factors comprising consequences of insomnia, worry about sleep, sleep expectations, and medication. These factors are scored on a scale of 1–5

(strongly disagree to strongly agree). The total score is positively correlated with the reasonableness of sleep beliefs and attitudes[35, 36].

Sleep staging

The PARADISEP&D9600 (U.S.) Polysomnography Monitoring and Analysis System will be used to simultaneously monitor EEG, EOG, and EMG. A large clinical dataset of PSG recordings will be used to train a hybrid convolutional neural network (CNN) and recurrent neural network (RNN) to learn effective and generalizable features for sleep stage scoring[37, 38]. Then clinical data will be used to indentify the deep learning algorithm. Sleep staging for both datasets will be performed by expert sleep technicians in nonoverlapping 30-s epochs according to standards by the American Academy of Sleep Medicine(AASM), as one of five stages: wake(W), non-rapid eye movement(REM) stage 1(N1), non-REM stage 2(N2), non-REM stage 3(N3), and rapid eye movement (REM)[39].

Adverse events

During treatment and four week after treatment, a questionnaire will be administered to evaluate the various discomforts that may be caused by acupuncture: hangover, addiction, tolerance, fatigue after waking, insomnia rebound, daytime alertness, cognitive function, and behavior ability.

Patients and public involvement

Patients and the public are not involved in the design or conduct of the study or the outcome measures, and no attempt will be made to assess the burden of the intervention on the patients themselves. The results of this study will be disseminated to study participants via the website of our hospitals.

Statistical analysis

All analyses will be performed on the intention-to-treat population of participants who had at least one treatment. Missing data will be replaced according to the principle of the last observation carried forward. Data analyses will be performed using the SPSS version

25 (IBM Corp.) software. All available data will be analyzed descriptively. For continuous data, the normality test will be applied at the beginning of the analysis. Results will be presented as means, standard deviations, and 95% confidence intervals (CIs) for continuous data that conform to the normal distribution and medians, quartiles, and ranges for rank data and continuous data that are not normally distributed. Discrete data will be presented as percentages.

We will first examine the descriptive data for sample characteristics at baseline, and independent samples t-tests will be used to compare groups for continuous variables, whereas chi-square analysis will be used to compare groups for dichotomous variables. Second, we will perform two series of repeated-measures and univariate analyses of covariance (ANCOVA) models to examine treatment effects. We will use repeated-measures ANCOVAs to analyze the primary and secondary outcome measures (i.e., PSQI, BDI, BAI, DBAS-16, and sleep staging scores) from pre-treatment to post-treatment. If a significant effect is observed, we will conduct posthoc paired samples t-tests to examine within-group changes in study outcomes. For all study outcomes, we will then perform univariate ANCOVAs to test for group differences in post-treatment values while controlling for relevant covariates. This process will be repeated to examine changes in study outcomes from pretreatment to postnatal follow-up.

When necessary, sensitivity analysis will be used to assess the robustness of the conclusions of the entire clinical trial. To evaluate the consistency of the trial and explore the factors that affect efficacy or prognosis, subgroup analysis will be conducted to identify the population with better efficacy. Safety analysis will be used to assess the incidence of adverse events and related symptoms in patients with insomnia during treatment and follow-up.

Discussion

Currently, the main treatments recommended for insomnia are non-pharmaceutical and pharmaceutical treatments. Pharmaceutical treatments include benzodiazepines as well as new non-benzodiazepine drugs, which can shorten the latency to fall asleep and prolong total sleep time but also affect normal sleep physiology and cause adverse reactions [40, 41]. CBT-I, which is recommended as a first-line treatment for insomnia by the European insomnia guidelines, is limited in clinical practice because of insufficient professional therapists and poor compliance of patients with insomnia, especially in developing countries such as China[42-44].

As a complementary alternative therapy with a long history in China, acupuncture has been used as a clinical treatment for insomnia with fewer adverse effects and less permanent damage. Previous studies showed that either acupuncture or CBT-I could produce clinically meaningful improvements in insomnia symptoms, and our preliminary research have confirmed that acupuncture combined with CBT-I also alleviate not only insomnia symptoms but also negative emotions such as anxiety and depression[13, 14, 16]. But whether acupuncture combined with CBT-I could influence sleep habits and correct cognition, and what the clinic clinical mechanism worth futher research.

To ameliorate sleep habits, correct cognition, and alleviate anxiety, depression, and other emotions caused by insomnia, this study will use electroacupuncture combined with CBT-I and observe sleep architecture, sleep quality, and sleep attitudes and beliefs in patients with insomnia. In this study, PSQI will be used to assess the sleep quality, BDI and BAI will be used to evaluate the depression severity and anxiety. At the same time, we will use DBAS-16 to evaluate the sleep beliefs and attitudes before and after treatment. Because of the particularity of acupuncture therapy, the implementation of blinding is difficult in clinical research[45, 46]. A research team composed of researchers, therapists, testers, and statisticians will be established to reduce any bias that may occur

during the research process by blinding testers and statisticians. This study will provide clinical evidence for the effect and safety of electroacupuncture combined with CBT-I and provide a decision-making reference for clinicians, patients, and policymakers.

To analyze the effects of electroacupuncture combined with CBT-I on sleep architecture and sleep quality in patients with insomnia, deep learning will be used to analyze PSGs in various clinical settings in this study. PSGs are used widely for clinical evaluation because they are more sensitive than routine EEGs (typically 30–60 min duration) in capturing paroxysmal electrical abnormalities[47, 48]. During the past decade, there have been various advances in automated sleep staging of PSGs data using the ability of deep learning methods to automatically extract features from data that are relevant to the classification; moreover, the performance of deep neural networks continues to improve as datasets become larger[49-52]. Using deep learning, this study will develope a high-performing, reference channel-free, automated sleep staging algorithm to analyze the sleep architeture which will provide a clinical mechanism in artificial intelligence.

In summary, this study will use electroacupuncture combined with CBT-I to treat insomnia and observe the sleep beliefs and attitudes of patients with insomnia in different dimensions using deep learning. Moreover, we will provide a solid research basis for the combined application of electroacupuncture and CBT-I for insomnia in the clinic.

Acknowledgments

Not applicable.

Footnotes

Contributors: Wenya Pei and Te He designed the trial protocol and drafted the manuscript. Liming Lu, Jingwen Ruan, and Guihua Wen revised the manuscript. Pei Yang, Xiaozhou Lv, and Boyu Jiao will plan the data analysis. Liqian Cui, Yingshuo Yan, Fanqi Meng,

Guanheng He, and Xin Zhou will participate in participant recruitment. All authors discussed, read, and revised the manuscript, and all approved the publication of this protocol.

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Ethics statements

Patient consent for publication

Not applicable.

Ethics approval and consent to participate: The study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sun University (2021763). Participants will be included only after they provide written informed consent. The study was registered in the Chinese Clinical Trial Registry (No.ChiCTR2100052502, 30/10/2021).

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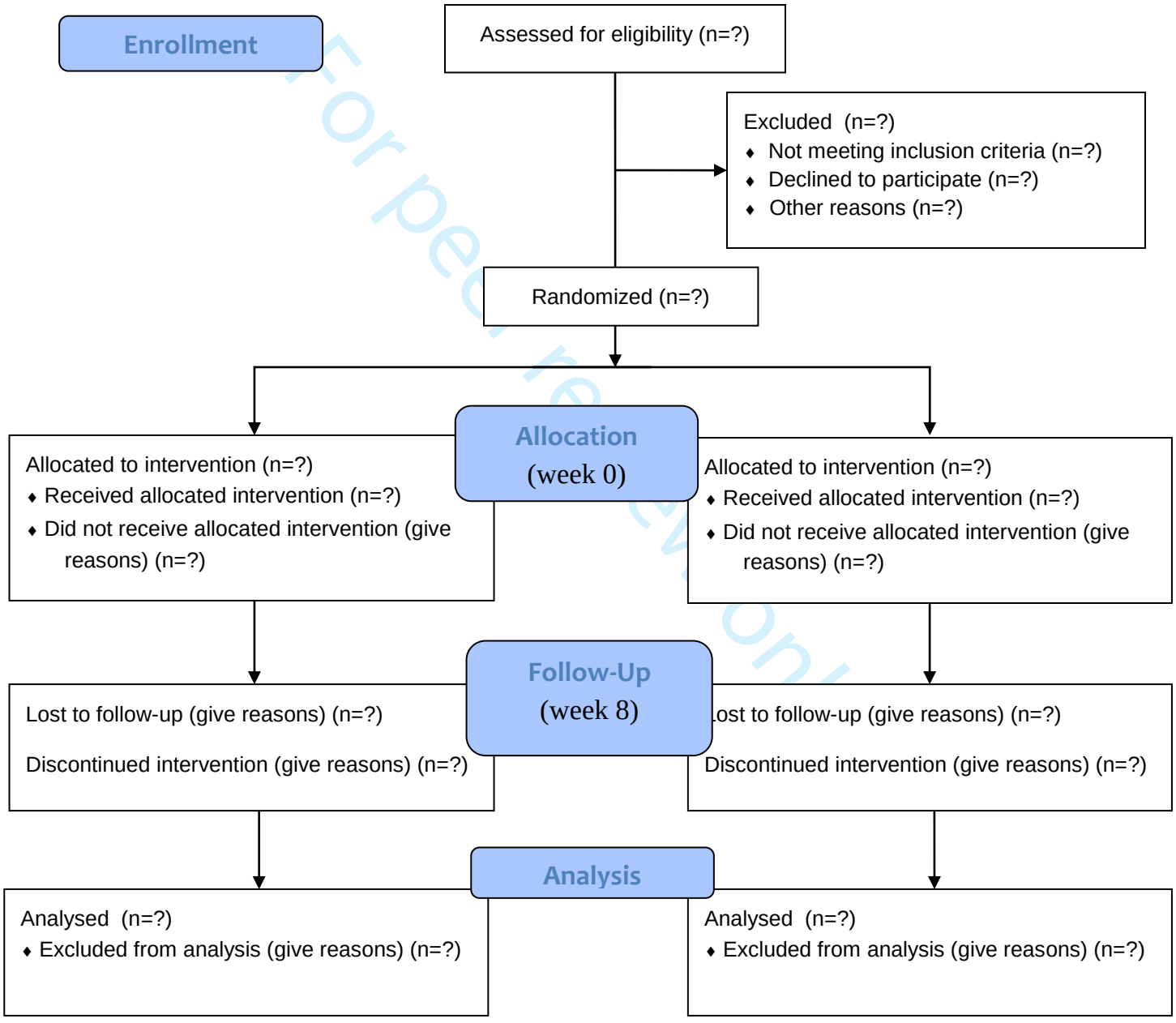
Fig 1. CONSORT 2010 Flow Diagram

CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,12
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4-5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4,Table 1,Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8-9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			5
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9-10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9-10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9-10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9-10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6
	31b	Authorship eligibility guidelines and any intended use of professional writers	6
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	6
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See The Ethics Approval Document
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in patients with insomnia: study protocol for a randomized controlled trial

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Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in patients with insomnia: study protocol for a randomized controlled trial

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Abstract

Introduction

Insomnia affects physical and mental health due to the lack of continuous and complete sleep architecture. Polysomnograms (PSGs) are used to record electrical information to perform sleep architecture using deep learning. Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) could not only improve sleep quality, solve anxiety, depression but also ameliorate poor sleep habits and detrimental cognition. However, the mechamnism of clinical study in this process remain unclear.

Methods and analysis

This randomized controlled trial will evaluate the efficacy and effectiveness of electroacupuncture combined with CBT-I in patients with insomnia. Participants will be randomized to receive either electroacupuncture combined with CBT-I or sham acupuncture and followed up for four weeks. The primary outcome is sleep quality, which is evaluated by the Pittsburgh sleep quality index(PSQI). The secondary outcome measures include a measurement of depression severity, anxiety, maladaptive cognitions associated with sleep, and adverse events. Sleep architecture will be assessed using deep learning on PSGs.

Ethics and dissemination

This trial has been approved by the institutional review boards and ethics committees of the First Affiliated Hospital of Sun Yat-sun University (2021763). The results will be disseminated through peer-reviewed journals.

Trial registration number

CTR2100052502

Keywords: insomnia, cognitive behavioral therapy for insomnia, electroacupuncture, randomized controlled trial

Strengths and limitations of this study

- This study will investigate the efficacy and effectiveness of electroacupuncture combined with CBT-I in patients with insomnia.
- A randomized controlled trial will be conducted to assess sleep quality, depression severity, anxiety, maladaptive cognitions associated with sleep, and adverse events.
- Deep learning will be used to observe the effects of electroacupuncture combined with CBT-I on sleep architecture in different dimensions.
- Using deep learning, this study will develope a high-performing, reference channel-free, automated sleep staging algorithm to analyze the sleep architecture.
- We will provide an insight into the combined application of electroacupuncture and CBT-I for insomnia in the clinic

Introduction

Insomnia is characterized by difficulties in initiating or maintaining sleep or impaired daytime functioning, which impact both physical and mental health[1-3]. The lack of continuous and complete sleep architecture due to long-term fragmented and light sleep in patients with insomnia causes a decrease in sleep quality, which affects daily functions, and even induces anxiety, depression, and other mental symptoms[4-6]. With the increasing pressures in daily life and work, insomnia is becoming a public health problem that needs to be solved urgently as it worsens the quality of life of patients, burdens caregivers, and increases social and economic costs[7-9].

Cognitive-behavioral therapy for insomnia (CBT-I) is recommended as first-line treatment for insomnia and may improve sleep quality and alleviate poor sleep cognition in patients with insomnia[10-12]. During the early stage of treatment, the sleep quality of patients with severe anxiety were improved slowly and the compliance of these patients were poor. Thus, as confirmed in previous studies, acupuncture combined with CBT-I could not only solve anxiety, depression, and other emotions caused by insomnia but also ameliorate poor sleep habits and detrimental cognition[13-16].

However, there is a lack of rigorous clinical evidence on the treatment of insomnia with acupuncture combined with CBT-I; moreover, the clinical mechanism is unclear. In previous studies, we found that by analyzing polysomnograms(PSGs), electroacupuncture improves sleep architecture and prolongs the duration of slow-wave and rapid-eye-movement (REM) sleep[17-19]. But whether acupuncture combined with CBT-I improves sleep architecture requires futher research.

During the past decade, the application of deep learning to automatic sleep staging using PSGs has shown promise for understanding the macrostructure of sleep. Deep learning allows the automatic extraction of features from data related to classification tasks, and the performance of deep neural networks continues to improve as the size of the dataset increases[20-22].

Using a high-performance automatic sleep staging algorithm to analyze PSGs recordings via deep learning, this study will focus on the effects of electroacupuncture combined with CBT-I on sleep architecture, sleep quality, and sleep attitudes and beliefs in patients with insomnia. Furthermore, this research will provide guidance for electroacupuncture combined with CBT-I using artificial intelligence.

Methods

Study design

The study will be an assessor-blinded, randomized controlled trial. The protocol was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sun University (2021763). We will follow the Consolidated Standards of Reporting Trials and Standards for Reporting Interventions in Clinical Trials of Acupuncture guidelines for the design and reporting of the trial[23, 24]. The flowchart of the trial is presented in Figure 1, and the schedule of enrolment, interventions, and outcome assessments are presented in Table 1.

Sample size calculations: Referring to the previous litetature[25], we assume that the expected PSQI value and determine that an alpha level of 0.05, which would allow us to detect a difference in PSQI score between the two groups. Allowing for a 15% dropout rate, a sample size of 36 in each group is sufficient to meet statistical requirements.

Randomization, allocation, and blinding

Patients who are interested in participating in the trial will initially be screened by phone and then asked to participate in a face-to-face interview to conduct further surveys. After recruiting all participants, random numbers will be generated and assigned by a central randomization system of the Clinical Research and Data Center of Guangzhou University of Chinese Medicine. The researcher who will screen the eligible patients after baseline

Table 1 Research flow chart

Project	Screening	Observation phase			Follow-up phase	
	assession 0 pre-treament	Assession 1 pre-treament	Assession 2 Week 2±1day	Assession 3 Week 4±2day	Assession 4 Week 8±1day	Unplanned follow-up
Medical history collection	√	-	-	-	-	
Sign the informed consent form	√	-	-	-	-	
Inclusion criteria	√	-	-	-	-	
Exclusion criteria	√	-	-	-	-	
Basic Information	√	-	-	-	-	
Vital signs	√	√	√	√	√	※
Index of laboratory inspection	※	※	※	※	※	
PSG	-	√	-	√	-	
Pittsburgh sleep quality index(PSQI)	-	√	√	√	√	
Beck depression inventory(BDI)	-	√	√	√	√	
Beck anxiety inventory(BAI)		√	√	√	√	
DBAS-16	-	√	√	√	-√	
Adverse Events	-	※	※	※	※	※
Medication records	-	√	√	√	√	
Terminate test evaluation	-	※	※	※	※	

Notes: **"※"**Record when necessary**;** PSG: Long-term scalp electroencephalogram recording; DBAS-16: Dysfunctional Beliefs and Attitudes about Sleep Scale 16 versio

will assign patients to either the treatment or control group. Researchers, which include statisticians, outcome assessors, and data analysts, will all be blinded to patients' group assignments. Although acupuncturists will be not blinded to group assignment, they will not be involved in outcome assessments or data analyses. In addition, all researchers will undergo training for specific procedures before the trial begins.

Participants and recruitment

Patients will be recruited using hospital-based advertisements in the Department of Acupuncture and Department of Neurology of the First Affiliated Hospital of Sun Yat-sen University from January 1,2022 to December 30,2025.

The inclusion criteria will be as follows: (1) meets diagnostic criteria for insomnia based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition[26] and the International Classification of Sleep Disorders, Third Edition[27], (2) aged 18–65 years, (3) experienced insomnia for more than 1 month but less than 2 years before the start of the trial, (4) voluntarily agrees to participate in the investigation and provides written informed consent before the clinical trial starts.

The exclusion criteria will be as follows: (1) serious cardiovascular, liver, kidney, or hematopoietic system disease, (2) insomnia was caused by a nervous system disease (e.g., stroke or Parkinson's disease), (3) insomnia was caused by a mental disorder, such as depression or anxiety, (4) history of sleep apnea, (5) pregnant or lactating women, (6) have received or currently receiving CBT-I.

Withdrawal criteria will be as follows: (1) patient withdrawal from the trial because of personal reasons, (2) patient has an adverse reaction related to acupuncture and refuses to continue treatment, (3) during the follow-up period, the patient cannot be contacted because of change of address and telephone number.

Intervention

The intervention will begin the day following randomization. All participants will receive 20 times treatments (five times per week for 4 weeks).

Observation group

Acupuncture treatment

Patients' skin will be disinfected with 75% alcohol, and patients will be asked to lie supine and wear eye masks for a better curative effect. Each participant will receive acupuncture treatment from the same acupuncturist who has more than 5 years of clinical experience in acupuncture therapy. The temperature of the treatment room will not be lower than 25°C.

Patients in the acupuncture group will receive electroacupuncture treatment on Sishenchong (EX-HN1), bilateral Neiguan (PC6), bilateral Taixi (KI3), bilateral Shenmen (HT7), and bilateral Sanyinjiao (SP6)[16]. Tube-guided acupuncture needles will be inserted to a depth of 17-25 mm at each acupoint (acupuncture location and method for each acupoint are provided in Table 2 and Figure 2). A low-frequency electronic pulse therapy instrument (G6805-2A, Shanghai Huayi Medical Instrument Co, Shanghai, China) will be used with 10-Hz continuous waves, and the current will range from 1 to 5 mA which will be adjusted based on the tolerance of each patient.

CBT-I treatment

CBT-I will be given while acupuncture treatment is in progress. The intervention will consist of behavioral components (e.g. sleep restriction and stimulus control), cognitive components (e.g., cognitive restructuring and paradoxical intention), progressive muscle relaxation, and sleep hygiene[28].

Control group

The procedure for the control group will be the same as that for the observation group with no CBT-I treatment. The major difference in interventions between the two groups being the tube needling method, in which no needle will be inserted through the tube for patients in the control group. To mimic the sensation of a real needle being inserted into the body, the acupuncturist will place the tube close to the skin at the acupoint and tap the top of the tube.

Quality control

The trial will be conducted under the supervision of the First Affiliated Hospital of Sun Yat-sun University. A qualified clinical trial expert will be invited to monitor the study to identify problems during the trial, examine collected data, and control bias.

Outcome measures

Primary outcome

Pittsburgh sleep quality index

The Pittsburgh sleep quality index (PSQI) is an internationally established tool that is used to evaluate sleep quality. The scale includes seven dimensions that consist of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleeping medication, and daytime dysfunction. The score correlates adversely with sleep quality which a higher score means the sleep quality is worse, and each factor has a score of 0 to 3 to provide a total score of 21 points[29, 30].

Secondary outcomes

The Beck depression inventory

The Beck depression inventory (BDI) is a valid self-assessment index to measure depression severity and consists of 13 items. Each item is scored from 0 to 3 (0 to 4 indicates no depression, 5 to 7 indicates mild depression, 8 to 15 indicates moderate depression), with a score of 16 points or more considered as severe depression[31-33].

The Beck anxiety inventory

The Beck anxiety inventory (BAI) is used to assess the degree of anxiety and consists of 21 items scored from 1 to 4 (15 to 25 points indicates mild anxiety, 26 to 35 points indicates moderate anxiety, and 36 points is considered severe anxiety)[34, 35].

Other Outcomes

The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version

The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version (DBAS-16) is used to evaluate maladaptive cognitions associated with sleep. There are 16 items in the index,

Table 2 Acupuncture location and method for each acupoint

Acupoint	Location	Needling method
Sishenchong (EX-HN1)	On the parietal region, 1 cun anterior ,posterior and lateral to Baihui, 4 acpoints totally.	The angle between the needle tip and the scalp is 30。. Move the needle tip backward along the anterioreposterior midline, and then insert the needle 0.5 cun.
Neiguan(PC6)	On the line joining Daling and Quze, between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist.	Puncture perpendicularly 1-1.5 cun.
Taixi (KI3)	In the depression between the tip of the medial malleolus and the Achilles tendon.	Puncture perpendicularly 0.5-1 cun.
Shenmen (HT7)	On the palmar ulnar end of the transverse crease of the wrist,and on the radial aspect of the tendon of the ulnar flexor m. of the wrist.	Puncture perpendicularly 0.5-1 cun.
Sanyinjiao (SP6)	Posterior to the mesial border of the tibia,and 3 cun above the tip of the medial malleolus	Puncture perpendicularly 1-1.5 cun.

which are divided into four factors comprising consequences of insomnia, worry about sleep, sleep expectations, and medication. These factors are scored on a scale of 1-5(strongly disagree to strongly agree). The total score is positively correlated with the reasonableness of sleep beliefs and attitudes[36, 37].

Sleep staging

The PARADISEP&D9600 (U.S.) Polysomnography Monitoring and Analysis System will be used to simultaneously monitor EEG, EOG, and EMG. A large clinical dataset of PSG recordings will be used to train a hybrid convolutional neural network (CNN) and recurrent neural network (RNN) to learn effective and generalizable features for sleep stage scoring[38, 39]. Then clinical data will be used to indentify the deep learning algorithm. Sleep staging for both datasets will be performed by expert sleep technicians in nonoverlapping 30-s epochs according to standards by the American Academy of Sleep Medicine(AASM), as one of five stages: wake(W), non-rapid eye movement(REM) stage 1(N1), non-REM stage 2(N2), non-REM stage 3(N3), and rapid eye movement (REM)[40].

Adverse events

During treatment and four week after treatment, a questionnaire will be administered to evaluate the various discomforts that may be caused by acupuncture: hangover, addiction, tolerance, fatigue after waking, insomnia rebound, daytime alertness, cognitive function, and behavior ability.

Patients and public involvement

Patients and the public are not involved in the design or conduct of the study or the outcome measures, and no attempt will be made to assess the burden of the intervention on the patients themselves. The results of this study will be disseminated to study participants via the website of our hospitals.

Statistical analysis

All analyses will be performed on the intention-to-treat population of participants who had at least one treatment. Missing data will be replaced according to the principle of the last observation carried forward. Data analyses will be performed using the SPSS version 25 (IBM Corp.) software. All available data will be analyzed descriptively. For continuous data, the normality test will be applied at the beginning of the analysis. Results will be presented as means, standard deviations, and 95% confidence intervals (CIs) for continuous data that conform to the normal distribution and medians, quartiles, and ranges for rank data and continuous data that are not normally distributed. Discrete data will be presented as percentages.

We will first examine the descriptive data for sample characteristics at baseline, and independent samples t-tests will be used to compare groups for continuous variables, whereas chi-square analysis will be used to compare groups for dichotomous variables. Second, we will perform two series of repeated-measures and univariate analyses of covariance (ANCOVA) models to examine treatment effects. We will use repeated-measures ANCOVAs to analyze the primary and secondary outcome measures (i.e., PSQI, BDI, BAI, DBAS-16, and sleep staging scores) from pre-treatment to post-treatment. If a significant effect is observed, we will conduct posthoc paired samples t-tests to examine within-group changes in study outcomes. For all study outcomes, we will then perform univariate ANCOVAs to test for group differences in post-treatment values while controlling for relevant covariates. This process will be repeated to examine changes in study outcomes from pretreatment to postnatal follow-up.

When necessary, ITT analysis and sensitivity analysis will be used to assess the robustness of the conclusions of the entire clinical trial. To evaluate the consistency of the trial and explore the factors that affect efficacy or prognosis, subgroup analysis will be conducted to identify the population with better efficacy. Safety analysis will be used to assess the incidence of adverse events and related symptoms in patients with insomnia during treatment and follow-up.

Discussion

Currently, the main treatments recommended for insomnia are non-pharmaceutical and pharmaceutical treatments. Pharmaceutical treatments include benzodiazepines as well as new non-benzodiazepine drugs, which can shorten the latency to fall asleep and prolong total sleep time but also affect normal sleep physiology and cause adverse reactions[41, 42]. CBT-I, which is recommended as a first-line treatment for insomnia by the European insomnia guidelines, is limited in clinical practice because of insufficient professional therapists and poor compliance of patients with insomnia, especially in developing countries such as China[42-45].

As a complementary alternative therapy with a long history in China, acupuncture has been used as a clinical treatment for insomnia with fewer adverse effects and less permanent damage. Previous studies showed that either acupuncture or CBT-I could produce clinically meaningful improvements in insomnia symptoms, and our preliminary research have confirmed that acupuncture combined with CBT-I also alleviate not only insomnia symptoms but also negative emotions such as anxiety and depression[13, 14, 16]. But whether acupuncture combined with CBT-I could influence sleep habits and correct cognition, and what the clinic clinical mechanism worth futher research.

To ameliorate sleep habits, correct cognition, and alleviate anxiety, depression, and other emotions caused by insomnia, this study will use electroacupuncture combined with CBT-I and observe sleep architecture, sleep quality, and sleep attitudes and beliefs in patients with insomnia. In this study, PSQI will be used to assess the sleep quality, BDI and BAI will be used to evaluate the depression severity and anxiety. At the same time, we will use DBAS-16 to evaluate the sleep beliefs and attitudes before and after treatment. Because of the particularity of acupuncture therapy, the implementation of blinding is difficult in clinical research[46, 47]. A research team composed of researchers, therapists, testers, and statisticians will be established to reduce any bias that may occur

during the research process by blinding testers and statisticians. This study will provide clinical evidence for the effect and safety of electroacupuncture combined with CBT-I and provide a decision-making reference for clinicians, patients, and policymakers.

To analyze the effects of electroacupuncture combined with CBT-I on sleep architecture and sleep quality in patients with insomnia, deep learning will be used to analyze PSGs in various clinical settings in this study. PSGs are used widely for clinical evaluation because they are more sensitive than routine EEGs (typically 30–60 min duration) in capturing paroxysmal electrical abnormalities[48, 49]. During the past decade, there have been various advances in automated sleep staging of PSGs data using the ability of deep learning methods to automatically extract features from data that are relevant to the classification; moreover, the performance of deep neural networks continues to improve as datasets become larger[50-52]. Using deep learning, this study will develope a high-performing, reference channel-free, automated sleep staging algorithm to analyze the sleep architeture which will provide a clinical mechanism in artificial intelligence.

In summary, this study will use electroacupuncture combined with CBT-I to treat insomnia and observe the sleep beliefs and attitudes of patients with insomnia in different dimensions using deep learning. Moreover, we will provide a solid research basis for the combined application of electroacupuncture and CBT-I for insomnia in the clinic.

Acknowledgments

Not applicable.

Footnotes

Contributors: Wenya Pei and Te He designed the trial protocol and drafted the manuscript. Liming Lu, Jingwen Ruan, and Guihua Wen revised the manuscript. Pei Yang, Xiaozhou Lv, and Boyu Jiao will plan the data analysis. Liqian Cui, Yingshuo Yan, Fanqi Meng,

Guanheng He, and Xin Zhou will participate in participant recruitment. All authors discussed, read, and revised the manuscript, and all approved the publication of this protocol.

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Patient consent for publication: Not applicable

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Ethics and dissemination: The study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sun University (2021763). Participants will be included only after they provide written informed consent. The study was registered in the Chinese Clinical Trial Registry (No.ChiCTR2100052502, 30/10/2021).

Ethics statements

Patient consent for publication

Not applicable.

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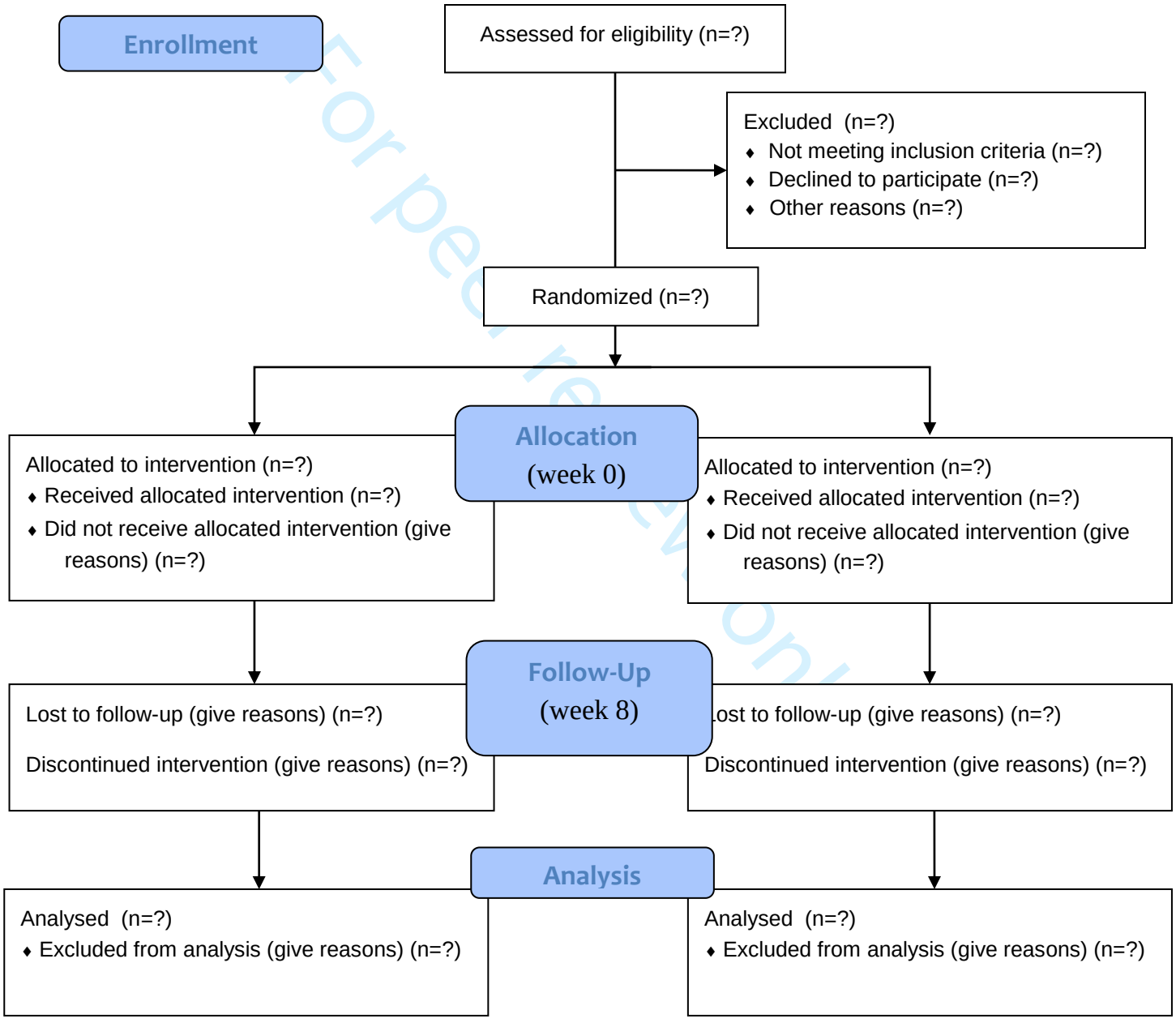
Fig 1. CONSORT 2010 Flow Diagram

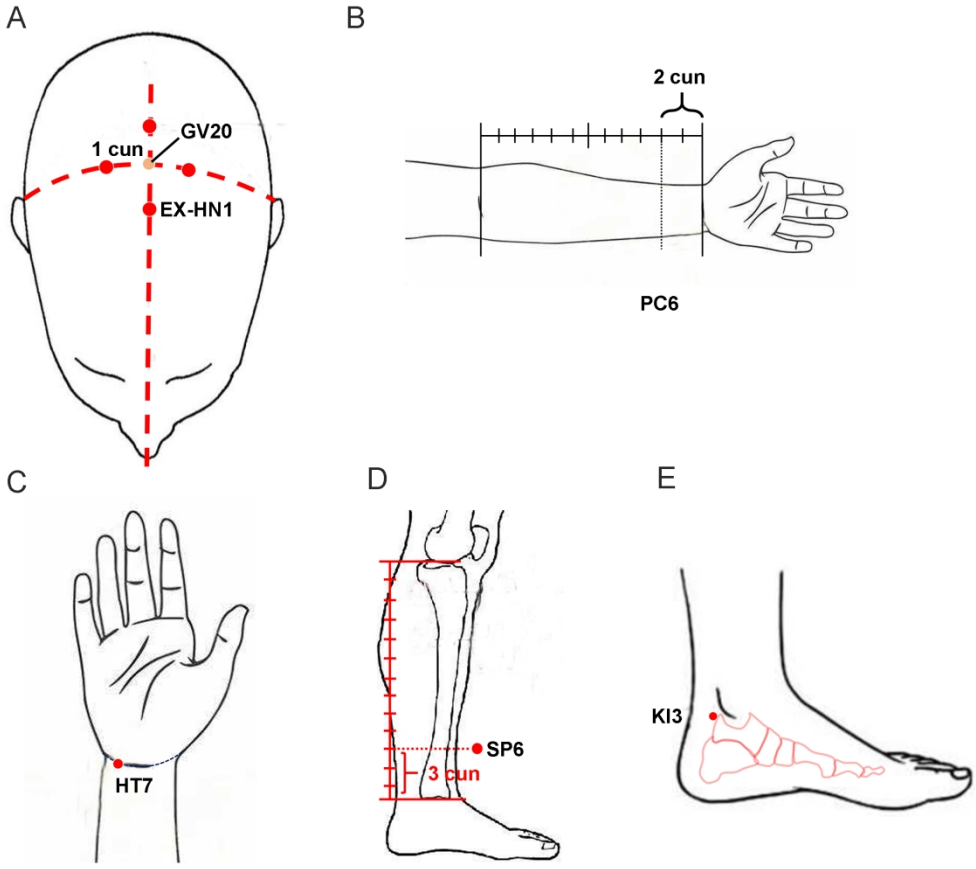
Fig 2. Location of acupoints

CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram





location of accupoints

209x202mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,12
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4-5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4,Table 1,Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8-9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			5
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9-10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9-10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9-10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9-10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6
	31b	Authorship eligibility guidelines and any intended use of professional writers	6
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	6
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See The Ethics Approval Document
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in patients with insomnia: study protocol for a randomized controlled trial

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Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in patients with insomnia: study protocol for a randomized controlled trial

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Abstract

Introduction

Insomnia affects physical and mental health due to the lack of continuous and complete sleep architecture. Polysomnograms (PSGs) are used to record electrical information to perform sleep architecture using deep learning. Although acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) could not only improve sleep quality, solve anxiety, depression but also ameliorate poor sleep habits and detrimental cognition. Therefore, this study will focus on the effects of electroacupuncture combined with CBT-I on sleep architecture with deep learning.

Methods and analysis

This randomized controlled trial will evaluate the efficacy and effectiveness of electroacupuncture combined with CBT-I in patients with insomnia. Participants will be randomized to receive either electroacupuncture combined with CBT-I or sham acupuncture combined with CBT-I and followed up for four weeks. The primary outcome is sleep quality, which is evaluated by the Pittsburgh sleep quality index(PSQI). The secondary outcome measures include a measurement of depression severity, anxiety, maladaptive cognitions associated with sleep, and adverse events. Sleep architecture will be assessed using deep learning on PSGs.

Ethics and dissemination

This trial has been approved by the institutional review boards and ethics committees of the First Affiliated Hospital of Sun Yat-sun University (2021763). The results will be disseminated through peer-reviewed journals. The results of this trial will be disseminated through peer-reviewed publications and conference abstracts or posters.

Trial registration number

CTR2100052502

Keywords: insomnia, cognitive behavioral therapy for insomnia, electroacupuncture, randomized controlled trial

Strengths and limitations of this study

- This study will investigate the efficacy and effectiveness of electroacupuncture combined with CBT-I.
- We will observe the effects of electroacupuncture combined with CBT-I on sleep quality and sleep beliefs and attitudes of patients with insomnia.
- We will use deep learning to observe the effects of electroacupuncture combined with CBT-I on sleep architecture in different dimensions.
- The efficacy and effectiveness of electroacupuncture on sleep quality and sleep beliefs and attitudes of patients with insomnia will be further studied in the future.

Introduction

Insomnia is characterized by difficulties in initiating or maintaining sleep or impaired daytime functioning, which impact both physical and mental health[1-3]. The lack of continuous and complete sleep architecture due to long-term fragmented and light sleep in patients with insomnia causes a decrease in sleep quality, which affects daily functions, and even induces anxiety, depression, and other mental symptoms[4-6]. With the increasing pressures in daily life and work, insomnia is becoming a public health problem that needs to be solved urgently as it worsens the quality of life of patients, burdens caregivers, and increases social and economic costs[7-9].

Cognitive-behavioral therapy for insomnia (CBT-I) is recommended as first-line treatment for insomnia and may improve sleep quality and alleviate poor sleep cognition in patients with insomnia[10-12]. During the early stage of treatment, the sleep quality of patients with severe anxiety were improved slowly and the compliance of these patients were poor. Thus, as confirmed in previous studies, acupuncture combined with CBT-I could not only solve anxiety, depression, and other emotions caused by insomnia but also ameliorate poor sleep habits and detrimental cognition[13-16].

However, there is a lack of rigorous clinical evidence on the treatment of insomnia with acupuncture combined with CBT-I; moreover, the clinical mechanism is unclear. In previous studies, we found that by analyzing polysomnograms (PSGs), electroacupuncture improves sleep architecture and prolongs the duration of slow-wave and rapid-eye-movement (REM) sleep[17-19]. But whether acupuncture combined with CBT-I improves sleep architecture requires futher research.

During the past decade, the application of deep learning to automatic sleep staging using PSGs has shown promise for understanding the macrostructure of sleep. Deep learning allows the automatic extraction of features from data related to classification tasks, and the performance of deep neural networks continues to improve as the size of the dataset increases[20-22].

Using a high-performance automatic sleep staging algorithm to analyze PSGs recordings via deep learning, this study will focus on the effects of electroacupuncture combined with CBT-I on sleep architecture, sleep quality, and sleep attitudes and beliefs in patients with insomnia. Furthermore, this research will provide guidance for electroacupuncture combined with CBT-I using artificial intelligence.

Methods

Study design

The study will be an assessor-blinded, randomized controlled trial. The protocol was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sun University (2021763). We will follow the Consolidated Standards of Reporting Trials and Standards for Reporting Interventions in Clinical Trials of Acupuncture guidelines for the design and reporting of the trial[23, 24]. The flowchart of the trial is presented in Figure 1, and the schedule of enrolment, interventions, and outcome assessments are presented in Table 1.

Sample size calculations: Referring to the previous litetature[25], we assume that the expected PSQI value of the observation group is 9.45 ± 1.84 and the control 6.43 ± 2.10. We determine that a sample size of 11 per group would provide a power of 90% and an alpha level of 0.05, which would allow us to detect a difference in PSQI score between the two groups. Allowing for a 20% dropout rate, a sample size of 30 in each group is sufficient to meet statistical requirements.

Randomization, allocation, and blinding

Patients who are interested in participating in the trial will initially be screened by phone and then asked to participate in a face-to-face interview to conduct further surveys. After recruiting all participants, random numbers will be generated and assigned by a central randomization system of the Clinical Research and Data Center of Guangzhou University of Chinese Medicine. The researcher who will screen the eligible patients after baseline

Table 1 Research flow chart

Project	Screening	Observation phase			Follow-up phase	
	assession 0 pre-treament	Assession 1 pre-treament	Assession 2 Week 2±1day	Assession 3 Week 4±2day	Assession 4 Week 8±1day	Unplanned follow-up
Medical history collection	√	-	-	-	-	
Sign the informed consent form	√	-	-	-	-	
Inclusion criteria	√	-	-	-	-	
Exclusion criteria	√	-	-	-	-	
Basic Information	√	-	-	-	-	
Vital signs	√	√	√	√	√	※
Index of laboratory inspection	※	※	※	※	※	
PSG	-	√	-	√	-	
Pittsburgh sleep quality index(PSQI)	-	√	√	√	√	
Beck depression inventory(BDI)	-	√	√	√	√	
Beck anxiety inventory(BAI)		√	√	√	√	
DBAS-16	-	√	√	√	-√	
Adverse Events	-	※	※	※	※	※
Medication records	-	√	√	√	√	
Terminate test evaluation	-	※	※	※	※	

Notes: **"※"**Record when necessary**;** PSG: Long-term scalp electroencephalogram recording; DBAS-16: Dysfunctional Beliefs and Attitudes about Sleep Scale 16 versio

will assign patients to either the treatment or control group. Researchers, which include statisticians, outcome assessors, and data analysts, will all be blinded to patients' group assignments. Although acupuncturists will be not blinded to group assignment, they will not be involved in outcome assessments or data analyses. In addition, all researchers will undergo training for specific procedures before the trial begins.

Participants and recruitment

Patients will be recruited using hospital-based advertisements in the Department of Acupuncture and Department of Neurology of the First Affiliated Hospital of Sun Yat-sen University from January 2022 to December 2025.

The inclusion criteria will be as follows: (1) meets diagnostic criteria for insomnia based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition[26] and the International Classification of Sleep Disorders, Third Edition[27], (2) aged 18–65 years, (3) experienced insomnia for more than 1 month but less than 2 years before the start of the trial, (4) voluntarily agrees to participate in the investigation and provides written informed consent before the clinical trial starts.

The exclusion criteria will be as follows: (1) serious cardiovascular, liver, kidney, or hematopoietic system disease, (2) insomnia was caused by a nervous system disease (e.g., stroke or Parkinson's disease), (3) insomnia was caused by a mental disorder, such as depression or anxiety, (4) history of sleep apnea, (5) pregnant or lactating women, (6) have received or currently receiving CBT-I.

Withdrawal criteria will be as follows: (1) patient withdrawal from the trial because of personal reasons, (2) patient has an adverse reaction related to acupuncture and refuses to continue treatment, (3) during the follow-up period, the patient cannot be contacted because of change of address and telephone number.

Intervention

The intervention will begin the day following randomization. All participants will receive 20 times treatments (five times per week for 4 weeks).

Observation group

Acupuncture treatment

Patients' skin will be disinfected with 75% alcohol, and patients will be asked to lie supine and wear eye masks for a better curative effect. Each participant will receive acupuncture treatment from the same acupuncturist who has more than 5 years of clinical experience in acupuncture therapy. The temperature of the treatment room will not be lower than 25°C.

Patients in the acupuncture group will receive electroacupuncture treatment on Sishenchong (EX-HN1), bilateral Neiguan (PC6), bilateral Taixi (KI3), bilateral Shenmen (HT7), and bilateral Sanyinjiao (SP6)[28]. Tube-guided acupuncture needles will be inserted to a depth of 17-25 mm at each acupoint (acupuncture location and method for each acupoint are provided in Table 2 and Figure 2). A low-frequency electronic pulse therapy instrument (G6805-2A, Shanghai Huayi Medical Instrument Co., Shanghai, China) will be used with 10-Hz continuous waves, and the current will range from 1 to 5 mA which will be adjusted based on the tolerance of each patient.

CBT-I treatment

CBT-I will be given while acupuncture treatment is in progress. The intervention will consist of behavioral components (e.g. sleep restriction and stimulus control), cognitive components (e.g., cognitive restructuring and paradoxical intention), progressive muscle relaxation, and sleep hygiene[29].

Control group

The procedure for the control group will be the same as that for the observation group with no CBT-I treatment. The major difference in interventions between the two groups being the tube needling method, in which no needle will be inserted through the tube for patients in the control group. To mimic the sensation of a real needle being inserted into the body, the acupuncturist will place the tube close to the skin at the acupoint and tap the top of the tube.

Quality control

The trial will be conducted under the supervision of the First Affiliated Hospital of Sun Yat-sun University. A qualified clinical trial expert will be invited to monitor the study to identify problems during the trial, examine collected data, and control bias.

Outcome measures

Primary outcome

Pittsburgh sleep quality index

The Pittsburgh sleep quality index (PSQI) is an internationally established tool that is used to evaluate sleep quality. The scale includes seven dimensions that consist of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleeping medication, and daytime dysfunction. The score correlates adversely with sleep quality which a higher score means the sleep quality is worse, and each factor has a score of 0 to 3 to provide a total score of 21 points[30, 31].

Secondary outcomes

The Beck depression inventory

The Beck depression inventory (BDI) is a valid self-assessment index to measure depression severity and consists of 13 items. Each item is scored from 0 to 3 (0 to 4 indicates no depression, 5 to 7 indicates mild depression, 8 to 15 indicates moderate depression), with a score of 16 points or more considered as severe depression[32-34].

The Beck anxiety inventory

The Beck anxiety inventory (BAI) is used to assess the degree of anxiety and consists of 21 items scored from 1 to 4 (15 to 25 points indicates mild anxiety, 26 to 35 points indicates moderate anxiety, and 36 points is considered severe anxiety)[35, 36].

The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version

The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version (DBAS-16) is used to evaluate maladaptive cognitions associated with sleep. There are 16 items in the index, which are divided into four factors comprising consequences of insomnia, worry about

Table 2 Acupuncture location and method for each acupoint

Acupoint	Location	Needling method
Sishenchong (EX-HN1)	On the parietal region, 1 cun anterior ,posterior and lateral to Baihui, 4 acpoints totally.	The angle between the needle tip and the scalp is 30。. Move the needle tip backward along the anterioreposterior midline, and then insert the needle 0.5 cun.
Neiguan(PC6)	On the line joining Daling and Quze, between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist.	Puncture perpendicularly 1-1.5 cun.
Taixi (KI3)	In the depression between the tip of the medial malleolus and the Achilles tendon.	Puncture perpendicularly 0.5-1 cun.
Shenmen (HT7)	On the palmar ulnar end of the transverse crease of the wrist,and on the radial aspect of the tendon of the ulnar flexor m. of the wrist.	Puncture perpendicularly 0.5-1 cun.
Sanyinjiao (SP6)	Posterior to the mesial border of the tibia,and 3 cun above the tip of the medial malleolus	Puncture perpendicularly 1-1.5 cun.

sleep, sleep expectations, and medication. These factors are scored on a scale of 1–5(strongly disagree to strongly agree). The total score is positively correlated with the reasonableness of sleep beliefs and attitudes[37, 38].

Sleep staging

The PARADISEP&D9600 (U.S.) Polysomnography Monitoring and Analysis System will be used to simultaneously monitor EEG, EOG, and EMG. A large clinical dataset of PSG recordings will be used to train a hybrid convolutional neural network (CNN) and recurrent neural network (RNN) to learn effective and generalizable features for sleep stage scoring[39, 40]. Then clinical data will be used to indentify the deep learning algorithm. Sleep staging for both datasets will be performed by expert sleep technicians in nonoverlapping 30-s epochs according to standards by the American Academy of Sleep Medicine(AASM), as one of five stages: wake(W), non-rapid eye movement(REM) stage 1(N1), non-REM stage 2(N2), non-REM stage 3(N3), and rapid eye movement (REM)[41].

Adverse events

During treatment and four week after treatment, a questionnaire will be administered to evaluate the various discomforts that may be caused by acupuncture: hangover, addiction, tolerance, fatigue after waking, insomnia rebound, daytime alertness, cognitive function, and behavior ability.

Patients and public involvement

Patients and the public are not involved in the design or conduct of the study or the outcome measures, and no attempt will be made to assess the burden of the intervention on the patients themselves. The results of this study will be disseminated to study participants via the website of our hospitals.

Statistical analysis

All analyses will be performed on the intention-to-treat population of participants who had at least one treatment. Missing data will be replaced according to the principle of the

last observation carried forward. Data analyses will be performed using the SPSS version 25 (IBM Corp.) software. All available data will be analyzed descriptively. For continuous data, the normality test will be applied at the beginning of the analysis. Results will be presented as means, standard deviations, and 95% confidence intervals (CIs) for continuous data that conform to the normal distribution and medians, quartiles, and ranges for rank data and continuous data that are not normally distributed. Discrete data will be presented as percentages.

We will first examine the descriptive data for sample characteristics at baseline, and independent samples t-tests will be used to compare groups for continuous variables, whereas chi-square analysis will be used to compare groups for dichotomous variables. Second, we will perform two series of repeated-measures and univariate analyses of covariance (ANCOVA) models to examine treatment effects. We will use repeated-measures ANCOVAs to analyze the primary and secondary outcome measures (i.e., PSQI, BDI, BAI, DBAS-16, and sleep staging scores) from pre-treatment to post-treatment. If a significant effect is observed, we will conduct posthoc paired samples t-tests to examine within-group changes in study outcomes. For all study outcomes, we will then perform univariate ANCOVAs to test for group differences in post-treatment values while controlling for relevant covariates. This process will be repeated to examine changes in study outcomes from pretreatment to postnatal follow-up.

When necessary, ITT analysis and sensitivity analysis will be used to assess the robustness of the conclusions of the entire clinical trial. To evaluate the consistency of the trial and explore the factors that affect efficacy or prognosis, subgroup analysis will be conducted to identify the population with better efficacy. Safety analysis will be used to assess the incidence of adverse events and related symptoms in patients with insomnia during treatment and follow-up.

Limitations

Currently, CBT-I is recommended as a first-line treatment for insomnia, but it is limited in clinical practice especially in developing countries such as China[42-45]. As a complementary alternative therapy with a long history in China, acupuncture has been used as a clinical treatment for insomnia with fewer adverse effects and less permanent damage in previous studies[13, 14, 16]. In this study, we will focus on whether electroacupuncture combined with CBT-I could influence sleep quality and sleep architecture, but whether acupuncture therapy alone could influence sleep habits and correct cognition, also sleep architecture worth futher research.

During the past decade, there have been various advances in automated sleep staging of PSGs data using the ability of deep learning methods to automatically extract features from data that are relevant to the classification, moreover, the performance of deep neural networks continues to improve as datasets become larger[46-50]. To analyze the effects of electroacupuncture combined with CBT-I on sleep architecture, deep learning will be used to analyze PSGs in various clinical settings in this study. But due to lack of acceptability among patients, some of the participants received placebo treatment will drop, which may make analyses no meaningful due to the small number of participants in each arm. Notwithstanding, we will be able to optimize the randomized design and statistical analysis to avoid systematic errors and minimize the bias.

Acknowledgments

Not applicable.

Footnotes

Contributors: Wenya Pei and Te He designed the trial protocol and drafted the manuscript. Liming Lu, Jingwen Ruan, and Guihua Wen revised the manuscript. Pei Yang, Xiaozhou Lv, and Boyu Jiao will plan the data analysis. Liqian Cui, Yingshuo Yan, Fanqi Meng,

Guanheng He, and Xin Zhou will participate in participant recruitment. All authors discussed, read, and revised the manuscript, and all approved the publication of this protocol.

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Patient consent for publication: Not applicable

Provenance and peer review: Not commissioned; externally peer-reviewed.

Ethics statements

Patient consent for publication

Not applicable.

Ethics approval and consent to participate: The study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sun University (2021763). Participants will be included only after they provide written informed consent. The study was registered in the Chinese Clinical Trial Registry (No.ChiCTR2100052502, 30/10/2021).

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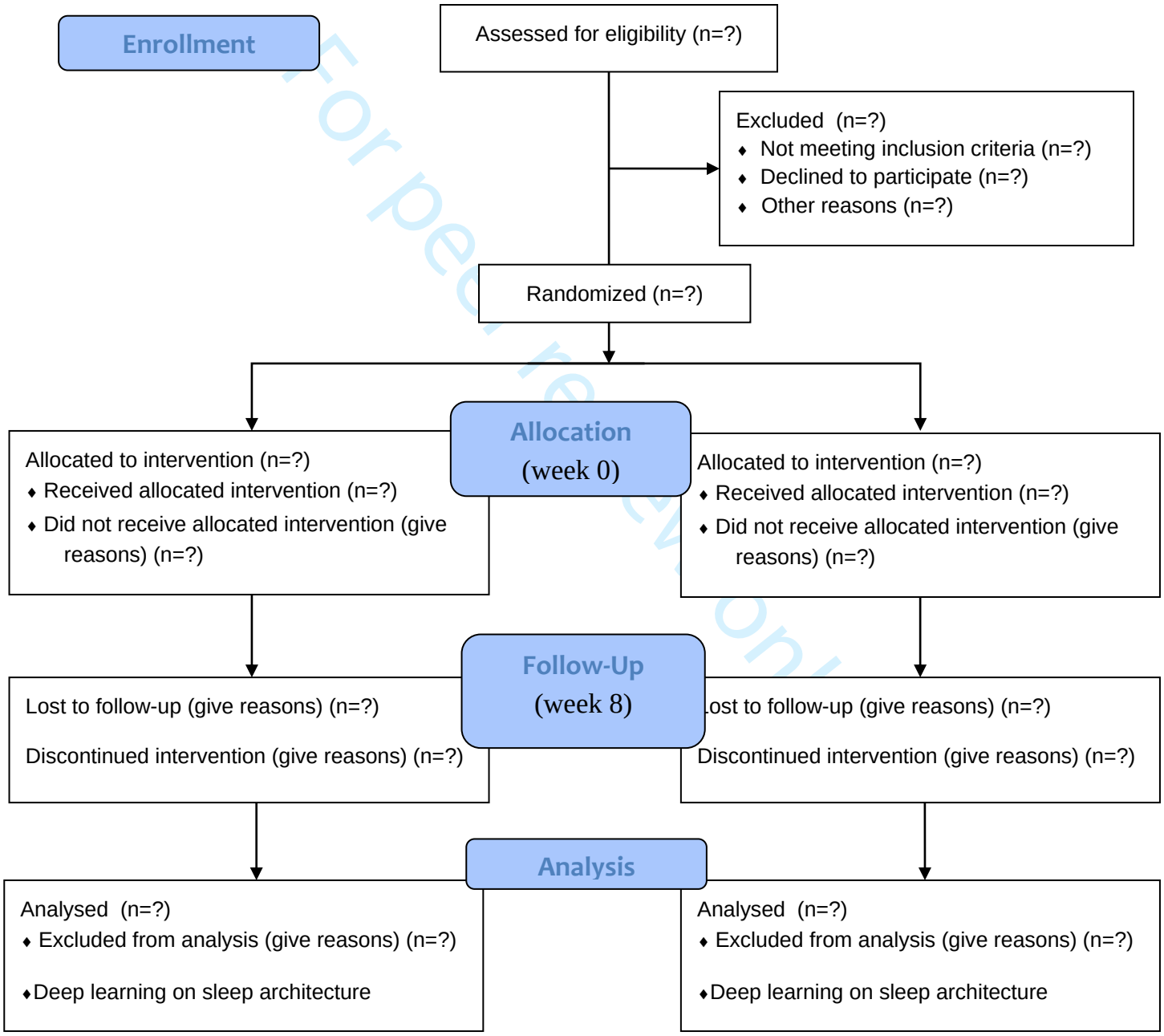
Fig 1. CONSORT 2010 Flow Diagram

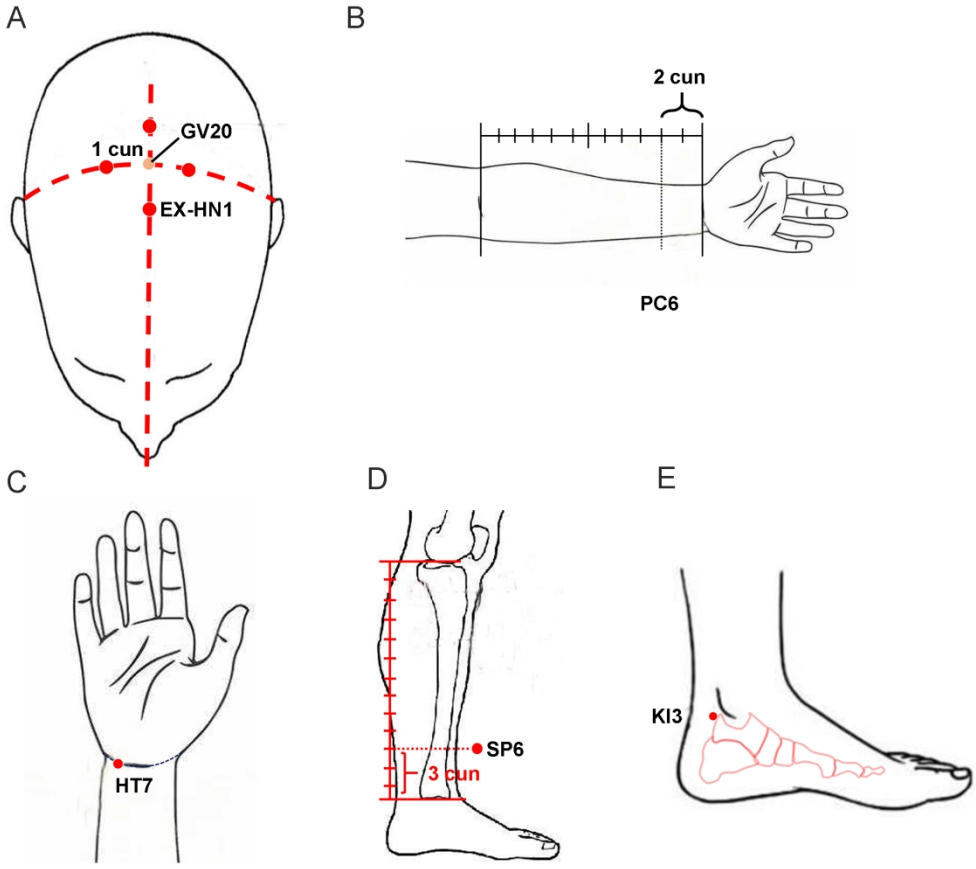
Fig 2. Location of acupoints

CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram





location of accupoints

209x202mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,12
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4-5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4,Table 1,Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8-9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			5
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9-10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9-10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9-10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9-10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6
	31b	Authorship eligibility guidelines and any intended use of professional writers	6
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	6
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See The Ethics Approval Document
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in patients with insomnia: study protocol for a randomized controlled trial

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Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in patients with insomnia: study protocol for a randomized controlled trial

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Abstract

Introduction

Insomnia affects physical and mental health due to the lack of continuous and complete sleep architecture. Polysomnograms (PSGs) are used to record electrical information to perform sleep architecture using deep learning. Although acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) could not only improve sleep quality, solve anxiety, depression but also ameliorate poor sleep habits and detrimental cognition. Therefore, this study will focus on the effects of electroacupuncture combined with CBT-I on sleep architecture with deep learning.

Methods and analysis

This randomized controlled trial will evaluate the efficacy and effectiveness of electroacupuncture combined with CBT-I in patients with insomnia. Participants will be randomized to receive either electroacupuncture combined with CBT-I or sham acupuncture combined with CBT-I and followed up for four weeks. The primary outcome is sleep quality, which is evaluated by the Pittsburgh sleep quality index(PSQI). The secondary outcome measures include a measurement of depression severity, anxiety, maladaptive cognitions associated with sleep, and adverse events. Sleep architecture will be assessed using deep learning on PSGs.

Ethics and dissemination

This trial has been approved by the institutional review boards and ethics committees of the First Affiliated Hospital of Sun Yat-sun University (2021763). The results will be disseminated through peer-reviewed journals. The results of this trial will be disseminated through peer-reviewed publications and conference abstracts or posters.

Trial registration number

CTR2100052502

Keywords: insomnia, cognitive behavioral therapy for insomnia, electroacupuncture, randomized controlled trial

Strengths and limitations of this study

- This study will investigate the efficacy and effectiveness of electroacupuncture combined with CBT-I.
- We will use deep learning to observe the effects of electroacupuncture combined with CBT-I on sleep architecture in different dimensions.
- The efficacy and effectiveness of electroacupuncture on sleep quality and sleep beliefs and attitudes of patients with insomnia will be further studied in the future.
- Although we explained the randomized design and statistical analysis through ITT analysis and sensitivity analysis to some extent, systematic errors and bias remained uncertain.

Introduction

Insomnia is characterized by difficulties in initiating or maintaining sleep or impaired daytime functioning, which impact both physical and mental health[1-3]. The lack of continuous and complete sleep architecture due to long-term fragmented and light sleep in patients with insomnia causes a decrease in sleep quality, which affects daily functions, and even induces anxiety, depression, and other mental symptoms[4-6]. With the increasing pressures in daily life and work, insomnia is becoming a public health problem that needs to be solved urgently as it worsens the quality of life of patients, burdens caregivers, and increases social and economic costs[7-9].

Cognitive-behavioral therapy for insomnia (CBT-I) is recommended as first-line treatment for insomnia and may improve sleep quality and alleviate poor sleep cognition in patients with insomnia[10-12]. During the early stage of treatment, the sleep quality of patients with severe anxiety were improved slowly and the compliance of these patients were poor. Thus, as confirmed in previous studies, acupuncture combined with CBT-I could not only solve anxiety, depression, and other emotions caused by insomnia but also ameliorate poor sleep habits and detrimental cognition[13-16].

However, there is a lack of rigorous clinical evidence on the treatment of insomnia with acupuncture combined with CBT-I; moreover, the clinical mechanism is unclear. In previous studies, we found that by analyzing polysomnograms (PSGs), electroacupuncture improves sleep architecture and prolongs the duration of slow-wave and rapid-eye-movement (REM) sleep[17-19]. But whether acupuncture combined with CBT-I improves sleep architecture requires futher research.

During the past decade, the application of deep learning to automatic sleep staging using PSGs has shown promise for understanding the macrostructure of sleep. Deep learning allows the automatic extraction of features from data related to classification tasks, and the performance of deep neural networks continues to improve as the size of the dataset increases[20-22].

Using a high-performance automatic sleep staging algorithm to analyze PSGs recordings via deep learning, this study will focus on the effects of electroacupuncture combined with CBT-I on sleep architecture, sleep quality, and sleep attitudes and beliefs in patients with insomnia. Furthermore, this research will provide guidance for electroacupuncture combined with CBT-I using artificial intelligence.

Methods

Study design

The study will be an assessor-blinded, randomized controlled trial. The protocol was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sun University (2021763). We will follow the Consolidated Standards of Reporting Trials and Standards for Reporting Interventions in Clinical Trials of Acupuncture guidelines for the design and reporting of the trial[23, 24]. The flowchart of the trial is presented in Figure 1, and the schedule of enrolment, interventions, and outcome assessments are presented in Table 1.

Sample size calculations: Referring to the previous litetature[25], we assume that the expected PSQI value of the observation group is 9.45 ± 1.84 and the control 6.43 ± 2.10. We determine that a sample size of 11 per group would provide a power of 90% and an alpha level of 0.05, which would allow us to detect a difference in PSQI score between the two groups. Allowing for a 20% dropout rate, a sample size of 30 in each group is sufficient to meet statistical requirements.

Randomization, allocation, and blinding

Patients who are interested in participating in the trial will initially be screened by phone and then asked to participate in a face-to-face interview to conduct further surveys. After recruiting all participants, random numbers will be generated and assigned by a central randomization system of the Clinical Research and Data Center of Guangzhou University of Chinese Medicine. The researcher who will screen the eligible patients after baseline

Table 1 Research flow chart

Project	Screening	Observation phase			Follow-up phase	
	assession 0 pre-treament	Assession 1 pre-treament	Assession 2 Week 2±1day	Assession 3 Week 4±2day	Assession 4 Week 8±1day	Unplanned follow-up
Medical history collection	√	-	-	-	-	
Sign the informed consent form	√	-	-	-	-	
Inclusion criteria	√	-	-	-	-	
Exclusion criteria	√	-	-	-	-	
Basic Information	√	-	-	-	-	
Vital signs	√	√	√	√	√	※
Index of laboratory inspection	※	※	※	※	※	
PSG	-	√	-	√	-	
Pittsburgh sleep quality index(PSQI)	-	√	√	√	√	
Beck depression inventory(BDI)	-	√	√	√	√	
Beck anxiety inventory(BAI)		√	√	√	√	
DBAS-16	-	√	√	√	-√	
Adverse Events	-	※	※	※	※	※
Medication records	-	√	√	√	√	
Terminate test evaluation	-	※	※	※	※	

Notes: **"※"**Record when necessary**;** PSG: Long-term scalp electroencephalogram recording; DBAS-16: Dysfunctional Beliefs and Attitudes about Sleep Scale 16 versio

will assign patients to either the treatment or control group. Researchers, which include statisticians, outcome assessors, and data analysts, will all be blinded to patients' group assignments. Although acupuncturists will be not blinded to group assignment, they will not be involved in outcome assessments or data analyses. In addition, all researchers will undergo training for specific procedures before the trial begins.

Participants and recruitment

Patients will be recruited using hospital-based advertisements in the Department of Acupuncture and Department of Neurology of the First Affiliated Hospital of Sun Yat-sen University from January 2022 to December 2025.

The inclusion criteria will be as follows: (1) meets diagnostic criteria for insomnia based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition[26] and the International Classification of Sleep Disorders, Third Edition[27], (2) aged 18–65 years, (3) experienced insomnia for more than 1 month but less than 2 years before the start of the trial, (4) voluntarily agrees to participate in the investigation and provides written informed consent before the clinical trial starts.

The exclusion criteria will be as follows: (1) serious cardiovascular, liver, kidney, or hematopoietic system disease, (2) insomnia was caused by a nervous system disease (e.g., stroke or Parkinson's disease), (3) insomnia was caused by a mental disorder, such as depression or anxiety, (4) history of sleep apnea, (5) pregnant or lactating women, (6) have received or currently receiving CBT-I.

Withdrawal criteria will be as follows: (1) patient withdrawal from the trial because of personal reasons, (2) patient has an adverse reaction related to acupuncture and refuses to continue treatment, (3) during the follow-up period, the patient cannot be contacted because of change of address and telephone number.

Intervention

The intervention will begin the day following randomization. All participants will receive 20 times treatments (five times per week for 4 weeks).

Observation group

Acupuncture treatment

Patients' skin will be disinfected with 75% alcohol, and patients will be asked to lie supine and wear eye masks for a better curative effect. Each participant will receive acupuncture treatment from the same acupuncturist who has more than 5 years of clinical experience in acupuncture therapy. The temperature of the treatment room will not be lower than 25°C.

Patients in the acupuncture group will receive electroacupuncture treatment on Sishenchong (EX-HN1), bilateral Neiguan (PC6), bilateral Taixi (KI3), bilateral Shenmen (HT7), and bilateral Sanyinjiao (SP6)[28]. Tube-guided acupuncture needles will be inserted to a depth of 17-25 mm at each acupoint (acupuncture location and method for each acupoint are provided in Table 2 and Figure 2). A low-frequency electronic pulse therapy instrument (G6805-2A, Shanghai Huayi Medical Instrument Co., Shanghai, China) will be used with 10-Hz continuous waves, and the current will range from 1 to 5 mA which will be adjusted based on the tolerance of each patient.

CBT-I treatment

CBT-I will be given while acupuncture treatment is in progress. The intervention will consist of behavioral components (e.g. sleep restriction and stimulus control), cognitive components (e.g., cognitive restructuring and paradoxical intention), progressive muscle relaxation, and sleep hygiene[29].

Control group

The procedure for the control group will be the same as that for the observation group with no CBT-I treatment. The major difference in interventions between the two groups being the tube needling method, in which no needle will be inserted through the tube for patients in the control group. To mimic the sensation of a real needle being inserted into the body, the acupuncturist will place the tube close to the skin at the acupoint and tap the top of the tube.

Quality control

The trial will be conducted under the supervision of the First Affiliated Hospital of Sun Yat-sun University. A qualified clinical trial expert will be invited to monitor the study to identify problems during the trial, examine collected data, and control bias.

Outcome measures

Primary outcome

Pittsburgh sleep quality index

The Pittsburgh sleep quality index (PSQI) is an internationally established tool that is used to evaluate sleep quality. The scale includes seven dimensions that consist of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleeping medication, and daytime dysfunction. The score correlates adversely with sleep quality which a higher score means the sleep quality is worse, and each factor has a score of 0 to 3 to provide a total score of 21 points[30, 31].

Secondary outcomes

The Beck depression inventory

The Beck depression inventory (BDI) is a valid self-assessment index to measure depression severity and consists of 13 items. Each item is scored from 0 to 3 (0 to 4 indicates no depression, 5 to 7 indicates mild depression, 8 to 15 indicates moderate depression), with a score of 16 points or more considered as severe depression[32-34].

The Beck anxiety inventory

The Beck anxiety inventory (BAI) is used to assess the degree of anxiety and consists of 21 items scored from 1 to 4 (15 to 25 points indicates mild anxiety, 26 to 35 points indicates moderate anxiety, and 36 points is considered severe anxiety)[35, 36].

The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version

The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version (DBAS-16) is used to evaluate maladaptive cognitions associated with sleep. There are 16 items in the index, which are divided into four factors comprising consequences of insomnia, worry about

Table 2 Acupuncture location and method for each acupoint

Acupoint	Location	Needling method
Sishenchong (EX-HN1)	On the parietal region, 1 cun anterior ,posterior and lateral to Baihui, 4 acpoints totally.	The angle between the needle tip and the scalp is 30。. Move the needle tip backward along the anterioreposterior midline, and then insert the needle 0.5 cun.
Neiguan(PC6)	On the line joining Daling and Quze, between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist.	Puncture perpendicularly 1-1.5 cun.
Taixi (KI3)	In the depression between the tip of the medial malleolus and the Achilles tendon.	Puncture perpendicularly 0.5-1 cun.
Shenmen (HT7)	On the palmar ulnar end of the transverse crease of the wrist,and on the radial aspect of the tendon of the ulnar flexor m. of the wrist.	Puncture perpendicularly 0.5-1 cun.
Sanyinjiao (SP6)	Posterior to the mesial border of the tibia,and 3 cun above the tip of the medial malleolus	Puncture perpendicularly 1-1.5 cun.

sleep, sleep expectations, and medication. These factors are scored on a scale of 1–5(strongly disagree to strongly agree). The total score is positively correlated with the reasonableness of sleep beliefs and attitudes[37, 38].

Sleep staging

The PARADISEP&D9600 (U.S.) Polysomnography Monitoring and Analysis System will be used to simultaneously monitor EEG, EOG, and EMG. A large clinical dataset of PSG recordings will be used to train a hybrid convolutional neural network (CNN) and recurrent neural network (RNN) to learn effective and generalizable features for sleep stage scoring[39, 40]. Then clinical data will be used to indentify the deep learning algorithm. Sleep staging for both datasets will be performed by expert sleep technicians in nonoverlapping 30-s epochs according to standards by the American Academy of Sleep Medicine(AASM), as one of five stages: wake(W), non-rapid eye movement(REM) stage 1(N1), non-REM stage 2(N2), non-REM stage 3(N3), and rapid eye movement (REM)[41].

Adverse events

During treatment and four week after treatment, a questionnaire will be administered to evaluate the various discomforts that may be caused by acupuncture: hangover, addiction, tolerance, fatigue after waking, insomnia rebound, daytime alertness, cognitive function, and behavior ability.

Patients and public involvement

Patients and the public are not involved in the design or conduct of the study or the outcome measures, and no attempt will be made to assess the burden of the intervention on the patients themselves. The results of this study will be disseminated to study participants via the website of our hospitals.

Statistical analysis

All analyses will be performed on the intention-to-treat population of participants who had at least one treatment. Missing data will be replaced according to the principle of the

last observation carried forward. Data analyses will be performed using the SPSS version 25 (IBM Corp.) software. All available data will be analyzed descriptively. For continuous data, the normality test will be applied at the beginning of the analysis. Results will be presented as means, standard deviations, and 95% confidence intervals (CIs) for continuous data that conform to the normal distribution and medians, quartiles, and ranges for rank data and continuous data that are not normally distributed. Discrete data will be presented as percentages.

We will first examine the descriptive data for sample characteristics at baseline, and independent samples t-tests will be used to compare groups for continuous variables, whereas chi-square analysis will be used to compare groups for dichotomous variables. Second, we will perform two series of repeated-measures and univariate analyses of covariance (ANCOVA) models to examine treatment effects. We will use repeated-measures ANCOVAs to analyze the primary and secondary outcome measures (i.e., PSQI, BDI, BAI, DBAS-16, and sleep staging scores) from pre-treatment to post-treatment. If a significant effect is observed, we will conduct posthoc paired samples t-tests to examine within-group changes in study outcomes. For all study outcomes, we will then perform univariate ANCOVAs to test for group differences in post-treatment values while controlling for relevant covariates. This process will be repeated to examine changes in study outcomes from pretreatment to postnatal follow-up.

When necessary, ITT analysis and sensitivity analysis will be used to assess the robustness of the conclusions of the entire clinical trial. To evaluate the consistency of the trial and explore the factors that affect efficacy or prognosis, subgroup analysis will be conducted to identify the population with better efficacy. Safety analysis will be used to assess the incidence of adverse events and related symptoms in patients with insomnia during treatment and follow-up.

Limitations

Currently, CBT-I is recommended as a first-line treatment for insomnia, but it is limited in clinical practice especially in developing countries such as China[42-45]. As a complementary alternative therapy with a long history in China, acupuncture has been used as a clinical treatment for insomnia with fewer adverse effects and less permanent damage in previous studies[13, 14, 16]. In this study, we will focus on whether electroacupuncture combined with CBT-I could influence sleep quality and sleep architecture, but whether acupuncture therapy alone could influence sleep habits and correct cognition, also sleep architecture worth futher research.

During the past decade, there have been various advances in automated sleep staging of PSGs data using the ability of deep learning methods to automatically extract features from data that are relevant to the classification, moreover, the performance of deep neural networks continues to improve as datasets become larger[46-50]. To analyze the effects of electroacupuncture combined with CBT-I on sleep architecture, deep learning will be used to analyze PSGs in various clinical settings in this study. But due to lack of acceptability among patients, some of the participants received placebo treatment will drop, which may make analyses no meaningful due to the small number of participants in each arm. Notwithstanding, we will be able to optimize the randomized design and statistical analysis to avoid systematic errors and minimize the bias.

Ethics and dissemination

This trial has been approved by the institutional review boards and ethics committees of the First Affiliated Hospital of Sun Yat-sun University (2021763). The results will be disseminated through peer-reviewed journals. The results of this trial will be disseminated through peer-reviewed publications and conference abstracts or posters.

Acknowledgments

Not applicable.

Footnotes

Contributors: Wenya Pei and Te He designed the trial protocol and drafted the manuscript. Liming Lu, Jingwen Ruan, and Guihua Wen revised the manuscript. Pei Yang, Xiaozhou Lv, and Boyu Jiao will plan the data analysis. Liqian Cui, Yingshuo Yan, Fanqi Meng, Guanheng He, and Xin Zhou will participate in participant recruitment. All authors discussed, read, and revised the manuscript, and all approved the publication of this protocol.

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Patient consent for publication: Not applicable

Provenance and peer review: Not commissioned; externally peer-reviewed.

Ethics statements

Patient consent for publication

Not applicable.

Ethics approval and consent to participate: The study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sun University (2021763). Participants will be included only after they provide written informed consent. The study was registered in the Chinese Clinical Trial Registry (No.ChiCTR2100052502, 30/10/2021).

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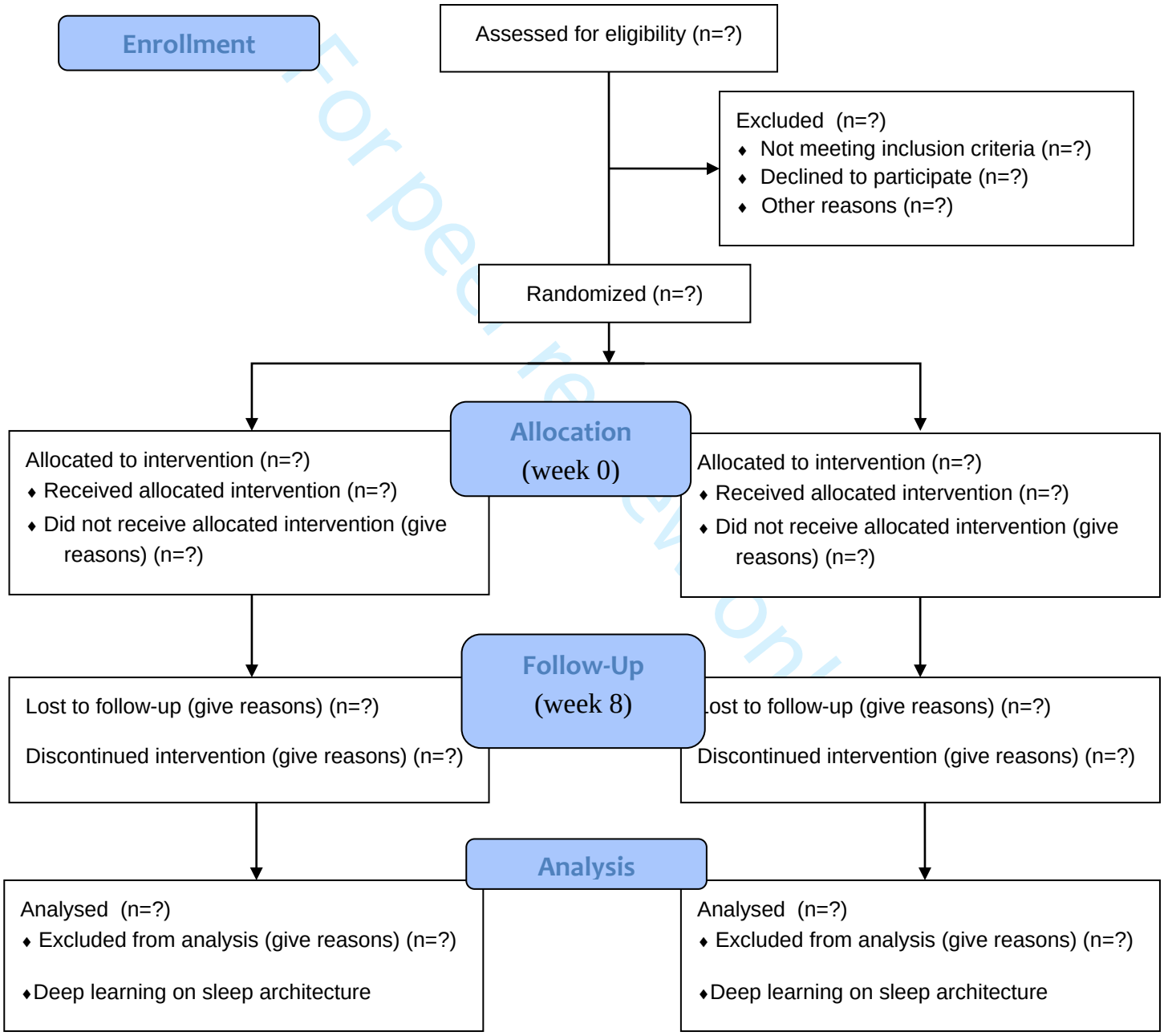
Fig 1. CONSORT 2010 Flow Diagram

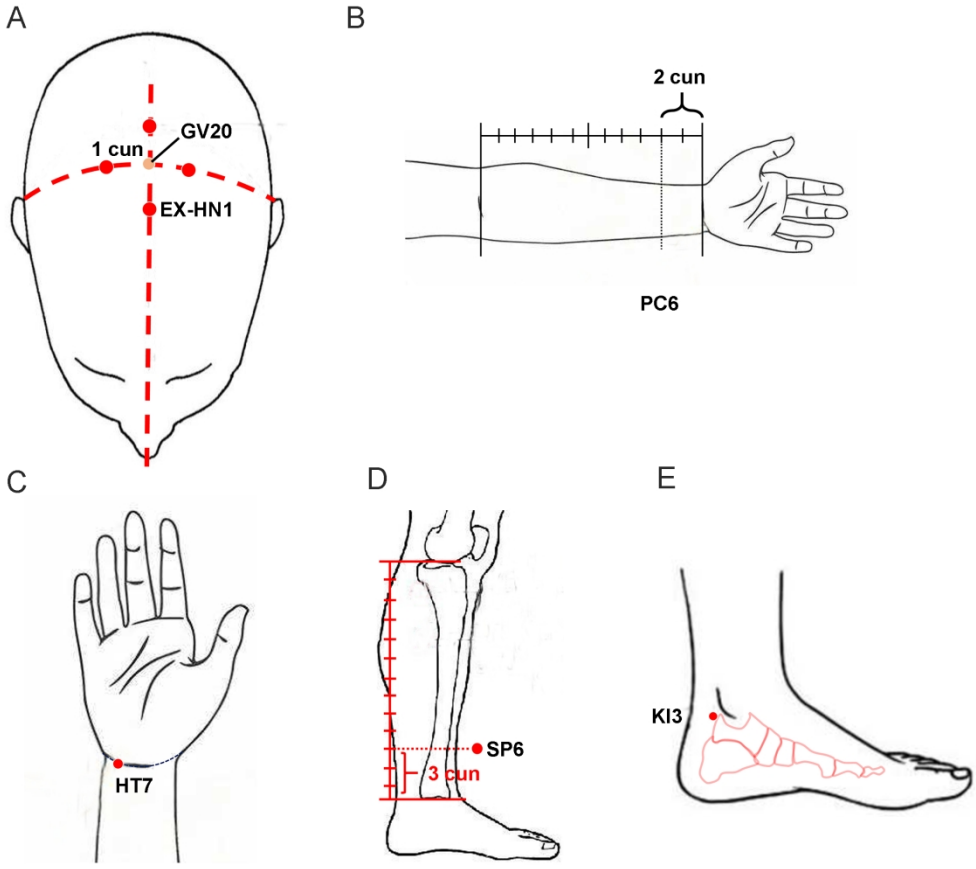
Fig 2. Location of acupoints

CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram





location of accupoints

209x202mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,12
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4-5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	4,Table 1,Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8-9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			5
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9-10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9-10
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9-10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9-10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	6
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6
	31b	Authorship eligibility guidelines and any intended use of professional writers	6
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	6
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See The Ethics Approval Document
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.