# Efficacy And Central Mechanism of Acupuncture Treatment In Patients With Neck Pain: Study Protocol For A Randomized Controlled Trial

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**Research Article**

**Keywords:** Neck pain, Acupuncture, Central mechanism, Functional magnetic resonance imaging, Protocol

**Posted Date:** May 24th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-377610/v1

**Version of Record:** A version of this preprint was published at Trials on August 14th, 2021. See the published version at https://doi.org/10.1186/s13063-021-05507-y.

# Abstract

**Background:** Acupuncture is effective for reducing the symptoms of neck pain (NP). However, the underlying mechanisms are not fully elucidated. Based on evaluating the efficacy of two acupuncture prescriptions for treating NP. This study aims to investigate the potential central mechanism of acupuncture treatment for NP by functional magnetic resonance imaging (fMRI).

**Methods:** This is a randomized controlled trial, 86 patients will be randomly assigned into two acupuncture treatment groups at a ratio of 1:1. The whole study period includes 2 weeks baseline, 2 weeks treatments and 12 weeks follow-up (4 and 12 weeks after treatment). The pain severity, the neck disability index, the cervical range of motion, the pressure pain threshold, etc. will be used to evaluate clinical efficacy of two acupuncture prescriptions for NP treatment. The MRI scans will be performed to detect cerebral activity changes of 20 patients in each group. The clinical data and MRI data will be analysed, respectively. *Pearson* correlation coefficient will be used to evaluate the association between changes of cerebral activity features and improvement of clinical symptoms.

**Discussion:** The results might provide further evidence for the clinical application of acupuncture in the treatment of NP.

**Trial registration**: Chinese Clinical Trial Registry, ChiCTR2000040930. Registered on December 16, 2020.


# Background

Neck pain (NP), as a common musculoskeletal disorder, has become an important healthcare and social problem due to its high prevalence and heavy economic burden. [1] It is estimated that more than 30% of the population suffer from NP every year, [2] and its lifetime prevalence in adults ranges from 14.2–71%.[3] Due to the increasing prevalence of NP, the health care costs of NP have rapidly increased. [4–6] In the United States, the cumulative annual cost for treating lower back pain and NP is $ 87.6 billion. [7] The treatment of NP has been challenging, because its etiology is complex and the symptoms are easy to recur. Although medications (e.g. muscle relaxants and non-steroidal anti-inflammatory drugs) are effective in alleviating acute pain, their side effects, including hepatotoxicity, etc. cannot be ignored. [8] Therefore, more patients tend to purchase non-drug therapies to relieve symptoms.

Acupuncture has been used to relieve pain for thousands of years in China. As early as 1997, the National Institutes of Health (NIH) had identified pain as one of the dominant diseases for acupuncture. Recently, some large-scale clinical studies confirmed the efficacy of acupuncture in improving NP symptoms.[9–11] However, the underlying mechanisms of acupuncture for NP have not been fully elucidated.

Advances in neuroimaging techniques have enhanced studies into the central mechanisms of acupuncture as an analgesic *in vivo*. In the last two decades, many neuroimaging studies have been performed to elucidate the mechanisms of acupuncture analgesia, and achieved gratifying results.[12–15] For example, an fMRI study on migraines found that acupuncture was effective in improving abnormally

reduced functional activity in the rostral ventromedial medulla/trigeminocervical complex area of patients.[16] Recently, significant alterations in both brain structure and function of NP patients have been reported by neuroimaging studies. Compared to healthy subjects, NP patients shown decreased functional activity in the left sensorimotor cortex and right temporoparietal junction,[17] as well as increased functional connectivity between the right dorsolateral prefrontal cortex and the right anterior insula, which are associated with pain intensity.[18] Based on these findings, the utilization of neuroimaging techniques to investigate the central mechanisms of acupuncture treatment of NP is practical and feasible. Therefore, by fMRI, this study aims at: 1) evaluating the therapeutic effects of different acupoints prescription on NP; and 2) investigating the cerebral activity changes elicited by acupuncture treatment; and 3) analyzing the possible correlations between the improvement of clinical symptoms and changes in brain activity, so as to explore the potential central mechanism of acupuncture for NP.

# Methods

# Design

This is a randomized controlled trial. The protocol was drawn up in accordance with the Consolidated Standards of Reporting Trials guidelines and the Standards for Reporting Interventions in Clinical Trials of Acupuncture guidelines (STRICTA).[1920] The protocol has been approved by the Institutional Review Board of the Hospital of Chengdu University of Traditional Chinese Medicine (approved number: 2020KL-007) and registered at Chinese Clinical Trial Registry (registration number: ChiCTR2000040930, protocol version number: V1.0).

This study period last for 16 weeks, which included a 2-week baseline period, a 2-week intervention period, and a 12-week following period. A total of 86 patients with NP will be randomly assigned to the two acupuncture groups with a 1:1 ratio. 20 patients in each group will be randomly selected to undertake fMRI scans. Clinical outcome evaluation and fMRI scans will be conducted at baseline and after treatment. The study procedure is outlined in Fig. 1 and Table 1.

Table 1
Study schedule for data collection.

| Period | Baseline | | Treatment | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|
| Assessment | | 1 | | | | | | 2 | 3 | 4 |
| Time (week) | 0 | 2 | 3 | | | 4 | | | 8 | 16 |
| **Pick-up information** | | | | | | | | | | |
| Inclusion/exclusion criteria | √ | | | | | | | | | |
| Informed consent | √ | | | | | | | | | |
| Vital signs | √ | | | | | | | | | |
| Medical history | √ | | | | | | | | | |
| Physical examination | √ | | | | | | | √ | | |
| **Acupuncture intervention** | | | | | | | | | | |
| Group A (n = 43) | | | √ | √ | √ | √ | √ | √ | | |
| Group B (n = 43) | | | √ | √ | √ | √ | √ | √ | | |
| **Clinical assessment** | | | | | | | | | | |
| VAS | √ | √ | | | | | | √ | √ | √ |
| NDI | | √ | | | | | | √ | √ | √ |
| ROM | √ | √ | | | | | | √ | √ | √ |
| PPT | | √ | | | | | | √ | √ | √ |
| SF-36 | | √ | | | | | | √ | √ | √ |
| MSUS | | √ | | | | | | √ | | |
| SAS and SDS | | √ | | | | | | √ | √ | √ |
| fMRI (n = 40) | | √ | | | | | | √ | | |

This is a randomized controlled trial of neuroimaging including a 2-week baseline period, a 2-week treatment period, and a 12-week follow-up period. At baseline, participants will be screened based on inclusion and exclusion criteria; eligible individuals will then sign informed consent and undergo a physical examination. After randomized into 2 groups, 6 acupuncture treatments will be performed for 2 weeks. Clinical data will be evaluated at baseline, after treatment ends, and at 4 and 12 weeks after completion, fMRI scans will be performed before the first and sixth acupunctures. After the treatment, laboratory tests will be performed, including routine blood test, C-reactive protein, and erythrocyte sedimentation tests. Adverse events will be recorded in the CRF at any time during treatment.

fMRI functional magnetic resonance imaging, VAS Visual Analogue Acales, NDI Neck Disability Index, ROM Cervical Range of Motion, PPT Pressure Pain Threshords, MSUS musculoskeletal ultrasound, SF-36 short-form 36-item Health Survey, SAS Self-Rating Anxiety Scale, SDS Self-Rating Depression, CRF case report form

| Period | Baseline | Treatment | Follow-up |
|---|---|---|---|
| Laboratory test | √ | | √ |
| Adverse event | | | √ |
| This is a randomized controlled trial of neuroimaging including a 2-week baseline period, a 2-week treatment period, and a 12-week follow-up period. At baseline, participants will be screened based on inclusion and exclusion criteria; eligible individuals will then sign informed consent and undergo a physical examination. After randomized into 2 groups, 6 acupuncture treatments will be performed for 2 weeks. Clinical data will be evaluated at baseline, after treatment ends, and at 4 and 12 weeks after completion, fMRI scans will be performed before the first and sixth acupunctures. After the treatment, laboratory tests will be performed, including routine blood test, C-reactive protein, and erythrocyte sedimentation tests. Adverse events will be recorded in the CRF at any time during treatment. | | | |
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# Participants

# Recruitment procedures

Patients will be recruited at the outpatient of the Hospital of Chengdu University of Traditional Chinese Medicine (TCM) and Sichuan Integrated Medicine Hospital. In addition, patients will also be recruited from the community and campus of Chengdu University of TCM through advertising (posting notices, distributing leaflets, web publishing). Patients who agree to participate in this study will be diagnosed by an orthopedic specialist. The eligible patients will be screened by the research assistant based on the inclusion and exclusion criteria.

# Inclusion criteria

Participants who match the inclusion criteria will be included: 1) those with NP as the main complaint and a visual analog scale (VAS) score of pain severity exceeding 4 points but less than 10 points (range 0–10 points); and 2) for a duration of ≤ 3 months; and 3) aged 18–60 years; and 4) agreeing to sign informed consent.

# Exclusion criteria

Participants with any of the following conditions will be excluded: 1) they are pregnant or lactating women; or 2) they have any organic or metabolic diseases of the digestive, hematopoietic, endocrine, or immune systems, or other severe primary diseases; or 3) they have local skin damage or severe skin diseases that affect acupuncture manipulation; or 4) they combine with mental or neurological diseases; or 5) they have received acupuncture for NP within one month; or 6) they have MRI contraindications, such as heart pacemaker, metallic foreign bodies, or severe claustrophobia, etc.; or 7) they are participating in other clinical trials.

# Sample size

This study aims to compare the difference of the clinical efficacy of two acupuncture prescriptions (Group A and Group B). According to the results of the pilot study, the average reduction of VAS score in Group A was 2.86 ± 0.99, and the average reduction of VAS score in Group B was 2.14 ± 0.99. According to the formula, $n = \frac{2\sigma^2}{(\mu 1 - \mu 2)^2} \times (\mu_{\alpha/2} + \mu_{\beta})^2$, with α = 0.05 (both sides) and 1-β = 0.80.[21] The sample size of each group was calculated to be 34, considering a 20% dropout rate, the final sample size was set to 43 per group, making the total of 86 in this study.

There is no widely accepted method for sample size calculation in neuroimaging study. Referring to the previous study,[22] 15 participants in each group is the smallest size in neuroimaging studies. Considering a 20% dropout rate and the unavailability of data due to various reasons, this study will randomly select 20 patients from each group for fMRI scans.

# Randomization and blinding

Randomization will be carried out in two steps: 1) an independent, blinded statistician will generate a random allocation sequence using SPSS 26.0 (IBM, Chicago, IL, USA). The 86 patients will be randomly assigned into Group A and Group B at a ratio of 1:1; 2) 20 patients from each group will be randomly selected for fMRI. Allocation concealment will be achieved by sequentially numbered, opaque, sealed envelopes.

In this study, the patients, outcome assessors and statistical analysts will be blinded. The patients will be treated at the separate rooms to reduce communication. However, due to the particularity of acupuncture manipulation, blinding operator cannot be achieved.

# Interventions

Patients in Group A will receive acupuncture at three acupoints (Lieque (LU7), Chize (LU5) and neck tenderness point on the affected side) (Fig. 2A). The acupoints of Group B (control group) will receive acupuncture at three acupoints (Shaohai (HT3), Lingdao (HT4) and neck tenderness point on the affected side) (Fig. 2B). Tenderness points will be detected using a PX25 hand-held pressure pain tester (Wagner FPX™ 25).

The acupuncture manipulations are as follows: disposable sterile filiform needles (0.30 × 40 mm, Huatuo Medical Instrument Co.,Ltd., China) will be inserted into acupoints at a depth of 20–30 mm after skin disinfection, and the Deqi sensation (a sensation of acid distension or numbness, or other acupuncture sensation) will be achieved.[23] Then, HANS-200A acupoint nerve stimulator (Nanjing Jisheng Medical Technology Company, Nanjing city, China) will connect LU7 and LU5 of Group A or HT3 and HT4 of Group B respectively in the two groups for 30 minutes with dilatational waves (2-100 Hz, 1 mA). Patients will receive a total of 6 sessions of acupuncture in two weeks with 3 sessions per week.

Acupuncture treatment will be performed by acupuncturists who have held a practitioner license for more than 3 years.

# Concomitant medications

Patients will be instructed not to take any other analgesic medications for NP during this study. In cases of severe NP, ibuprofen (300 mg per capsule with sustained release) will be allowed as rescue medication and should be recorded on the case report form (CRF).

# Outcome measurements

The measurements will be conducted by independent assessors who have been trained prior to the study. The primary outcome is the change of VAS scores for pain severity from baseline to 2 weeks. VAS scores range from 0 to 10, with 0 indicating no pain and 10 indicating pain is unbearable. The secondary outcome measurements including: Neck Disability Index (NDI), Short-Form 36-Item Health Survey (SF-36), Self-rating Anxiety Scale (SAS), Self-rating Depression Scale (SDS), Range of Motion (ROM) and Pressure Pain Threshold (PPT) will be evaluated at baseline, after treatment, and at 4 and 12 weeks after the end of treatment. In addition, we will perform musculoskeletal ultrasound (MSUS) before and after treatment. Among them, NDI is the most widely used clinical tool for self-assessment of disability caused by NP.[24] The SAS and SDS are the commonly used psychometric tools to measure the severity of anxiety and depression.[25] [26] SF-36 is a general health-based survey of quality of life, which can be self-administered by the patient with reliability.[27] ROM is one of the quantitative outcomes assessing the extent and degree of joint motor impairment. The changes of the tenderness threshold can quantitatively reflect the improvement of the pain severity.[28] Meanwhile, MSUS is an important means for clinical diagnosis of rehabilitation medicine, tracking disease progression and assessing curative effect.[29]

# Patient safety

Adverse events during treatment will be reported in the CRF. The record should include the time, reason, clinical symptoms, and signs of the adverse event, as well as the corresponding emergency treatment plan.

# MRI data acquisition

The resting-state fMRI (RS-fMRI) will be performed at the baseline and the end of treatment, respectively. Patients will be asked to do not drink tea, coffee, or alcohol, avoid strenuous exercise, and ensure adequate sleep before the scan.

Patients will undergo RS-fMRI scan with a 3.0T MR scanners (Siemens 3T Tim trio, Erlangen, Germany) at the West China Hospital of Sichuan University. Patients will be asked to stay awake and to keep their heads still during the scan, with their eyes closed and ears plugged. Scans will be performed with the following procedures: localizer, three-dimensional T1-weighted imaging (3D-T1WI), blood oxygenation level-dependent fMRI (BOLD-fMRI) and diffusion tensor imaging (DTI) sequence. The 3D-T1WI scanning parameters will be as follows: repetition time (TR) = 6.008 ms, echo time (TE) = 1.7 ms, data matrix = 256 × 256, field of view (FOV) = 256 × 256 $mm^2$. The BOLD-fMRI scanning parameters will be as follows: 31 contiguous slices with a slice thickness of 5 mm, TR = 2000 ms, TE = 30 ms,FOV = 240 × 240 $mm^2$,

Matrix = 64 × 64, flip angle (FA) = 90°, total volumes = 240. The DTI data will be acquired using a single-shot echo planar image sequence with the following parameters: FOV = 256 × 256 $mm^2$, TR = 8500 ms, matrix = 128 × 128, slice thickness = 2 mm with no gap. Two diffusion-weighted sequences were acquired using gradient values b = 1000 $s/mm^2$ and b = 0 $s/mm^2$ with the diffusion-sensitizing gradients applied in 64 non-collinear directions.

# Statistical analysis

# Clinical data analysis

The comprehensive effectiveness analysis will use the per protocol set (PPS) and the full analysis set (FAS). The FAS population will be used as the primary population for all efficacy analyses. The safety set (SS) included all subjects who received at least one treatment after randomization. When the results of PPS analysis and FAS analysis are inconsistent, PPS and FAS are discussed separately to find out the reasons for the inconsistency. Missing data will be handled using the last-observation-carried-forward (LOCF) method.

Statistical analysis will be conducted using SPSS 26.0 (IBM, Chicago, IL, USA) statistical software. $P < 0.05$ (two-sided) is considered statistically significant. Quantitative data are described with mean ± standard deviation (SD). Qualitative data are described with frequency and percentage (N, %). *Student's t*-test and *chi-square* test will be used to compare the differences between groups at baseline. The primary outcome will be carried out with a paired samples *t*-test, and the secondary outcome will be compared at four timepoints using the repeated measures ANOVA. Clinical data on skewed distribution will be compared using a non-parametric test.

# MRI data analysis

The fMRI data preprocessing and comparison will be performed using SPM12 software (http://www.fil.ion.ucl.ac.uk/spm/) based on MATLAB 2018a (Mathworks, Inc., USA). The steps including: format conversion, slice timing correction, head motion correction, spatial standardization, linear trend removal, spatial smoothing, and band-pass filtering. After pre-processing, the amplitude of low frequency fluctuation and regional homogeneity will be calculated to reflect the local cerebral functional activity, and the seeds-based functional connection analysis will be performed to reflect the functional integration of the brain. ANOVA will be used for comparisons between the two groups, with multiple comparison corrections.

Furthermore, the *Pearson* correlation analysis will be conducted to assess the associations between the changes of fMRI and the improvement of clinical symptoms.

## Discussion

To the best of our knowledge, this is the first randomized controlled study that is aimed at investigating the clinical efficacy and underlying mechanisms of different acupuncture prescriptions for NP. The results

of this study are beneficial for the prescription selection of acupuncture for treating NP, and elucidates on the mechanisms of acupuncture for NP.

# Selection of acupoint prescription

Many clinical studies have been performed on acupuncture for NP, and its efficacy has been identified. In clinical practice, the combination of local and distal points is a basic principle of acupoint prescriptions, but the number of prescriptions and acupoints involved is enormous. Therefore, in this study, two different prescriptions will be selected to compare their efficacy and possible mechanisms. Neck tenderness point will be selected as the basic acupoint, which is the most commonly used local acupoint in NP' treatment. LU7 and LU5, located in the forearm, will be selected as distal points in Group A. HT4 and HT3, also located in the forearm, will be selected as distal points in Group B. All these distal points are reported to be effective in some clinical trials on acupuncture for treating NP.[30–32]

# The combination of subjective and objective outcome measures

Pain is an unpleasant sensory and emotional perception that is associated with actual or underlying tissue pathology.[33] Human behavior, psychological and social factors play a crucial role in the long-term maintenance of pain.[34] Therefore, the multidimensional nature of pain requires that the measurement of NP should include both subjective outcomes and objective outcomes. In this study, subjective outcomes including VAS, NDI, SAS and SDS will be used to assess pain perception, dysfunction, and emotional state of the patients. Moreover, objective outcomes including tenderness threshold, musculoskeletal ultrasound and ROM will be used to evaluate the improvement of symptoms in NP patients. The combination of subjective and objective outcomes can be more complementary to assess the efficacy from multiple perspectives and reduce the occurrence of potential bias, so as to improve the quality of clinical evidence.

# Application of neuroimaging technology

Previous neuroimaging studies have demonstrated that patients with NP present with abnormalities in brain activity and structure. For example, Chen et al.[35] found increased spontaneous brain activity in the supplementary motor area of NP patients, and subsequently suggested a correlation between abnormality of the salience network with the disease. Another single fMRI-based case control study associated NP with activation and/or recall of pain memory.[36] Elsewhere, a voxel-based morphometry study performed on NP patients revealed that the loss of bilateral clusters of gray matter in the sensorimotor cortex and pulvinar nucleus with NP pathophysiology.[37]

Moreover, it has been reported that central integration is the key determinant of the effectiveness of acupuncture.[38] With previous studies, performed on individuals with shoulder pain,[39] fibromyalgia,[40] and low back pain,[41] as well as knee osteoarthritis[12] indicating that regulation of brain activity might be an important factor influencing acupuncture's modulating effects on pain. For example, acupuncture has

been shown to effectively reduce pain by modulating brain regions related to both sensory-discriminative and emotional aspects.[42] Such regions were found to be important for the therapeutic effects of acupuncture on NP.[35] Based on these evidences, we hypothesize that acupuncture can effectively treat NP by modulating alteration of brain activity.

This trial is the first study to use fMRI to explore the potential central mechanisms of different acupuncture prescriptions for the treatment of NP. The results of this trial will help to provide visualization evidence for the clinical application of acupuncture for NP treatment.

# Trial Status

The trial is currently in the recruitment phase and the study is expected to end in December 2021.

# Abbreviations

3D-T1WI Three-dimensional T1-weighted imaging

BOLD-fMRI Blood oxygenation level-dependent fMRI

RS-fMRI Resting state functional magnetic resonance imaging

CRF Case report form

DTI Diffusion tensor imaging

FA Flip angle

FAS Full analysis set

FDR False Discovery Rate

FOV Field of view

GLM General Linear Model

HbO Oxygenated hemoglobin

HbR Deoxygenated hemoglobin

LOCF Last observation carry-forward

MRI Magnetic resonance imaging

MSUS Musculoskeletal ultrasound

NDI Neck Disability Index

NP Neck Pain

NIH National Institutes of Health

PPS Per protocol set

PPT Pressure pain threshold

ROM Range of motion

SD Standard Deviation

SF-36 Short-form 36-item Health Survey

SAS Self-Rating Anxiety Scale

SDS Self-Rating Depression

SS Safety set

TCM Traditional Chinese Medicine

TE Echo time

TR Repetition time

VAS Visual Analogue Scale

# Declarations

### Ethics approval and consent to participate

This trial has been approved by the Institutional Review Boards and Ethics Committees of the First Teaching Hospital of CDUTCM (Approved number: 2020KL-007) and has been registered in the Chinese Clinical Trial Registry (ID: ChiCTR2000040930). Only patients who have signed the informed consent form will be included.

### Ethics and dissemination

Ethical approval of this study has been approved by the Ethics Committee of the Hospital of Chengdu University of Traditional Chinese Medicine (No. 2020KL-007). The outcomes of the trial will be disseminated through peer-reviewed publications.

### Consent for publication

Not applicable.

### Availability of data and materials

Not applicable.

### Competing interests

The authors declare that they have no competing interests.


### Funding

The study is financially supported by the National Key Research and Development Program in China (2018YFC1704606).


### Authors' contributions

FZ and LJ are responsible for this study. FZ, LJ, ZG, TY, and LL conceived and designed the study. ZG, TY, and LL participated in drafting the trial protocol and preparing the manuscript. SR, LD, HG, JC, and HZ participated in data collection and were in charge of recruitment and treatment of patients. All authors read and approved the final manuscript.


### Acknowledgments

We thank Haifa Qiao and Gang Lu for the help of participants enrollment.


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# Figures

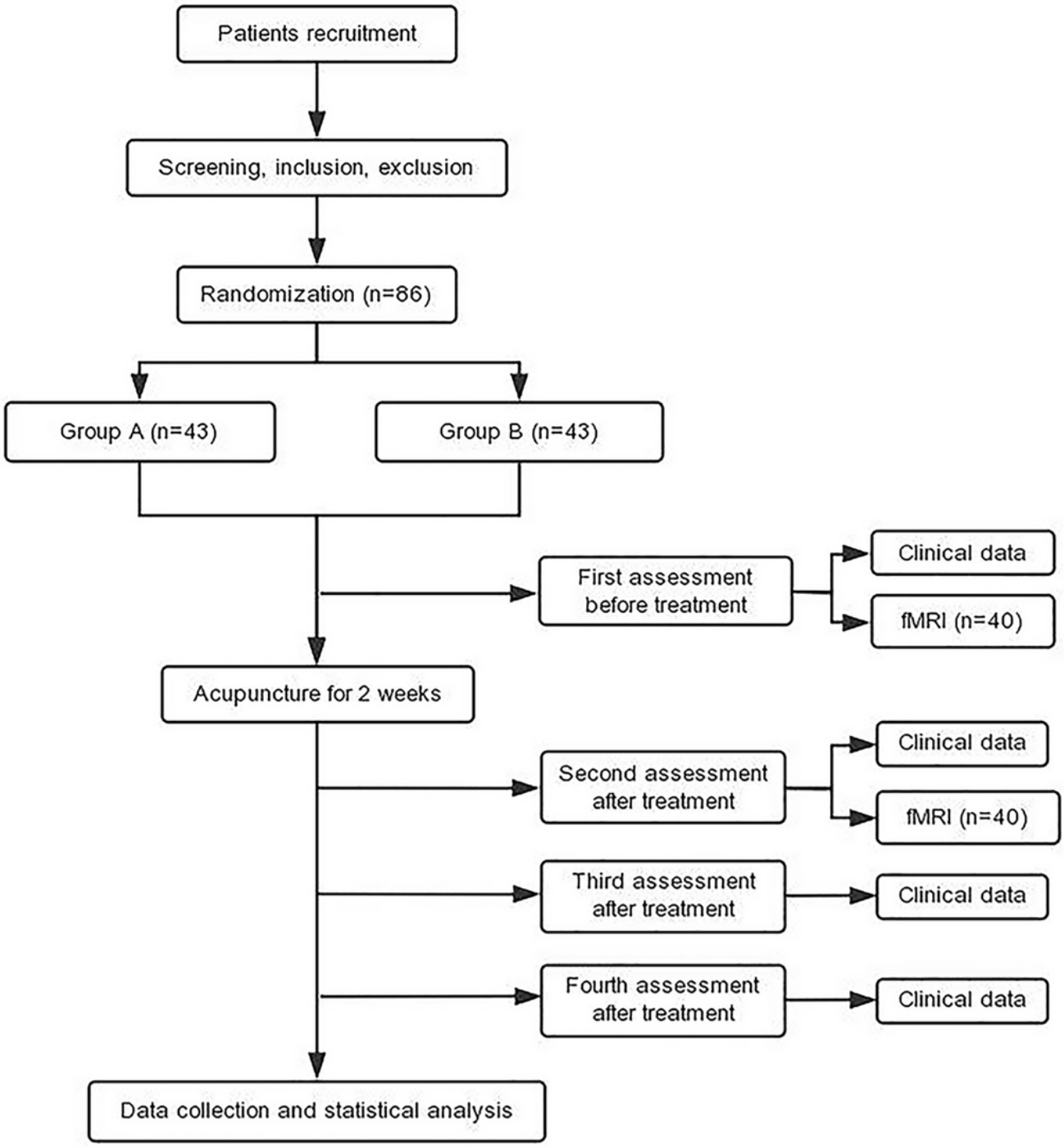


**Figure 1**

Flowchart of the procedure through the trial. The randomized controlled trial will enroll 86 eligible patients and divide them randomly into two groups at a 1: 1 ratio. 20 patients from each group will be randomly selected for fMRI data collection. During the 2-week treatment, the patient will receive 6 acupuncture treatments. Clinical assessment will be performed at 4 time points: baseline, end of treatment, and 6 and 14 weeks after completion. The fMRI will be performed before the first and sixth acupuncture.
Abbreviations: fMRI functional magnetic resonance imaging

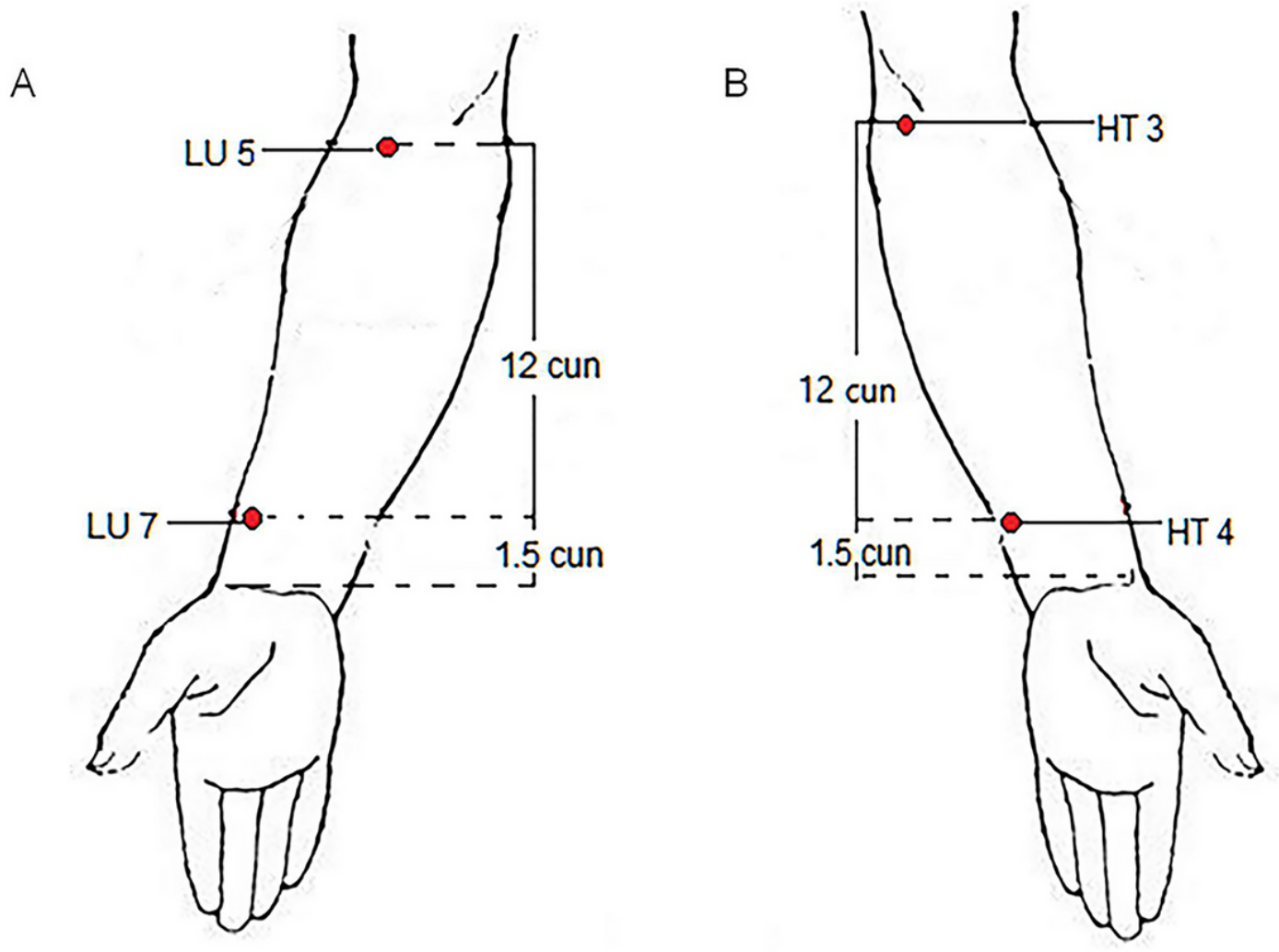


**Figure 2**

Locations of acupoints. A: Locations of acupoints (Group A). Lieque (LU 7), on the radial side of the forearm, above the styloid process of the radius and 1.5 cun above the horizontal stripes of the wrist. Chize (LU 5), in the transverse elbow, the radial side of the biceps tendon is sunken. B: Locations of acupoints (Group B). Lingdao (HT 4), in the anterior area of the forearm, the radial side of the ulnar carpi flexor tendon is 1.5 cun above the transverse stripes of the carpal palm. Shaohai (HT 3), at the midpoint of the line between the medial end of the transverse line of the elbow and the medial epicondyle of the humerus.

# Supplementary Files

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