Clinical Efficacy and Central Mechanisms of Electroacupuncture Treatment for Low Back Pain in Primary Osteoporosis: Study Protocol for a Randomized Controlled Trial

Chihuan Huang
Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine
Jing Liu
Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine
Zun Wang
Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine
Di Zhang
Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine
Zhijie Guo
Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine
Liyu Wei
Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine
Shaowei Liu
Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine
Lanying Liu
Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine
Daoming Xu (xudaoming@126.com)
Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine

Study protocol

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Abstract

Background

Primary osteoporosis is a common disease in the elderly, often causing low back pain and limited mobility. Electroacupuncture is considered a combination of traditional acupuncture and modern transcutaneous electrical nerve stimulation. Due to its strong stimulation, it has shown certain efficacy in relieving low back pain associated with primary osteoporosis (POP). It has the potential to be a complementary or alternative treatment for drug therapy of POP-related low back pain. However, the underlying mechanisms have not been fully elucidated. Therefore, this study, by evaluating the efficacy of electroacupuncture in treating POP-related low back pain, aims to explore the potential central mechanisms using resting-state functional magnetic resonance imaging (rs-fMRI).

Methods

This study is a randomized controlled trial in which 60 patients were randomly divided into two groups: the calcium group (n = 30) and the calcium + electroacupuncture group (n = 30). The study lasted for 17 weeks, including a 1-week baseline, 4 weeks of treatment, and 12 weeks of follow-up (at the 4th and 12th week after treatment). The primary outcome measure is McGill Pain Questionnaire (MPQ), and secondary outcome measures include the Oswestry dysfunction index(ODI), Young's Modulus, and the use of analgesic medications after treatment. These measures will be used to evaluate the clinical efficacy of the two intervention methods for treating low back pain associated with primary osteoporosis (POP). Twenty patients from each group will be randomly selected for rs-fMRI examinations to observe changes in brain functional activity and correlate them with changes in pain severity.

Discussion

This study aims to evaluate the clinical efficacy and potential central mechanisms of electroacupuncture in treating low back pain associated with POP. Provided that we obtain imaging-based evidence of the effectiveness of electroacupuncture intervention for POP-related low back pain, this study will provide supporting evidence for the clinical application of electroacupuncture in the treatment of low back pain associated with POP.

Trial registration:

Chinese Clinical Trial Registry ChiCTR2300075736. Registered on 14 September 2023

Background

POP is a systemic skeletal disease characterized by low bone mass and degeneration of bone tissue microstructure, which placed third in senile diseases[1]. According to the survey conducted by Salari et al [2], the prevalence rate of osteoporosis in the elderly is 21.7% worldwide, with the highest in Asia as high as 24.3%. Osteoporosis often leads to pain in elderly patients, and this symptom is also the most important factor in prompting patients to go to the hospital for a diagnosis of osteoporosis. 70–80% of the patients show low back pain [3], which reduces their daily activities and leads to the decline of motor function, which seriously affects their quality of life.

At present, in relieving pain caused by osteoporosis, the anti-bone resorption drug salmon calcitonin has an obvious analgesic effect, but its long-term use will increase the risk of cancer, so it is no longer recommended as a first-line drug in clinics [4]. Among the commonly used clinical analgesic drugs, non-steroidal anti-inflammatory drugs have the risk of gastrointestinal bleeding, and the long-term use of opioids is addictive, which limits their wide clinical use [5]. Therefore, finding a safe and effective treatment to reduce the pain scale of osteoporosis and reducing the use of analgesic drugs remains an urgent problem to be solved.

As a green therapy, acupuncture has a significant effect on the treatment of pain with few adverse reactions. in recent years, it has been gradually favored by patients and doctors as a treatment for osteoporosis. As one of the most commonly used acupuncture treatments in the clinic, electroacupuncture combines filiform acupuncture with electrophysiological effects. The difference from ordinary acupuncture is that electroacupuncture stimulates acupoints and neuromuscular tissue through electric current and has a

two-way regulating effect. At present, electroacupuncture is also widely used in the study of POP at home and abroad[6–7]. It can affect bone remodelling by regulating bone morphology, biomechanics, bone metabolic indexes, hormones, cytokine gene proteins, etc., and also improve muscle excitability, strengthen bone stress stimulation, and reduce bone loss. Our previous study [8] has confirmed the efficacy of electroacupuncture in relieving pain and motor function in patients with POP, but did not investigate the use of analgesics and the potential mechanism of central analgesia.

Therefore, in this study, a randomized controlled trial was designed to observe whether electroacupuncture can reduce the use of analgesics while improving the clinical symptoms of patients with low back pain in POP. This study also aims to explore the correlation between the changes in brain activity and the improvement of pain symptoms in patients with low back pain treated with electroacupuncture, to elucidate the potential mechanism of central analgesia.

Methods and design

Study design

This study is a randomized controlled trial. The experiment has been approved by the Ethics Committee of Jiangsu Provincial Hospital of Traditional Chinese Medicine (approval number: 2023NL-165-02). Registered in China Clinical Trials Registration Center (Registration No: ChiCTR2300075736).

The study will last for 17 weeks, including 1-week baseline, 4-week treatment, and 12-week follow-up (4 and 12 weeks after treatment). A total of 60 patients with POP low back pain will be randomly assigned to two groups, with a ratio of 1:1. Twenty patients in each group will be randomly selected for rs-fMRI scans. Clinical data will be evaluated at baseline and at the end of treatment and 4 and 12 weeks after treatment; rs-fMRI scans will be performed at baseline and after treatment. The study procedure is outlined in Fig. 1 and Table 1.

Table 1 Study schedule of enrollment, intervention, and assessments

Study period week	Baseline		Treatment period				Follow-up											
Time point	a0-wk	1-wk	1-wk	3-wk	4-wk	5-wk	6-wk	7-wk	8-wk	9-wk	10-wk	11-wk	12-wk	13-wk	14-wk	15-wk	16-wk	17-wk
Enrolment																		
Patient screen																		
Informed consent		√																
Randomization		√																
Interventions																		
Control group (n = 30)			√	√	√	√												
Test group (n = 30)			√	√	√	√												
Assessments																		
rs-fMRI scans		√				√												
MPQ		√				√				√								√
ODI		√				√				√								√
Young's modulus		√				√				√								√
The use of analgesics			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Adverse event			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Participants

Source of recruitment

The study will recruit patients from the affiliated Hospital of Nanjing University of Traditional Chinese Medicine. Patients who agree to participate in this study must meet the diagnostic criteria for primary osteoporosis. Eligible patients will be screened according to inclusion and exclusion criteria.

Inclusion criteria

1. meet the diagnostic criteria of the disease;
2. have the manifestation of low back pain and VAS score: 3–7;
3. age from 50 to 75 years old;
4. voluntarily fill in the informed consent form and agree to participate in the clinical trial.

Exclusion criteria

1. patients with secondary osteoporosis such as hyperthyroidism, rheumatoid arthritis and multiple myeloma;
2. Fresh vertebral compression fracture in recent 3 months;
3. A history of taking anti-osteoporotic drugs in the past 6 months;
4. Patients with lumbar disc herniation, lumbar spinal canal narrowing, lumbar tuberculosis and other lumbar diseases;
5. Complicated with cardiovascular, cerebrovascular, liver, kidney, hematopoietic system and other severe primary diseases or systemic multiple organ failure;
6. The amplitude of head movement is greater than that of 2 mm;
7. There are taboos in fMRI detection

Randomization

Randomization will be divided into two parts. First, random numbers generated by SPSS26.0 software are written on cards and placed in 60 sealed, opaque envelopes. When the patients who met the inclusion criteria entered the study, the patients were randomly divided into the experimental group (n = 30) and the control group (n = 30). After being divided into groups, patients in each group will be randomly selected for rs-fMRI examination according to another random sequence, with 20 patients in each group.

Blinding

This clinical study follows the principle of the blind method. In the process of implementation, the blind method is applied to outcome evaluators and data statisticians, but not to patients and acupuncturists.

Sample size

The sample size is calculated using pass15 software. According to the results of Wenetuo et al[9], the test level (α) was located at 0.025, the test efficiency (1-β) was 0.9, 1.32 in the test group (meant), 1.81 in the control group (meanc), 0.40 in the test group (st), 0.57 in the control group (sc), and the sample size ratio (Nt:Nc) between the test group and the control group was 1. The loss rate (GroupDropoutRate) is 20%. The total sample size was 60 cases, 30 cases in the experimental group and 30 cases in the control group.

Interventions

Control group

Oral calci D (calcium 600 mg and vitamin D3 125 IU per tablet), 1 tablet at a time, once daily.

Test group: Combined with electroacupuncture on the basis of the control group. The specific process is as follows: Select acupoints: Ganshu (BL18), Shenshu (BL23), Pishu (BL20), Yanglingquan (GB 34), Xuanzhong (GB39), Zusanli (ST 36), Weizhong (BL40). The location is strictly in accordance with the National Standard of the People's Republic of China: Meridian points (GB12346-90).Operation: patients take prone position, after routine skin disinfection, choose 0.25 mm × 40 mm disposable aseptic acupuncture needle, Ganshu, Pishu and skin at an angle of 45° oblique to the spine, acupuncture 15 mm, Shenshu straight 25 mm, Weizhong straight 15 mm, Zusanli, Xuanzhong and Yanglingquan all straight 25 mm, after entering the needle, the method of twirling, tonifying, relieving and relieving is performed. Bilateral Ganshu and Shenshu needles were connected with XS- 998B04 low-frequency pulse electroacupuncture instrument (Nanjing Institute of Medical Instruments). The dense wave was given at the frequency of 2 Hz and 10 Hz for 30 min. All acupuncture was performed by the same acupuncture clinician. Course of treatment: once every other day, 3 times a week, 4 weeks, a total of 12 times.

Concomitant medications

During the period of this study, patients with unbearable pain can be given Qimingshu 60 mg once a day for no more than 3 days. The usage and dosage of each medication should be recorded in time with a record card.

Outcomes

Main index

McGill pain scale

Secondary indicator

Oswestry Disability Index(ODI) Young's modulus The use of painkillers rs-fMRI.

Adverse event record

Any adverse reactions during the trial should be recorded in the "adverse event form", follow up investigation should be performed, and the treatment process and its result should be recorded in detail until the reaction returns to normal and the symptoms and signs

disappear. The follow-up method can vary according to the severity of adverse reactions, such as hospitalization, outpatient service, home visit, telephone, communication and so on. When adverse reactions are found, the researchers decide the diagnosis and treatment measures according to the condition and decide whether to stop the observation to ensure the safety of the subjects.

MRI data acquisition

MRI data were acquired on a 3.0 Tesla Siemens MRI scanner. All individuals were instructed to relax with their eyes closed, think of nothing and move as little as possible during the scan. (1) Structural images were acquired with a T1-weighted 3D spoiled gradient-echo sequence as follows: repetition time (TR) = 1900 ms, echo time (TE) = 2.52 ms, number of slices = 176, slice thickness = 1 mm, field of view (FOV) = 250×250 mm^2, Matrix = 256×256, flip angle (FA) = 9°. (2) Functional images were obtained axially using a gradient echo-planar sequence as follows: TR = 2000 ms, TE = 30 ms, slice thickness = 4 mm, slice gap = 1 mm, FOV = 256×256 mm^2, Matrix = 64×64, FA = 90°. None of the participants had obvious structural damages examined by 2 experienced radiologists based on conventional MRI sequences.

Data management

Clinical data will be managed through printed case reports and electronic data acquisition (EDC). An independent data administrator will retain the data. Only key researchers can access the complete data set and will perform dual data entry. The results will be published in peer-reviewed journals.

Data analysis

Clinical data analysis

SPSS26.0 software was used for statistical analysis. The measurement data are expressed by ($\bar{x} \pm s$). If it conforms to the normal distribution, t-test is used; if it does not conform to the normal distribution, the rank sum test is used; the counting data are compared by X^2 test; and the rank sum test is used in the comparison of grade data. The difference was statistically significant ($P < 0.05$).

MRI data preprocessing

MRI data preprocessing was conducted with the software of Data Processing Assistant for Resting-State fMRI (DPARSF)[20], a software plug-in within Data Processing & Analysis for Brain Imaging (DPABI). The procedures were as follows: (1) removal of the first 6 functional volumes; (2) slice-timing correction; (3) head motion correction; (4) removing subjects who had more than 2 angular motions or more than 2 mm movement; (5) spatial normalization to the Montreal Neurologic Institute (MNI) template; (6) smoothing using a 4 mm full-width at half-maximum (FWHM) Gaussian kernel; (7) temporal filtering and linear detrending; (8) regressing out nuisance signals, including Friston-24 head motion parameters, global signal, white matter signal, and cerebrospinal fluid signal.

Discussion

This is the first clinical study on electroacupuncture intervention on the use of analgesics for low back pain in patients with POP.

Acupuncture has a history of thousands of years. Because of its wide application, quick effect and few adverse reactions, acupuncture has become a recognized green analgesia method at home and abroad [10]. Acupuncture not only relieves pain, but also improves the quality of life of patients with pain, and can avoid addiction, immunosuppression, gastrointestinal injury and other adverse reactions caused by analgesics to a certain extent[11]. Acupuncture has been a means of relieving opioid withdrawal symptoms for more than 50 years. More and more clinical studies have shown that acupuncture is effective to treat musculoskeletal pain and even cancer pain[12–14]. LiuCT et al.[15] pointed out that acupuncture can reduce the use of analgesics after rib fracture. A systematic review shows that acupuncture can reduce postoperative pain and opioid consumption and reduce adverse reactions such as nausea, vomiting and itching [16].The American Association of Physicians Clinical practice Guide [17] recommends acupuncture as an initial non-drug therapy for acute or chronic low back pain. Acupuncture has become widely accepted as a supplementary treatment for pain relief. In recent years, acupuncture has attracted more and more attention in the treatment of osteoporosis. A systematic review points out that the potential benefits of acupuncture in the treatment of osteoporosis mainly include pain relief and improved bone mineral density[18]. Schiller J et al. [19] through randomized controlled studies have shown that acupuncture can relieve the pain of osteoporosis and improve their quality of life. Through the current research situation at home and abroad, it is found that only a few RCT have investigated acupuncture treatment to reduce the use of analgesics addiction. Therefore, more

randomized controlled trials are needed to support the evidence that acupuncture relieves pain symptoms and reduces the use of analgesics.

In our previous study [20], we emphasized the importance of muscles and bones and demonstrated that electroacupuncture, based on calcium, can improve pain symptoms and motor function in patients with POP. However, the effects of analgesics after electroacupuncture treatment have not yet been investigated. Therefore, in this study, we observed the clinical effect of electroacupuncture on pain relief in POP, recorded the use of analgesics, and explored its potential central analgesic mechanism through rs-fMRI.

Pain is a complex physical and mental activity, which is one of the most common clinical symptoms. The International Association for Pain Research revised the definition of pain in 2020, emphasizing that in addition to the perception of pain, pain emotion, cognitive and social skills are important dimensions for the assessment of pain [21]. Therefore, in this study, McGill pain scale was used to evaluate patients' pain from many aspects, such as pain sensation, intensity, emotion and so on. McGill pain scale was taken as the main outcome index. ODI is used to evaluate lumbar dysfunction in patients with low back pain. In this study, it is used as a secondary observation index to reflect the situation of low back pain and the severity of pain affecting their life in patients with primary osteoporosis. This study also takes the use of analgesics as its therapeutic index to observe whether electroacupuncture in the treatment of POP pain can reduce the use of analgesics from two aspects of its utilization rate and intensity (total oral dose). DeZordo et al. [22] applied real-time shear wave ultrasonic elastography (SWE) to the field of muscle and bone for the first time, described the elasticity of Achilles tendon in healthy adults, and confirmed its application value. In recent years, in the field of acupuncture research, SWE technology has made progress in acupoint determination, acupuncture qi extraction, manipulation research and curative effect evaluation[23]. Our group's previous study [24] found that the value of Young's modulus measured by SWE has the same trend as the improvement of pain symptoms, so we use Young's modulus as a secondary index in this study to explore the application value of its technique in the evaluation of patients with low back pain in POP.

With the widespread recognition of acupuncture analgesia, exploring the central mechanism of acupuncture analgesia has attracted more and more attention [25]. Functional magnetic resonance imaging (fMRI), as a non-invasive visualization technology, can directly reflect the external stimuli received by the brain, and has been widely used in the study of the mechanism of acupuncture in the treatment of chronic pain [26]. A neuroimaging systematic review showed that acupuncture improved abnormal brain structure and functional activity in patients with low back pain mainly through pain matrix, default pattern network (DMN), saliency network (SN) and descending pain regulation system (DPMS) [27]. Kong J et al. [28] have shown that the efficacy of acupuncture in the treatment of knee osteoarthritis pain is positively correlated with the activation of brain regions related to the marginal reward system (NAc, PFC and ACC). HaG et al. [29] have shown that acupuncture can regulate different brain regions, including thalamus, insular lobe, caudate body, claustrophobia and lenticular nucleus. The above studies provide an idea for exploring the central analgesic mechanism of acupuncture in relieving POP pain.

To the best of our knowledge, this study is also the first to explore the central mechanism of electroacupuncture in the treatment of POP low back pain. The results of this experiment will be helpful to provide visual evidence for the clinical application of electroacupuncture in the treatment of POP low back pain.

Trial status

The trial is currently in the recruitment stage and the study is expected to end in August 2024.

Abbreviations

POP osteoporosis

rs-fMRI resting-state functional magnetic resonance imaging

MPQ McGill Pain Questionnaire

ODI Oswestry dysfunction index

SWE shear wave ultrasonic elastography

DMN default pattern network

SN saliency network

DPMS descending pain regulation system

Declarations

Acknowledgements

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Availability of data and materials

The individual participant data during the study are available from the cor-

responding author upon reasonable request.

Authors'contributions

Lanying Liu and Daoming Xu are responsible for this study. Chihuan Huang, Jing Liu, Lanying Liu and Daoming Xu conceived and designed the study. Chihuan Huang, Jing Liu and Zun Wang participated in drafting the trial protocol and preparing the manuscript. Chihuan Huang, Jing Liu, Zun Wang, Di Zhang, Zhijie Guo, Liyu Wei, Shaowei Liu participated in the data collection and were in charge of the recruitment and treatment of patients. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

This trial was approved by the ethics committee of Jiangsu Provincial Hospital of Traditional Chinese Medicine (No. 2023NL-165-02). Registered in China Clinical Trials Registration Center (Registration No: ChiCTR2300075736).The informed consent will be signed by subject or legal guardian. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China.

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Figures

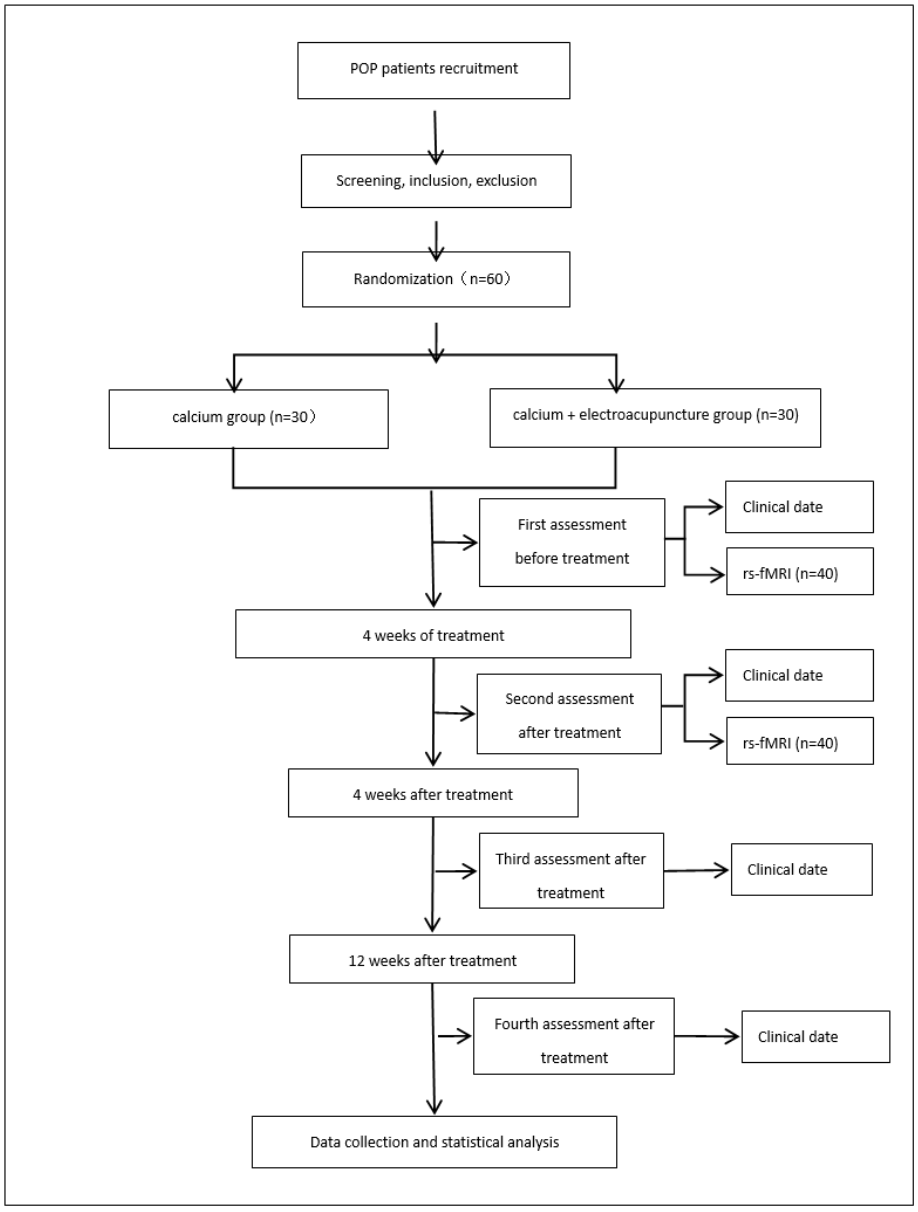

Figure 1

Legend not included with this version