Acupuncture for Comorbid Mild-Moderate Depression and Chronic Musculoskeletal Pain: Study Protocol for A Randomized Controlled Trial

sheng Li (lisheng@gzucm.edu.cn)

2nd clinical hospital of Guangzhou university of chinese medicine https://orcid.org/0000-0003-1401-0923

Jing Liu

2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine

Jianpeng Huang

2nd Clinical Hospital of Guangzhou Chinese Traditional Medicine College: Guangdong Provincial Hospital of Traditional Chinese Medicine

Ding Luo

2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine

Qian Wu

2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine

Baile Ning

2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine

Ling Chen

2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine

Jianhua Liu

2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine

Wen-Bin Fu

2nd Clinical Hospital of Guangzhou University of Chinese Medicine: Guangdong Provincial Hospital of Traditional Chinese Medicine

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Study protocol

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Abstract

Background: Depression and Chronic musculoskeletal pain (CMSP) are the leading causes of global years lived with disability diseases. Moreover, they often commonly coexist, which made a great difficult to diagnosis and treatment. A safe and effective treatment was urgently need. Previous studies showed that acupuncture was a cost-effective treatment for simple depression or CMSP. But limited evidence showed that acupuncture was effective for depression comorbid CMSP.

Methods: This is a randomized, sham acupuncture-controlled trial with three arms: real acupuncture (RA), sham acupuncture (SA) and healthy control (HC). 48 depression combined CMSP participants and 12 healthy people will be recruited from GDTCM hospital and randomized 2:2:1 to RA, SA, HC group. The patients will receive RA or SA intervention for 8 weeks, and HC will not receive any intervention. Upon completion of the intervention, there is a 4 weeks follow-up. The primary outcome measures will be severity of depression and pain which assessed by Hamilton depression rating scale (HAMD-17) and brief pain inventory (BPI), respectively. The secondary outcome measures will be cognitive function, and quality of life which measured by Montreal cognitive assessment (MoCA), P300 and world health organization quality of life (WHOQOL-BREF). In addition, the correlation between brain derived neurotrophic factor (BDNF) and symptoms will also be determined.

Discussion: The aim of this study is to evaluate the clinic efficacy and underlying mechanism of acupuncture on depression comorbid CMSP. This study will provide a convenient and cost-effectively means for future prevention and treatment of combined depression and CMSP.

Trial registration: This study pre-registered at 2th Feb 2018, at Chinese Clinical Trail Registry (ChiCTR1800014754). The study is on the recruiting status.

Background

Chronic musculoskeletal pain (CMSP) and depression are the leading causes of global years lived with disability disease[1]. Moreover, CMSP and depression are highly intertwined and could exacerbate one another symptoms [2 3]. Unfortunately, the overlapping symptoms lead to poor physical functional outcomes, longer duration of symptoms and lower treatment response. This make profound burden for both people and society. Notably, this burden far exceeds social service capacity.

High prevalence of depression and CMSP comorbidity may foreshadow common pathogenesis. Both of depression and chronic pain are associated with cognitive function[4]. Growing studies showed that people who are suffer chronic pain and depression respectively has poor performance on cognitive function test[5 6]. And at the meanwhile, other studies found that cognitive function acts as a protective factor against the emergence of chronic pain. Brain derived neurotrophic factor (BDNF) is a member of neurotrophin family, which is crucial for survival and neuroplasticity of neurons. Decreased BDNF levels and increased BDNF methylation stat, especially in the promoter region of exon Ⅸand Ⅳ were identified in patients with

depression[7 8]. More interestingly,after anti-depressive treatment the BDNF methylation decreased, and serum BDNF level increased[9 10]. Some study demonstrated that serum BDNF levels were tightly correlated with the courses of depression[11]. Thus, some scientists consider BDNF and BDNF promoter methylation could be as a biomarker for depression[10 12–14].

Acupuncture has been widely used to improve chronic pain and depression[15–17]. But the research on depression comorbid chronic pain is rare. A random control trial of acupuncture or counselling compared with usual care for depression showed that acupuncture is a cost-effective treatment for depression patients with or without comorbid pain [18]. Even so, the evidence on the effect of acupuncture is not conclusive. Therefore, we proposed to conduct a pilot RCT of acupuncture on comorbid mild-moderate depression and CMSP. The objective of this study was to: (1) determine the clinical efficacy of acupuncture on comorbid mild-moderate depression and CMSP; (2) investigate the association between BDNF and comorbidity of depression and CMSP.

Methods

Study design

This project is a randomized controlled clinical trial with 3 groups: Real acupuncture (RA), Sham acupuncture (SA) and healthy control (HC) with a ratio of 2:2:1. This trial has been approved by the ethics committee of Guangdong Provincial Hospital of Chinese Medicine (Z2017-162-01). Before randomization, written informed consent will be obtained from all participants prior to their involvement. Primary and secondary outcome measures will be assessed at baseline, 4,8, and 12 weeks. Outcome assessors and statisticians will be blinded in this study. The overview of the trial was shown in Figure 1. This protocol was reported according to the Standard protocol items: recommendation for interventional trials (SPIRIT) statement requirements. The complete SPIRIT checklist was available in Additional file 1 and Figure 2).

Types of participants

In this trial we will recruit mild-moderate depression comorbid CMSP patients and healthy participants. The healthy participants need to meet the following criteria: no history of depressive disorder, the score of the 17-item Hamilton Depression Rating Scale (HAMD-17) < 8; no chronic pain in the past 3 months; no complications of severe systematic diseases such as diabetes mellitus, tumors or other considered not suitable to participate the trial. The mild-moderate depression comorbid CMSP patients need to meet the following criteria.

Inclusion criteria

Participants will include if they meet the following criteria:

1. Meet the criteria of DSM-5^{TM} and ICD-10 for the mild-moderate depression;

2. HAMD-17 £24 and ≥8.
3. Suffering chronic musculoskeletal pain (location at neck, back and limb) more than 3 months and VAS score ≥4;
4. Aged between 18 and 65;
5. No acupuncture therapy during the past 3 months before enrollment;
6. Voluntarily participating in this trial with a written informed consent form.

Exclusion criteria

Participants with the following conditions will be excluded:

1. Suicidal ideation or SCL-90 depression score >26;
2. Bipolar disorder or schizophrenia;
3. Malignant pain caused by cancer pain syndrome;
4. Severity pain, VAS ≥7;
5. Headache and visceral pain such as stomachache;
6. Pregnancy or breastfeeding women;
7. Complications of severe systematic diseases such as diabetes mellitus, tumors or other considered not suitable to participate the trial.

Sample size calculation

In this study, priori analysis was used to calculate the sample size. The score of HAMD-17 and BPI was separately used to calculate the sample size, and the larger one as chose. According to the two sample T test with α=0.05, 32 depression comorbid CMSP participants are required to achieve 80% power. Allowing for a dropout of 15% at end treatment time point, the recruitment goal of depression comorbid CMSP participant was 48 subjects□24 per group□. The HC participant was 12, with the ratio of 2:2:1, as previous. So total of 60 participants will be recruited.

Recruitment of participants

This trial will take place at the outpatient department of acupuncture and moxibustion, second affiliated hospital of Guangzhou University of Chinese Medicine, China. Outpatients will be recruited via posters in the hospital and via internet advertisement.

Randomization

All eligible depression comorbid CMSP participants will be randomly allocated to RA or SA, and the healthy participants will be directedly allocated to HC. The SPSS 22.0 software will be used to create the sequence of randomization. After that the random numbers will be contained in opaque sealed envelopes and assigned to the patients by the researcher JL.

Blinding

The participants, outcome assessors and statisticians will be blinded to treatment allocation. All participants will inform that have an equal opportunity of allocation to the RA group or SA group before enrolling. In addition, in order to reduce the bias during intervention period, participants will treat separately to prevent communication. All the treatment session will be performed by the trained and experienced acupuncturists. The acupuncturist will not provide any clues about the allocation information to the participants, assessors and statisticians.

Patient and Public Involvement

Patients and the public will not be directly involved in the design of the study and will not be involved in the conduct of the study. The intervention in the study will free for the participants. We will disseminate the main results to all the participants in the form or an accessible newsletter. Patient advisors were not used in the conduction of this study.

Intervention

The study interventions protocol was determined according to the classical principles of traditional Chinese medicine. All acupuncturists had at least 5 years of acupuncture experience. The participants will requested not take any other medications for pain or depression. If any, will need to document the pills and dosage. In addition, the HC participants will not receive any medical intervention, except receive blood measurement and P300 test at the baseline.

Real acupuncture treatment

Participants in the RA group will receive acupuncture at Baihui (DU20), Yintang (EX-HN3), Renzhong (DU27), Chenjiang (RN24), Hegu (LI4, bilateral) and Taichong(LR3, bilateral). After skin disinfection, sterile adhesive pads will be placed on the above points, and then needles (Hwato, Suzhou, China) will insert through the pad. DU20 and EX-HN3 point, needles will be obliquely inserted about16 mm deep, and DU27、RN24, L14, LR3 points, needles will vertically insert about 12 mm, 12mm, 25mm, 25mm, respectively. All these points will stimulate manually until patients feel heaviness, soreness, distension or numbness sensation (deqi), as reported in our previous study[15]. Each acupuncture session will be continued for 30 minutes and then removed with a disinfection swab. The acupuncture treatment will be administered twice per week, and total of 16 sessions during a period of 8 weeks.

Sham acupuncture treatment

Participants in the SA group will receive the same procedure as RA group but using non-insertion sham acupuncture. Briefly, after skin disinfection, sterile adhesive pads will be placed on the above points. However, the blunt、non-insertion sham acupuncture will used in this group.

Discontinuations

If participants are unable or unwilling to complete the treatment, we consider them as treatment drop-outs. If participants withdraw consent to receive the study intervention. If psychiatrist assessment that it is inappropriate to continue the study intervention due to, for instance, depression or pain condition persists or gets worse, even serious suicidal ideation, or a severe adverse event.

Outcome measures

Primary outcomes

The primary outcome are the changes in HAMD-17 and BPI scores from baseline to 12 weeks. The HAMD-17 is a 17-item self-report questionnaire, the higher the score, the more severe the depression. Previous study showed that HAMD-17 has good validity and reliability for the assessment of depression severity. The BPI was firstly developed to measure the pain for cancer patients, but now it was become one of the most widely used pain measures, such as musculoskeletal pain, post-surgery pain[19 20]. The BPI is a 15-item inventory, contain 2 dimensions: the intensity of the pain and the interference with everyday activities. All the item is measured using numerical rating scale from 0 to 10. The higher score, the more severe pain.

Secondary outcomes

Secondary outcomes include the Beijing version of MoCA (MoCA), the World Health Organization Quality of Life BREF (WHOQOL-BREF), event related potential (P300), and the serum level of BDNF, DNA methylation of BDNF. The Beijing version MoCA is highly recommended as a clinical and research tool for evaluating the cognitive impairment. Previous studies proved that B-MoCA has a reliability of 0.73 Cronbach's alpha in patients with obstructive sleep apnea hypopnea syndrome with cognitive impairment[21]. The total score of MoCA is 30 points, less of 26 points is considered cognitive impairment. In addition, P300 will be used as objective indices to measure the cognitive impairment, since it based on the electrophysiological response of the brain. Previous studies showed that decrease of amplitude and increase of latency in depression patients[22]. The WHOQOL-BREF is an abbreviated version of WHOQOL-100, which contain 26 items. In this trial, the official Chinese version WHOQOL-BREF, which has approved by WHOQOL Group[23], will be used to evaluate the changes in quality of life. BDNF is a biomarker for depression patients[14 24]. All depression and CMSP participants will receive blood measurement and P300 test at baseline and 8 weeks. ELISA, RT-PCR and BSP will be applied to measure the serum BDNA level, and BDNF DNA methylation. The correlation between BDNF and symptoms will be determined.

Incidence of adverse events

Acupuncturist will be requested to report and record any acupuncture related adverse events (AEs) , such as local bleeding, hematoma, fainting, local infection, unbearable prickling, or other discomfort after treatment. Severe AEs will be reported to the Research Ethics Committee in 24 hours, which will provide medical advice to the research team and latter will evaluate whether the participant continue the trial.

Data management

All Case Report Forms (CRF) will be stored in a locked cabinet. The consent forms will be stored separately from the CRF. Data from CRFs will be entered and locked by 2 data managers, and only authorized researcher have access permission.

Statistical analysis of the trial outcomes

Outcome data will be analyzed according to the intention-to-treat principle, with all randomly assigned participants after baseline assessment regardless of received intervention or not. Missing data will be replaced by the data from the latest assessment. The outcome data will be analyzed with SPSS (version 22.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics (T- test, non-parametric test, Chi square test) will be used to summaries demographic features between the two groups. The HAMD-17, BPI, MoCA and WHOQOL-BREF will be analyzed using repeated measures method and post hoc comparison will be evaluated with Bonferroni test. The P300, blood measures will be analyzed by paired T test.

Discussion

Depression and CMSP are common coexist, which made a great difficulty for clinic treatment[25]. Despite huge costs, current pharmacological and psychological interventions have limited acceptability and effectiveness. Thus, patients are keen to a cost-effective treatment. According to the American college of physicians, acupuncture increased response for the second generation antidepressants[26]. Previous studies also showed that acupuncture has clinical efficacy on depression and related symptoms, such as insomnia[15 17 18]. A systematic review showed that acupuncture is cost-effective treatment for chronic pain[27]. Weather acupuncture has clinical efficacy on combined of depression and CMSP is uncertain. On this basis we designed this study, which meets CONSORT guidelines [28]. This trial will provide evidence for the clinic efficacy of acupuncture as potential treatment for comorbid depression and CMSP. In addition, we will explore the mechanism of acupuncture's anti-depression and analgesic effect from the point view of epigenetic.

Even so, there are some limitations in this study. First, it is a one-blind study, which may cause partial bias on the results. We will try our best to overcome this bias by dividing the different group in different place to accept treatment. Second, the adherence of participants may be poor since the treatment lasted 8 weeks. The study size is calculated on the hypothesis of loss rat at 15%, but it will be necessary to ascertain that no bias between the two-intervention group. Thirdly, in this study we made 4 weeks follow up, long term follow up will be more credible. Finally, there will be a skewed sex ratio in this study, since in the traditional Chinese culture, men are unwilling to seek help, especially in mental disease. It was also existed in our previous study.

we have presented the design and protocol for the clinical efficacy of acupuncture on mild-moderate depression comorbid with CMSP. Completion this study will confirm the clinic efficacy of acupuncture, and its underlying mechanism.

Abbreviations

CMSP
Chronic musculoskeletal pain BDNF:Brain Derived Neurotrophic Factor
RA
Real Acupuncture SA:Sham Acupuncture HC:Healthy Control
MoCA
Montreal Cognitive Assessment HAMD:Hamilton Depression Rating Scale BPI:Brief Pain Inventory
CRF:Case Report Forms
WHOQOL
World Health Organization Quality of Life

Declarations

Trial status

Protocol version 20170002/20171120. Recruitment started In February 2018 and it is ongoing. It is expected to end approximately on 30 November 2021.

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Availability of data and materials

Not applicable.

Authors’ contributions

SL is the principal investigator and developed the original idea for this study. JHL and WBF participated in the design of the study. JL, JPH and QW registered the protocol in Chinese clinical trial registry. DL, BLN and LC developed the statistical plan. All authors have read and approved the final manuscript version.

Competing interests

The authors declare that they have no competing interests.

Consents for publication

Not applicable.

Availability of data and materials

The authors declare that the data supporting the finds of this study are available within the article.

Dissemination

The study will be conducted and reported according to the CONSORT statement. Results will be disseminated both through community groups and peer-reviewed scientific literature.

Ethics approval and consent to participate

All procedures are approved by the ethics committee of Guangdong Provincial Hospital of Chinese Medicine (Z2017-162-01). Written informed consent will be obtained from all participants prior to their involvement. The researcher JL and JPH will responsible for ensuring that the patient completely understands the potential risks and benefits of participating in the study, and also will answer any questions relevant study.

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Figures

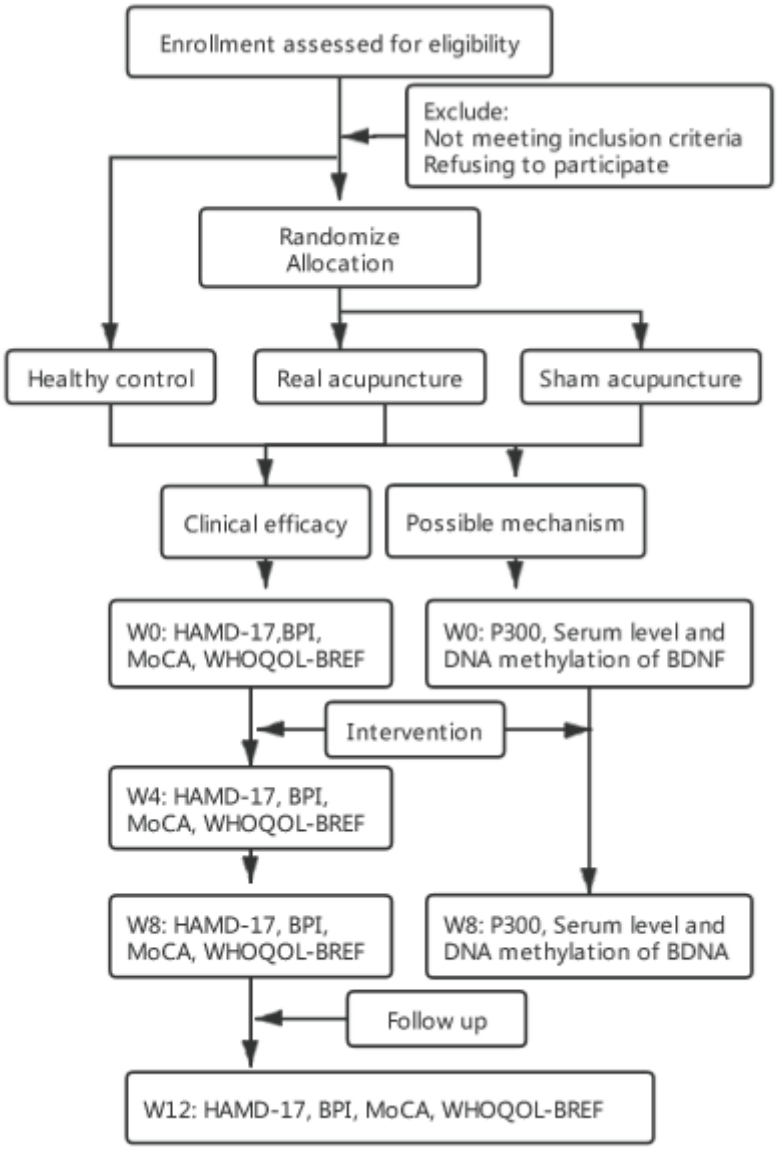

Figure 1

Flowchart of trial procedures.

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		
			Treatment		Follow-up
TIMEPOINT**	***Week -1***	**Week 0**	***Week 4***	***Week 8***	***Week 12***
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Recruitment form	X				
Allocation		X			
INTERVENTIONS:					
Real acupuncture		X	←	→	
Sham acupuncture		X	←	→	
Healthy control		X			
ASSESSMENTS:					
HAMD-17		X	X	X	X
BPI		X	X	X	X
MoCA		X	X	X	X
WHOQOL-BREF		X	X	X	X
P300		X		X	
Blood measures		X		X	
Adverse events			X	X	

Figure 2

SPIRIT figure

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- completedSPIRITchecklist1.docx