Acupuncture Treatment for Knee Osteoarthritis With Sensitive Acupoints and Tender Points (A multicenter randomized controlled trial)

ClinicalTrials.gov identifier: NCT03299439

STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

West China Hospital of Sichuan University

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1. Background

Knee osteoarthritis (KOA), the most common form of osteoarthritis, resulting in significant mobility limitations and a substantial socioeconomic burden[1]. International recommendations for management of KOA follows a stepwise approach that starts with conservative non-drug treatment (i.e., education and exercise), medications (i.e., nonsteroidal anti-inflammatory drugs (NSAIDs)) and ends with joint replacement surgery[2-4]. Given the potential side effects of long-term pharmacological therapy and the increasing economic burden of knee surgery[5-7], complementary and alternative treatments are frequently used in clinical practice[8]. Acupuncture is the most popular complementary and alternative treatments, with increasing use over time[9]. Up to 1.5% of the US population has received acupuncture for chronic pain[10].

Previous studies have found that certain acupoints or ashi points within the medial regions of knee in patients with KOA were sensitized, particularly presenting as pain[11]. A previous trial showed that acupuncture at pain-sensitized points could achieve a superior effect in relieving muscle pain compared against non-sensitized points[12]. The pressure pain threshold (PPT) is a valid and reliable measure of quantifiable localized pain, reflecting the magnitude of pain sensitivity[13]. Hence, a hypothesis can be generated that KOA patients receiving higher-sensitized (lower PPT) points acupuncture can be more effective in treating pain and dysfunction, but little evidence is available to support this hypothesis.

2. Study Aims

We will conduct a randomized controlled trial (RCT) to examine whether acupuncture at acupoints with higher pain sensitivity (lower PPT) was more efficacious than lower pain sensitivity (higher PPT).

3. Study Methods

3.1 Study design

A three-arm, parallel, 16-week, multi-center RCT will be conducted at the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, West China Hospital of Sichuan University, the Third Affiliated Hospital of Henan University of Traditional Chinese Medicine, and Wuhan Integrated Traditional Chinese Medicine and Western

Medicine Hospital, all of which are teaching and tertiary hospitals. Participants will be recruited from the outpatient departments of Acupuncture and Moxibustion, Integrated Chinese-Western Medicine and Rehabilitation Medicine. Patient enrolment started late October 2017 and is expected to end in December 2019. Eligible and consented patients will be randomly assigned to three groups through central randomization in a ratio of 1:1:1 (Figure 1).

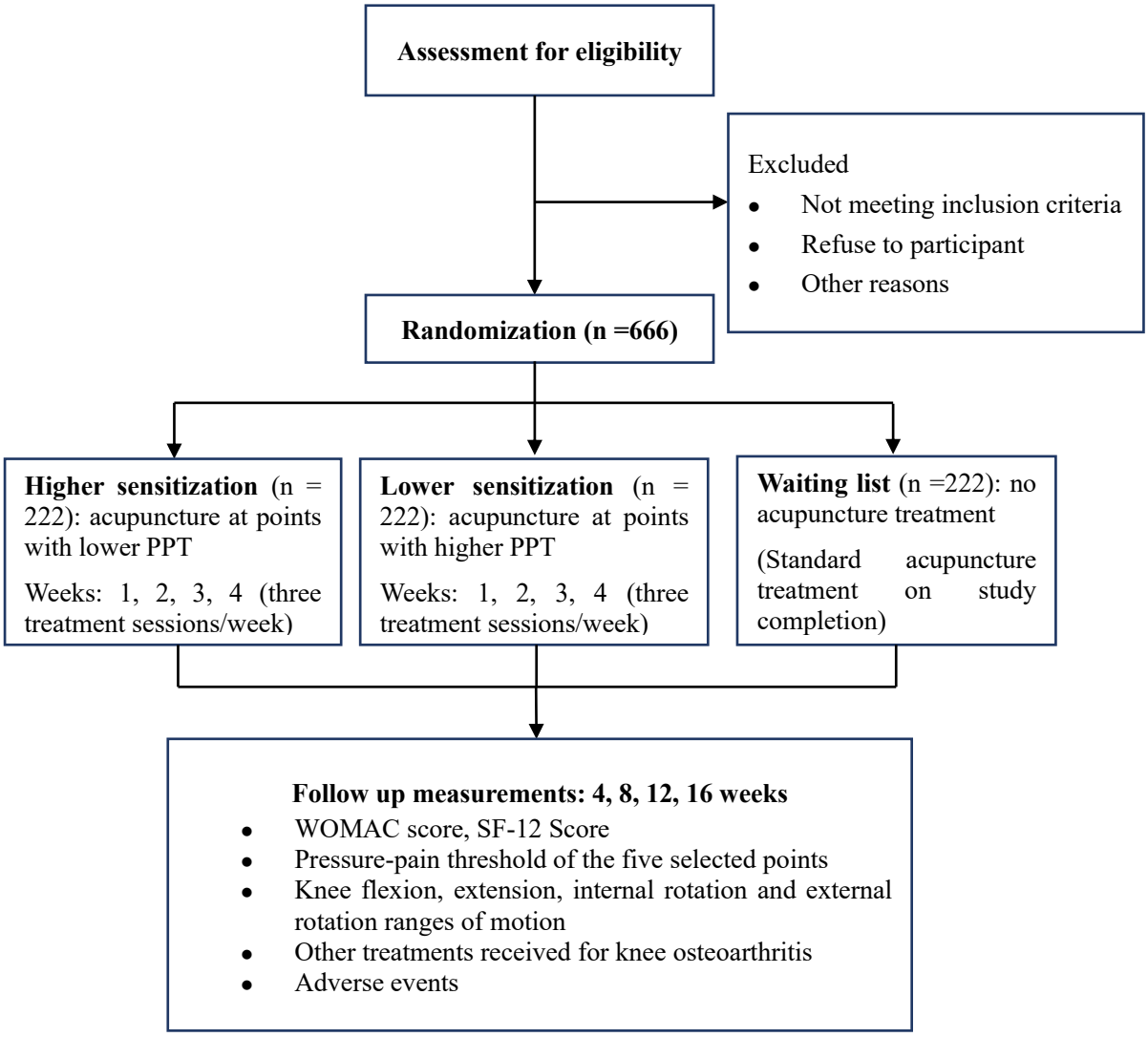

Figure 1 Trial design

3.2 Participants

Potentially eligible patients will be screened by the research physicians and research staff through physical examination and clinical tests. Patients will be informed of the aims and nature of the research both verbally and via an information sheet. They will be requested to complete and sign a consent form before enrollment. Patients information will remain confidential and they will have the right to withdraw without

prejudice at any time.

Inclusion criteria

Participants aged 40 years or older and diagnosed with mild or moderate KOA are eligible to participate in the study. The diagnostic criteria were followed the Chinese Guideline for the Medical Management of KOA[14]:

1) refractory knee pain for most days in the last month;
2) joint space narrowing, sclerosis or cystic change in subchondral bone (as demonstrated by X-ray);
3) laboratory examinations of arthritis: clear and viscous synovial fluid (≥2 times) and white blood cell count < 2000/mm^3;
4) aged 40 years or older;
5) morning stiffness continues less than 30 minutes;
6) bone sound exists when joints was taking flexion and/or extension.

If a patient meets the following combination of criteria (1 and 2), (1, 3, 5, and 6), or (1, 4, 5 and 6), a diagnosis of KOA is confirmed.

Exclusion criteria

Participants with any of the following conditions will be excluded:

1) diagnosed with conditions leading to skeletal disorders, such as tuberculosis, tumors or rheumatism of the knee joint and rheumatoid arthritis;
2) present with sprain or trauma in the lower limb;
3) unable to walk properly due to foot deformity or pain;
4) cannot answer the questionnaire due to mental disorders and/or intellectual disability;
5) present with comorbidities including severe cardiovascular disease, liver or kidney impairment, immunodeficiency, diabetes mellitus, blood disorder or skin disease;
6) females who are pregnant or lactating;
7) are using or have used physiotherapy treatments for osteoarthritis knee pain in the past month;
8) have used intra-articular injection of glucocorticoid or viscosupplementation in the past six months;
9) received knee-replacement surgery on the affected side(s);

10) diagnosed with severe (stage 4, according to Kellgren and Lawrence radiographic classification) or late clinical stage of KOA;
11) have a swollen knee or positive result of floating patella test;
12) are participating in the other clinical trials of acupuncture.

3.3 Recruitment and strategy

Each PI and other investigator will recruit subjects from her/his individual practice as well as faculty/resident continuity clinic. Flyers will be posted in the medical center and local clinics or other public places where allowed.

3.4 Randomization

Eligible patients who consent to participate will be randomly assigned to a higher sensitization group (patients receive acupuncture at acupoints with lower PPT), a lower sensitization group (patients receive acupuncture at acupoints with higher PPT) or a waiting-list group (no acupuncture) via a central randomization system for clinical research using 1:1:1 ratio. Randomization will be stratified by participating site in block sizes of 3 or 6. The study coordinator at each site will ensure that the informed consent form has been obtained from each participant prior to randomization. He/she will then log onto the central randomization system using a password-protected account and enter inclusion and exclusion criteria to ensure eligibility before entering the patient's name, identification card number to generate a random sequence.

3.5 Blinding

Patients in higher sensitization group and lower sensitization group will be blinded to acupuncture treatment, and were required not to release their treatment information to outcome assessors during the study. Study investigators, acupuncturists will be aware of the treatment allocation. Outcome assessors and data analysts will be blinded and participants will be asked not to reveal their allocation to assessors.

3.6 Identification, measurement and selection of acupoints for acupuncture

Identification of acupoints

Based on literature and expert consensus, we identified 13 candidate acupoints, namely Heding (EX-LE2), Neixiyan (EX-LE4), Dubi (ST35), Xuehai (SP10), Liangqiu (ST34), Yinlingquan (SP9), Yanglingquan GB34), Zusanli (ST36), Weizhong (BL40), Yingu

(KI10), Xiguan (LR7), Ququan (LR8), Weiyang (BL39).

We will also identify candidate ashi points using pre-specified approach. The front and back of the knee regions of each participant are divided into a total of 12 testing zones (Figure 2). The surface marking methods are as follows: (1) draw a line horizontally three body inches (cun) above the patella (the upper boundary of the testing zones); (2) draw a line horizontally across Zusanli (ST36) (the lower boundary of the testing zones); (3) draw two lines which horizontally trisect the area between the upper and lower boundaries; (4) in the front region, draw two lines vertically across the top corners of the basis patellae respectively; (5) in the back region, draw two lines which vertically trisect the popliteal area.

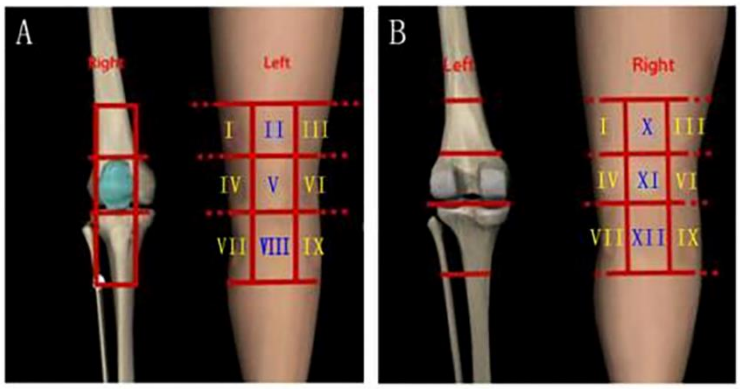

Figure 2 The front and back testing zones of the knee region

Ashi points in the testing areas will be identified when the participant reports the pain sensation while acupuncturist pressing vertically downward about 6~10 millimeter (mm) at an even speed with the thumb.

Measurement of PPT of acupoints

The electronic von Frey detector (2390 series, IITC Inc. Life Science) will be used by trained acupuncturists to measure the PPT of selected acupoints and ashi points. The acupuncturist moves the probe tip vertically downward the skin at an even speed. He/she will remove the probe immediately once the patient feels the pain. The data revealed by the detector (reported as numbers) will then be recorded as the PPT. Each point will be tested two times at an interval of two minutes. If the difference of two data values is larger than 15, the point will be measured for the third time. The average of the two values with the smallest difference will be taken as the final threshold.

Selection of acupoints for interventions

All points will be ranked based on PPT. The five points with the lowest PPT are identified as the higher sensitive points, whereas the five points with the highest PPT are selected as the lower sensitive points.

3.7 Interventions

The acupuncturists were specialists in traditional Chinese medicine and received specialized training in the acupuncture protocols prior to the start of the study. Acupuncture was performed by an acupuncturist who did not participate in identification and measurement of acupoints.

Participants in the higher sensitization group receive acupuncture treatment at the five higher sensitive (lowest PPT) points. Sterile, single-use filiform acupuncture needles (Hwato Needles, Sino-foreign Joint Venture Suzhou Hwato Medical Instruments Co., China) with a length of 40 mm and a diameter of 0.30 mm will be inserted to a depth of 15-30mm in acupoints. The insertion will be followed by stimulation performed with lifting and thrusting combined with twirling and rotating the needles sheath in order to produce the sensation known as achieve "*Deqi"*. The needles placed in the acupoints will be manually stimulated every 15 minutes and removed after 30 minutes. Participants receive three treatment sessions per week (every other day) for four consecutive weeks.

Participants in the lower sensitization group receive acupuncture treatment at the five lower sensitive (higher PPT) points. All other treatment settings will be the same as in the higher sensitization group.

In the higher and lower sensitization groups, the intervention will be performed on the affected side for patients with unilateral KOA, whereas bilateral KOA patients will have their most painful side treated and assessed. Furthermore, the non-trial affected lower limbs will receive standard acupuncture treatment on DUBI (ST35), NEIXIYAN (EX-LE4), YANGLINGQUAN GB34), ZUSANLI (ST36) and XUEHAI (SP10).

Patients in the waiting-list group will not receive any acupuncture during the study. For

the ethnic consideration, we will offer free, non-study standard acupuncture treatment at the following traditional acupoints after the study is completed: DUBI (ST35), NEIXIYAN (EX-LE4), YANGLINGQUAN GB34), ZUSANLI (ST36) and XUEHAI (SP10).

3.8 Basic treatment

All the participants will be advised not to take any other treatments for KOA. NSAIDs are allowed if patients have intolerable pain and the outcome assessment is not scheduled in the next 48 hours. In addition, non-acupuncture treatments, such as application of medicinal liquor on the knee, heat therapy using the Teding Diancibo Pu (TDP) device, massage and moxibustion, are allowed if patients in the waiting-list group request treatment during the study period. Patients will be asked to document all such treatments (including the name, dosage/frequency and duration of treatment) receiving for KOA.

3.9 Follow up

The pain, stiffness and physical function of the knee joint, quality of life, and knee ranges of motion (ROMs) of all the participants, as well as pressure-pain threshold of the points and the safety of treatment of patients in the higher and lower sensitization groups will be measured at follow ups at 4, 8, 12 and 16 weeks after randomization.

The following measures will be taken to optimize the retention of participants: free acupuncture treatments for other diseases provided they do not affect the treatment of KOA; text messages and phone calls to remind the participants about the impending appointments; flexibility in making appointment to suit the participants' schedule; in addition to contact details of the participants, phone numbers of close family members will also be recorded upon permission to facilitate tracking.

The outcome assessments will be performed by nurses or completed by patients in a separate space at the outpatient department of each participating site. All of the outcome assessors will be trained on conducting interviews and performing measurements before the study begins and will follow a standard protocol. The schedule of measurements is present in Table 1.

Table 1 Measurements to be taken at each point in trial

TIMEPOINT	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Post-allocation
	-1 week (-7~0 day)	Day 0	4 weeks (±3 days)	8 weeks (±3 days)	12 weeks (±3 days)	16 weeks (±3 days)
ENROLMENT						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS						
High sensitization group			X			
Low/non-sensitization group			X			
Waiting-list group			X			
ASSESSMENTS						
X-ray examination of the knee joint	X					
Measurement of sensitization intensity	X					
Measurement of PPT of the five selected points			X	X	X	X
WOMAC[a] score	X		X	X	X	X
SF-12[b] score	X		X	X	X	X
Knee ranges of motion	X		X	X	X	X
Adverse events						
Other treatments received for knee osteoarthritis						

X=Measurements to be taken at this point

[a] Western Ontario and McMaster Universities Osteoarthritis index

[b] Short Form-12 health survey

3.10 Drop outs

Patients who withdraw from the trial for any reason will be considered a drop out. The common reasons for dropping out including AEs, poor compliance with the protocol, unsatisfied efficacy, withdraw and quit, and others. Investigators should complete the case report form (CRF) and record the reason for dropping out.

3.11 Outcomes

Primary outcome

The primary outcome is the change of Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) total score from baseline to 16 weeks. The Chinese version of WOMAC will be used. It consists of 24 items assessing the KOA patients' pain (5 items), stiffness (2 items), and physical function (17 items). Each of the 24 items will be graded on a visual analog scale ranging from 0 to 10, with higher scores reflecting more pain, stiffness and poorer physical function. The score ranges for the pain, stiffness and physical function subscale are, respectively, 0-50, 0-20 and 0-170, resulting in a total range of 0-240. Each WOMAC item is rated on a Visual Analogue Scale (VAS) of 0 to 10, with a high score indicating a worse symptom.

Secondary outcomes

The secondary study outcomes are: (i) the change of Short Form (SF)-12 health survey score from baseline to 16 weeks, (ii) the changes of knee ranges of motion (ROMs) from baseline to 4 and 16 weeks, and (iii) the changes of PPT of the five selected points from baseline to 4 and 16 weeks.

The validated Chinese version of SF-12 includes 12 items: 2 items on physical functioning, 2 items on role limitations because of physical health problems, 1 item on bodily pain, 1 item on general health perceptions, 1 item on vitality (energy/fatigue), 1 item on social functioning, 2 items on role limitations because of emotional problems, and 2 items on general mental health (psychological distress and psychological well-being). The knee ROMs will be assessed both actively and passively by using a standard goniometer. It will include flexion, extension, internal rotation and external rotation. The PPT of the five selected acupuncture points will be measured using the electronic von Frey detector.

Assessment of safety

All unfavorable or unintended events affecting patients in the study, such as bleeding, bruising and/or soreness at the needle sites (assessment taken immediately after acupuncture by acupuncturists' and patients' report) and elevated blood pressure (standard measurement at each follow up), will be recorded during the study.

3.12 Monitoring

We will develop an independent Data Monitoring Committee (DMC), responsible for

the monitoring for quality and regulatory compliance of the trial, as well as ensuring the safety of participating patients. The DMC will consist of five members with expertise in acupuncture, trial methodology, and biostatistics (Table 2). Two DMC regular meetings will be held during this study. We will develop a procedural document for the DMC meeting, and strictly follow the document.

Table 2 DMC members

Name	Role on IDMC	Affiliation
Chen Yao, Professor	Chair of DMC voting member	Peking University First Hospital and Peking University Clinical Research Institute
Zhaoxiang Bian, Professor	Voting member	Chinese Medicine Clinical Study Center, School of Chinese Medicine, Hong Kong Baptist University
Hongcai Shang, Professor	Voting member	Key Laboratory of Chinese Internal Medicine of the Ministry of Education, Dongzhimen Hospital, Beijing University of Chinese Medicine
Honglai Zhang, Professor	Voting member	Guangzhou University of Chinese Medicine
Deying Kang, Professor	Voting member	Clinical Epidemiology and Evidence-based Medicine Research Center, West China Hospital, Sichuan University

3.13 Data Management

This study will use electronic Data Capturing (EDC) system for centralized data management.

Complete and upload case Report Form (CRF)

- The CRF should be completed by the investigator or an authorized person, and they must be read carefully before completing the CRF.
- Input the data of the CRF into the EDC system on the day of each visit, so that the general leader, the head of each center and the data manager can timely understand the progress of the study and the data collection situation.

Data review and modification

The data auditor will check the data in the EDC system, and the missing and wrong data will be returned to the investigator in time for verification, and the data will be re-

uploaded after supplement or modification. The data auditor rechecks whether the supplementary or modified data are correct. Repeat until all corrections are added or corrected.

The data review process is as follows: the investigator of each center initially review the uploaded data, and then the general coordinator reviews all uploaded data and completes the final review of all data; the another investigator of each center is required to manually compare a certain number (10%) of CRFs randomly selected from time to time with the data in the EDC system to ensure that the data in the database are consistent with the data in the original record form.

Data locking

After confirming the correctness of the data in the EDC system, a researcher from Chinese Evidence-based Medicine Center, West China Hospital, Sichuan University will lock the data. Locked data files cannot be modified. Problems found after data locking can be corrected in the statistical analysis after confirmation.

3.14 Statistical analysis plan

Sample Size

Our primary study hypothesis is that acupuncture on higher sensitive points would achieve more reduction in the total WOMAC score than acupuncture on lower sensitive points or waiting list group.

The sample size calculation was based on the mean difference of WOMAC total score changes from baseline to 16 weeks according to the pilot trial[15]. The following assumptions were made to calculate the sample size: a mean difference of 12 between the higher and lower sensitization groups, standard deviation of total score of 33, a two-sided significance level of 0.025 (adjusted for multiple testing), and a power of 0.9. With these assumptions, a sample size 189 patients per arm is required. This sample size would provide adequate power to detect the difference between high-sensitization group versus waiting list group, on the ground that the treatment effect between higher sensitization group and lower sensitization group would be smaller than that between higher sensitization group and waiting list group. To allow for a loss to follow up of 15%, a minimum sample size of 666 patients (222 patients per arm) at baseline was

required.

Statistical analysis

We will descriptively summarize patient characteristics, medical characteristics, outcome variables and the adverse events.

The primary analyses will examine if acupuncture at higher sensitive points will achieve statistically better treatment outcomes than acupuncture at lower sensitive points and waiting list group, respectively. To accommodate the correlation of repeated measures from the same participant and the nesting of observations within research sites, mixed-effect linear models with random effects (participants and research sites) will be fitted to assess the intervention effect on outcome variables over time, while accounting for the effects of potential confounders (e.g. baseline WOMAC total score, age, gender, BMI). We will also examine, in an exploratory analysis, if acupuncture at lower sensitization would achieve statistically better outcomes than waiting list.

The outcome analyses will be performed both on the intention-to-treat population, which includes all patients randomized, and on the per-protocol population, which includes eligible patients who adhere to the planned treatment and follow ups. We will use the multiple imputed or last value carried forward method to impute missing data for the primary and secondary outcomes.

We will also conduct subgroup analyses according to the following pre-specified baseline variables: BMI (<18.5 vs.18.5-23.9 vs. ≥ 24 kg/m^2), type of KOA (single vs. bilateral KOA), stage of KOA according to X-ray imaging, and duration of disease.

P values less than 0.05 will be considered significant and tests were 2-sided. All analyses will be implemented using R software.

4. Ethical Requirements and Registration

Ethics approval has been granted by the Bioethics Subcommittee of West China Hospital, Sichuan University: 2017(Number 228). The trial was registered in ClinicalTrials.gov with approval number NCT03299439.

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