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# **The KeyPlan of Zhejiang Province Traditional Chinese Medicine Prevention and Treatment of Major Diseases**

**Number: 2018ZY008**

**Research name:**

**Different kinds of acupuncture treatments for Knee  
Osteoarthritis: a Multi-center Randomized controlled  
trial**

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## **The Study Protocol of the project**

### **Different kinds of acupuncture treatments for Knee Osteoarthritis: a Multi-center Randomized controlled trial**

#### **Research objectives**

(1)The study aims to exam different kinds of acupuncture treatment for treating knee osteoarthritis (KOA), compared with the effective drug control group respectively, and confirm the efficacy of different acupuncture treatments of KOA, and further a safe, effective and easily-spread therapy for KOA.

(2)To observe and compare the effects between groups of different acupuncture treatment: acupuncture group, moxibustion group and warm-needling group, and make clear whether the moxibustion play a key role in the acupuncture treatment for KOA.

(3) To compare the effects of acupuncture group and sham-needle group and make clear whether acupuncture is effective in KOA treatment.

(4) To compare the effects of electro-acupuncture group and the warm-needling group, to explore whether there are different clinical effects of electric stimulation and warm stimulation in acupuncture treatment of KOA.

#### **Research Methods**

##### **Participants**

###### **1. Case source**

360 patients with knee osteoarthritis are planned to be recruited from May 2018 to December 2021 in the following six hospitals: Jiaxing TCM Hospital, The Third Affiliated Hospital of Zhejiang Chinese Medical University, Zhejiang provincial Hospital of TCM, Zhejiang Hospital, Hangzhou Red Cross Hospital ,Zhejiang Provincial Tongde Hospital.

**2. Diagnostic criteria:** The diagnostic criteria of KOA in western medicine refers to the diagnostic criteria of American College of Rheumatology (ACR)<sup>[1]</sup> and Kellgren-Lawrence Classification<sup>[2]</sup>; and the TCM diagnostic criteria refers to the Diagnostic efficacy of TCM syndrome<sup>[3]</sup>.

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1)The diagnostic criteria of western medicine: Meet the KOA diagnostic criteria, in I-III level of K-L classification.

According to the American College of Rheumatology (ACR) KOA diagnostic criteria:

- (1)Have knee pain of most days in a month;
- (2) There is a noise in the joint activity;
- (3)Morning knee stiffness lasting less than 30 minutes;
- (4)Over 38 years old;
- (5)Bony swelling and snapping sound of the knee joint;
- (6)Bony swelling and no snapping sound of the knee joint.

**At least 1-4 or 1, 2, 3, 5 or 1 and 6 can be diagnosed.**

The grade of knee osteoarthritis was graded, and the grading evaluation criteria of Kellyon-Lawrence (K-L) was adopted (level 5).

0:Normal;

I:Doubtful joint space narrow, possible osteophytes ;

II :Definite osteophytes, possible joint space narrow or normal;

III:Moderate osteophytes, definite joint space narrow, some sclerosis of subchondral bone , possible deformity;

IV:Large osteophytes, marked joint space narrow, severe sclerosis of subchondral bone, definite deformity.

2)The diagnostic criteria of TCM :

(1)For the first time, there was dull pain in the knee joint , with unfavorable flexion and extension of the knee joint; Knee pain released slightly by mild activity, and aggravated when the climate changes, and repeated lingering.

(2)The onset of the disease is slow, often among the middle aged or elderly;

(3)The joints can be mildly swollen, the joints have the kala or the frictions tone during the activity, and the severe ones can see the muscular atrophy and joint deformity;

(4)X-ray examination showed osteoporosis, irregular joint surfaces, narrow joint space, subchondral bone sclerosis, and lip-shaped hyperplasia, osteophyte formation;

(5)Check ESR, anti-chain "O", rheumatoid factors and more to identify with

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rheumatism and rheumatoid arthritis.

### **References:**

- [1] Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of non-pharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip and knee[J].Arthritis Care Res,2012,64 ( 4) : 465-474.
- [2] Kohn MD, Sasso AA, Fernando ND et al., Classifications in Brief Kellgren-Lawrence Classification of Osteoarthritis. Clin Orthop Relat Res, 2016. 474: p. 1886-1893.
- [3] State administration of traditional Chinese medicine. Diagnostic efficacy of TCM syndrome[M]. Nanjing: Nanjing university press, 1994:48-64.

### **3.Inclusion criteria**

- 1)Aged 40-75 years old;
- 2) History of knee pain for more than 3 months, and complain of knee pain on most days of the past month;
- 3) I-III level in K-L classification;
- 4)At visit an average knee pain severity of 4 point or more on an 10-point VAS;
- 5)Volunteer for this test and sign informed consent.

### **4.Exclusion criteria**

- 1) Knee osteoarthritis patients with history of gout, infection, tumor, autoimmune diseases, trauma or other causes of knee pain or knee deformities;
- 2)Patients who have local skin damage, poor skin conditions or coagulant dysfunction and patients who are not suitable for acupuncture;
- 3)Patients who are accompanied with serious medical problems, mental or shallow sensation disorder disorders, cognitive dysfunction or shallow sensation disorder who cannot cooperate with the treatment;
- 4)Patients who have received acupuncture or needle knife in the past month;
- 5)Other patients who are not suitable for acupuncture treatment.

### **5.Off standard**

- 1)The patient did not follow this test, quit or lost his visit;
- 2)Severe adverse reactions or adverse events occurred during treatment.

### **6.Withdrawal criteria**

- 1)A diagnostic physician at each center assessed the KOA exacerbations that occurred during the study. When a patient develops knee pain that cannot be alleviated by

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acupuncture (based on VAS score > 8 points), the physician evaluates the severity and discontinues the study;

2) Onset of serious adverse events such as severe infection, coma, shock, death, etc., the main investigator should be reported immediately and the study should be suspended immediately.

## **7. Clinical Ethics and Clinical Trial Registration**

The study follows the “Helsinki Declaration” and other relevant regulations, the clinical study was carried out after approved by the Central Ethics Committee. Before each subject was enrolled in the study, it was the investigator's responsibility to provide the subject or his agent with a complete and comprehensive introduction of the purpose, procedure, and potential risks of the study, and to sign an informed consent form so that the subject knowing that they have the right to withdraw from this study at any time, informed consent should be retained as a clinical research document. Before collecting the first case, the central ethics approval was completed and the clinical trial registration was completed.

## **Analysis methods**

### **1. Sample size estimation**

Sample size estimation was by using PASS(version 11.0) software. According to document analysis and trial test, the WOMAC joint function scores could change by  $13.0 \pm 5.6$  after treatment of positive drug control group.(Qilin Liu. Observation on clinical effect of KOA by needling with moxibustion[J]. TCM clinic Research,2016,8(09):108-109.), while needling group changed by  $8.8 \pm 3.7$ (Acupuncture for Chronic Knee Pain A Randomized Clinical Trial), EA group changed by  $8.9 \pm 4.0$ (trial test), Moxibustion group changed by  $10 \pm 4.7$ (trial test), Warm needling group changed by  $12.0 \pm 6.1$ (Jianbo Wang, Yanlin Wang, Yongqi Lu, Yaochi Wu. Effect analysis of KOA by needling with moxibustion[J]. Shanghai acupuncture magazine,2010,29(06):390-392.), Sham acupuncture group changed by  $5.8 \pm 3.0$ (Acupuncture for Chronic Knee Pain A Randomized Clinical Trial). In the condition of  $\alpha=0.05$ , the power of test was  $1-\beta=0.9$  and the six groups were distributed according to 1:1:1:1:1:1 ratio, and the sample amount is at least 42. The sample size is to be expanded by estimated 20% dropout rate, and finally, there are at least 53

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patients in each group. In view of the equality of the distribution of all cases in six centers, there were a total of 360 cases with 60 patients in each group. The following equation was used:

$$n = \psi^2 \left[ \sum_{i=1}^k s_i^2 / k \right] / \left[ \sum_{i=1}^k (\bar{X}_i - \bar{X})^2 / (k-1) \right]$$

## 2. Random allocation

The block randomization is operated by the central randomization system (by telephone and online). When the subjects met inclusion exclusion criteria of the study, The randomization of the central random system is conducted by assigned personnel or clinical investigators of each center. The randomization scheme of this study is produced by the Clinical Evaluation and Analysis Center of Zhejiang Provincial Hospital of TCM which is not involved in the statistical analysis of this project . The randomization scheme of this study and The parameters set during the process of the program are called the bottom of the blind, which is generated by the random scheme personnel to sign and seal, and taken care of by the specialized personnel not involved in the project of the Clinical Evaluation and Analysis Center of Zhejiang Provincial Hospital of TCM. The central random system has strict personnel authority, and other than the highest level system management staff, no one has access to the random scheme in the central random system.

## 3. Design and implementation of blind method

The blind(patient-blind) design is adopted in this program, and the patients are evaluated by blind method. Index evaluation and data recording, treatment operator and statistician are all separated. The random member and the therapist know the grouping; The curative evaluators and the statisticians were not aware of the grouping.

## 4. Interventions

The six groups of participants (except for western medicine group) will be treated with different kinds of acupuncture treatment. **The unified needle** is the single-use, sterile steel, size 0.30×25mm or 0.30×40mm needle(Huatuo brand disposable acupuncture needle, Suzhou Medical Co., Jiangsu, China),it will be used in Ordinary acupuncture group,

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electro-acupuncture group and Warm-needling acupuncture group; **The unified moxa** is the 2cm Yufu brand Qing Ai(Jiangsu Kangmei Pharmaceutical Co. Ltd. Jiangsu, China,Z32020253 ),it will be used in Mild moxibustion group and Warm-needling acupuncture group; **The unified Electro-acupuncture apparatuses** is the Huatuo SDZ-IIB electro-acupuncture apparatus(Jiangsu Suzhou Medical Supplies Factory LTD. Jiangsu China ),it will be used in electro-acupuncture group; **The unified Leather measuring tape** is: Type 8214 ,Size 1.5m\*7.5mm produced by Deli Group Limited; **The unified acupuncture time and therapy course** were: Each treatment lasts for 30 minutes which will be applied 3 times a week(ideally every 1 or 2 days ) for consecutive 4 weeks, 12 sessions in total; **Operator and attention:** Acupuncture treatments will be operated by the attending doctor and should pay attention to the disinfection of operator's hands and local skin before and after treatment. The treatment of acupuncture and moxibustion will be mainly aimed at the knee joint with pain symptoms, such as single or bilateral knee pain, the treatment of single / bilateral knee joint. **The unified emergency medication and treatment:** If the participants have unbearably knee pain during the study, we will allow them to take temporary emergency medication: oral Celebrex capsules (Celebrex, Capsules, Pfizer Pharmaceuticals Ltd), which will be applied once a day (0.2g a time orally).The situation of drug use should be recorded in detail; swelling of the knee joint during the test and temporary receiving treatment, but it should be recorded in detail. swelling in the knee joint effusion shown during test, allowed to accept fluid pumping treatment, but it should also be recorded in detail.

### **(1)Acupuncture group**

1)Acupoints: Liangqiu(ST34),Xuehai(SP10),Neixiyan (EX-LE4 ),Dubi (ST35),Yanglingquan (GB 34)and Yinlingquan (SP9)

2)Point location: According to the National Standard of The People's Republic of China, the Name and Location of Acupoints, issued in 2006 (GB/T 12346-2006).

3) Location and operation of acupoints

Liangqiu (ST34) is located in the anterior femoral region, the medial end of the patellar base was 2 cun and the medial femoral muscle was raised. Operation:

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straight 1.0-1.5 cun.

Xuehai (SP10) is located in the anterior femoral region, 2 cun of the patellar base, the lateral femoral muscle and the tendon of the rectus femoris. Operation: straight 1.0-1.5 cun.

Neixiyan (EX-LE4) is located in the center of the depression of the patellar ligament of the knee . Operation: Once outside and within the frontal plane at an angle of 45 degrees inclined 0.5-1 cun.

Dubi (ST35) is located in a depression lateral to the patellar ligament. Operation: At 90 degrees, the backward inclined 1-1.5 cun.

Yanglingquan (GB 34) is located in the depression anterior and inferior to the head of the fibula.Operation: straight 1.0-1.5 cun.

Yinlingquan (SP9) is located in the depression between the lower border of the medial condyle of the tibia and the medial border of the tibia. Operation: straight 1.0-2.0 cun.

In the Acupuncture group, the inserted needles will be manipulated using techniques including lifting, thrusting, twisting, and rotating to reach De Qi (A composite of sensations including soreness, numbness, distention, heaviness and other sensations).The treatment lasts for 30 minutes.

### **(2)Electro-acupuncture group**

Acupoints, location and acupuncture operation are the same to the above acupuncture group.

Operation: The electrode will be connected in Neixiyan (EX-LE4) and Dubi (ST35) and electrode wire will be connected to the Huatuo SDZ-IIB electro-acupuncture apparatus(Jiangsu Suzhou Medical Supplies Factory LTD. Jiangsu China ), dilatational wave with a frequency of 2/100 Hz, the current strength in participants within their tolerance (preferably with the skin around the acupoints shivering mildly without pain), for 30 minutes.

### **(3)Mild moxibustion group**

Operation: In this group, Liangqiu (ST34) ,Xuehai (SP10) ,Yanglingquan (GB 34) and Yinlingquan (SP9) are needled the same to the acupuncture group. At the same time ,mild

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moxibustion are applied at the distance of 2-3 cm away from the skin of both the Neixiyan (EX-LE4) and Dubi (ST35) by 2 two Zhuang for 30 minutes.

#### **(4)Warm-needling group**

Acupoints, location, and acupuncture are the same to the acupuncture group.

Operation: Warm-needling are applied at both Neixiyan (EX-LE4) and Dubi (ST35). That is to insert one zhuang(about 2cm)of Qing Ai on the top of the needle, and burn the moxa at the lower end ,each acupoint applied 2 Zhuang. In the process of moxibustion, if the participants feel unbearable hot , we should be put some paper between the skin and moxa to prevent burns.

#### **(5)Sham acupuncture group**

The sham Acupoints: Sham Liangqiu(ST34), Sham Xuehai(SP10), Sham Neixiyan(EX-LE4), Sham Yanglingquan (GB 34), Sham Yinlingquan (SP9)

Positioning and operation: Sham acupuncture group choose a non-meridian and non-acupoint needling method, respectively needle 1cm lateral to the above acupoints with a 0.18 \* 25mm disposable needle with depth of 1-2mm for 30 minutes.

#### **(6)Celebrex group**

Celebrex capsules (Celebrex, Capsules, Pfizer Pharmaceuticals Ltd), which will be applied 1 time daily( 1 time oral 0.2g) for 4 weeks.

### **5. Outcome measurements and observe time point**

All subjects received a clinical evaluation before treatment (baseline), in treatment (2 weeks), after treatment (4 weeks), and during follow-up (3 months, 6 months) at five time points. The primary outcome measurements includes McMaster University Osteoarthritis Index (WOMAC) function score and Visual Analogue Scale (VAS); Secondary outcomes measures including WOMAC pain score, WOMAC stiffness score, the Physical Activity Scale of the Elderly (PASE), knee joint swelling measurement and WHO-BREF quality of life scale.

#### **(1) Primary outcomes**

1)Visual Analogue Scale (VAS);

2)WOMAC function score;

The primary outcome measurements will take the average of the last three days.

#### **(2) Secondary outcomes**

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- 1)WOMAC pain score, taking the average of the last 3 days.
- 2)WOMAC stiffness score, taking the average of the last 3 days;
- 3)The Physical Activity Scale of the Elderly (PASE);
- 4)Knee joint swelling measurement;
- 5)WHO-BREF life quality scale.

(3) Acupuncture and moxibustion related safety evaluation

Stabbing pain of needle, faint, local hematoma, infection and abscess, burns, skin allergy etc. The safety assessment of acupuncture and moxibustion must be recorded after each treatment.

## **6. Statistical processing**

- 1)Full Analysis Set (FAS) : a collection of cases that are randomly enrolled and at least treated once.

In the analysis of the main curative effect indexes, the missing value of FAS is processed by LOCF (Last Observation Carried Forward) method, which was observed at the latest point of time. In the Case of secondary curative effect, general situation and safety Analysis, the Available Case Analysis principle is adopted to carry out missing value processing.

- 2) Per-protocol population set(PPS) : a set of cases that meet inclusion criteria and complete treatment according to the test plan. Good compliance with the test scheme and compliance ,no drug use, and the completion of efficacy evaluation(at least the primary efficacy).

- 3) Safety set (SAS) : at least one treatment, and a safety index to record the actual data.

## **(2)Statistical analysis**

- 1) the distribution of cases of six groups: the total loss rate of six groups and the loss rate due to adverse events.
- 2) comparability analysis: comparison of demographic data and other baseline values to measure the comparability of the six groups.
- 3) Compliance analysis: compared with the six groups of patients whether they meet the appropriate treatment on time and take the drug banned in the

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programme.

4)Effectiveness analysis: main efficacy indexes are analyzed by PP (per protocol)and ITT(Intend to treat); Since this study is a multicenter clinical trial, the effect of the central effect and baseline on the efficacy index should be considered.

5)Effect factor analysis: such as age, sex, course of disease, and combination of drugs, etc.

6) Safety analysis: first, according to the requirements of adverse reaction correlation list ,describes six groups of adverse events and adverse reactions, (including the number of cases of adverse events and laboratory test indexes before and after the test , abnormal turn cases and different rate). The adverse reactions were analyzed by chi-square test.

### (3)Statistical analysis method

1) Measurement data: first, the normal test is carried out, and t-test, paired t test, variance analysis, covariance analysis and other methods are adopted if it's in a normal distribution. Rank and inspection, matching rank and check are used for data that does not conform to normal distribution.

2) Counting data: using the chi-square test, Fisher exact test, etc.; The hierarchical data were analyzed by Ridit analysis, CMH(Cochran-mantel-Haensel statistics) or other non-parametric tests.

3) Multicenter analysis of comprehensive curative effect: using CMH method for counting data while analysis of covariance for measurement data.

4) All statistical tests were by bilateral inspection, and the P value was less than or equal to 0.05, which is statistically significant.

### (4) Statistical software

SAS9.3 software analysis.

## **Trial flow chart**



