A Randomized, Parallel Control And Multicenter Clinical Trial of Evidence-Based Traditional Chinese Medicine Massage Treatment VS External Diclofenac Diethylamine Emulgel For The Treatment of Knee Osteoarthritis

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Research Article

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Abstract

Background: Both massage and topically administered NSAIDs are safe and effective treatment for knee osteoarthritis (KOA); however, different massage technique sects in China caused assessment difficulties for the treatment of KOA. In order to standardize massage techniques and procedures, we organized multi-disciplinary experts in China to acquire an evidence-based traditional Chinese medicine massage treatment of knee osteoarthritis. The purposes of this study are to evaluate the efficacy and safety of evidence-based traditional Chinese medicine massage treatment of KOA compared to External Diclofenac Diethylamine Emulgel.

Methods and design: 300 participants diagnosed with KOA will be randomly divided into the experimental group, control group, and waiting list group in a ratio of 2:1. The participants will receive evidence-based traditional Chinese medicine massage 2 sessions per week for 10 weeks or External Diclofenac Diethylamine Emulgel 3-4 times per day for 10 weeks respectively. The MRI scans and X-ray will be performed at baseline and the end of the intervention period. The main evaluation index will include the Western Ontario and McMaster Osteoarthritis Index (WOMAC). The secondary evaluation index will include：(1) WOMAC each dimension; (2) the PRO scale for knee osteoarthritis based on the concept of Traditional Chinese Medicine：Chinese scale for knee osteoarthritis, CSKO；(3) MRI scan and X-ray evaluation.

Discussion: The results of our study will help to evaluate efficacy and safety of evidence-based traditional Chinese medicine massage treatment of KOA compared with External Diclofenac Diethylamine Emulgel combined with clinical, X-ray and MRI changes.

Trial registration: Chinese Clinical Trial Registry ChiCTR1800014400. Registered on 10 January 2018.

Introduction

Knee osteoarthritis (KOA) rank highly among global causes of disability and chronic pain, particularly in people over 50 years of age [1]. Structured exercise programs, dietary weight management and mind-body exercise (such as Tai Chi and Yoga) were considered by the panel to be effective and safe for all patients with Knee OA [2–5]. These updated OARSI guidelines recommended non-pharmacological as the core treatments for KOA in all cases [6].

Massage is a safe and non-pharmacological treatment with limited contraindications and no known serious adverse events [7]. Traditional Chinese massage has a positive effect on KOA and widely used in china. In recent several studies shown Chinese massage therapy decreased pain and may improve extensor muscle strength;and it may improve walking ability for these KOA patients; however, different massage sects in China caused assessment difficulties for the treatment of KOA. In order to standardize massage techniques and procedures, we organized multi-disciplinary experts in China to conduct a

questionnaire survey and field discussions, and successfully acquire an evidence-based traditional Chinese medicine massage treatment of knee osteoarthritis.

Topically administered NSAIDs (Non-Steroidal Anti Inflammatory Drugs) as Diclofenac solution attained significantly greater improvement in pain reduction in patients with KOA and widespread used in the world [8–11].

As yet there are not a randomized controlled and multicenter clinical trial between traditional Chinese massage and External Diclofenac Diethylamine Emulgel for the treatment of KOA. The purposes of this study are to evaluate the efficacy and safety of evidence-based traditional Chinese medicine massage treatment of KOA compared with External Diclofenac Diethylamine Emulgel. The overall design of experiment: this scheme has randomization, control, multi-center clinical trial.

Methods And Design

This clinical study to evaluate the efficacy and safety of evidence-based traditional Chinese medicine massage treatment of KOA compared to External Diclofenac Diethylamine Emulgel. 300 participants will be recruited in the study. Clinical data measurements, X-ray and MRI scans will be evaluated at baseline and the end of treatment (Figure 1). The study has been approved by the ethical committees of Guang'anmen Hospital (NO:201-135-KY-1) and registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn/showproj.aspx?proj=24457). The registration number: ChiCTR1800014400. The protocol will be reported following Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.

Study setting and recruitment

The study will be carried out at the five hospitals, including Guang'anmen Hospital, Beijing's Capital Medical University Traditional Chinese Medicine Hospital, Dongfang Hospital of Beijing University of Chinese Medicine, Xuan Wu TCM Hospital Beijing and Beijing Fengsheng trauma-orthopedic hospital of traditional Chinese Medicine. The study will recruit participants with KOA who meet the diagnostic criteria of the American College of Rheumatology criteria [12] through hospital outpatient. WeChat official account (one of Chinese popular social media platforms) of Guang'anmen Hospital and brochures. Meanwhile, the recruitment of participants has started in June 2018.

Participants

Inclusion criteria:

(1) Meet the diagnostic criteria of knee osteoarthritis according to the American College of Rheumatology (ACR) criteria [12]

(2) Scores for WOMAC pain dimensions were greater than 25

(3) K-L classification ≥ 1 [13]

(4) Age 40-80 years，male or female

(5) Signed informed consent

Excluded cases criteria

(1) Patients with secondary osteoarthritis

(2) Patients with obvious unstable knee joint

(3) Patients who have received intra-articular injection of sodium hyaluronate or hormone

(4) Patients who have combined with severe osteoporosis, diabetes, lower extremity vascular disease, limb malformation or nerve system disease

(5) Patients who have combined with severe mental illness, unable to understand others' intentions or express themselves correctly

(6) Pregnant women and those trying to conceive or lactating mother

(7) Patients who have combined with heart, lung, brain, liver, kidney and hematopoietic system and other serious diseases

(8) Patients who have contraindication for MRI

(9) Patients who have allergy history for investigational product, allergic constitution

(10) Patients who are participating in other clinical trials

(11) Patients who have been used to intemperance and (or)psychoactive drug substance, drug abuser and relier

(12) According to the researchers' judgment, other diseases or conditions that may reduce the possibility or complicate the inclusion, such as frequent changes in the work environment and unstable living environment, which may easily lead to loss of follow-up

Informed consent and participant safety

Participants will be required to sign an informed consent and have the same chance to receive appropriate treatment. During the treatment, any adverse events, such as local skin dryness, skin irritation, should be informed to the study researchers, who are responsible for monitoring and recording the adverse events and reactions throughout the study. If the participants cannot tolerate these adverse reactions, treatment will be discontinued and the participants will be withdrawn from the study.

Randomization

In this study, this clinical research adopts randomized blocks, and cases were randomly assigned to each center. The results of random groups were placed in sealed envelopes, which were numbered consecutively. When the patients were enrolled, they took the envelopes in the order of enrollment and were grouped according to the contents of the envelopes. waiting list group in a ratio of 2:1, 200 cases in the experimental group and 100 cases were in control group. The random sequence will be generated by an independent professional statistician who is not involved in the study with the software SPSS 11.5 (SPSS Company, Armonk, New York, USA). The random numbers will be stored by a fixed non-involved person.

Blinding

Due to the operation characteristics of massage therapists, the massage therapists and the participants cannot be blinded who will be informed of the grouping of participants before treatment. Participants will be told that they will randomly receive one of the interventions after enrollment.

Sample size

According to literature, the average effective rate of treating knee osteoarthritis only through massage is 95.6%, and 79.8% by application of external diclofenac diethylamine emulsion latex [9]. According to the sample size calculation formula, the minimum sample size of each group is n = 85.49. Considering expulsion case and getting significant results, we planned the ratio of the cases in experimental group and the control group is 2: 1, and the number of included cases was 300. There were 200 cases in the experimental group and 100 cases were in control group.

Interventions

Experimental group

200 patients in experimental group will receive 20 sessions of manual massage treatment (2 sessions weekly for 10 weeks,10 mints one session). Use the definite evidence-based traditional Chinese medicine massage technique for knee osteoarthritis to do the massage treatment.

During the treatment period, other Chinese & western drugs and treatment methods (including physical therapy and psychotherapy, etc.) for knee osteoarthritis are not used. In cases of intolerable knee pain, the patients will be instructed to take Loxoprofen Sodium Tablets (60mg□Oral 3 / day) as a rescue medication, The use of other treatments, such as injections of any kind, moxibustion, acupuncture or cupping, will not be allowed.

When combined with other diseases that the drugs and treatments must be continued and the drugs and treatments need to be recorded in detail in the combined medication list.

Control group

100 patients in control group will receive External Diclofenac Diethylamine Emulgel (Beijing Novartis Pharma Ltd producing, trade name: vitalin emulgel) treatment (3-4 times per day for 10 weeks). Other interventions will be similar with experimental group.

Clinical outcome assessments

If only one knee is affected, the assessment of the outcomes will relate to this knee. If the patient has two affected knees of which only one meets the ACR criterion and Kellgren-Lawrence grade II or III [13], only this knee will be evaluated. In the case that both knees are affected in accordance with the inclusion criteria (ACR and Kellgren-Lawrence grade II or III), the more painful knee will be randomly chosen for evaluation.

The WOMAC score was performed for each follow-up, with the calculation of the total score of WOMAC and each dimension were compared before and after treatment [14]. Clinical recovery: WOMAC score reduction by 95%; Excellent: WOMAC score reduction by 70%; Efficient: WOMAC score reduction by 30%; Inefficient: WOMAC score reduction less than 30%. Note: the calculation formula [(WOMAC score before treatment - WOMAC score after treatment) /WOMAC score before treatment] * 100%.

The CSKO score (Chinese scale for knee osteoarthritis) was performed for each follow-up, with the calculation of the total score of CSKO were compared before and after treatment.

X-ray data acquisition

Taking X-ray of double knee joint with weight loading at adem position. Kellgren and Lawrence classification criteria will be used on AP film to evaluate the degree of degeneration, and the width of medial and lateral tibiofemoral joint space [13]. At the end of treatment, the X-ray of double knee joint were taken again. Compare the width changes of medial and lateral tibiofemoral joint space on standard load positive X-ray before and after treatment.

MRI data acquisition

Using Siemens 3.0T MRI to obtain the patient's knee T2 mapping sequence. Using the Recht criteria to evaluate the cartilage degeneration [15]. Measure the average thickness and volume of cartilage at the same time.

After the end of treatment, MRI images were taken of the affected limb for MRI score of cartilage defect.

Safety evaluation data acquisition

(1) vital signs: body temperature, resting heart rate, respiratory, blood pressure after 10 minutes of rest (systolic blood pressure, diastolic blood pressure). (2) Laboratory examination: blood routine (RBC, WBC, platelet, hemoglobin), urine routines(urine red cell, LEU, urinary protein, glycated haemogobin alc), stool

routine+occult blood, liver function：ALT，AST, renal function：BUN，Cr, 12 lead routine electrocardiogram. (3) Manipulation-related adverse events, such as ecchymosis,subcutaneous hemorrhag, fracture, dislocation and so on. (4) Drug-related adverse events, such as gastro-intestinal tract response and so on. (5) Other adverse events.

The safety of massage therapy was evaluated by comparing the changes of blood and urine routine, liver & kidney function, electrocardiography before and after the treatment and the incidence of adverse events during the treatment.

Data management and monitoring

The case report form (CRF) will be used to record major clinical data, adverse events, and safety assessments during the study, with a unique numeric identifier for each participant. The clinical research assistant will validate the accuracy, missing, and consistent data in CRF. Clinical questionnaires will be administered to all participants in a separate room and administered by the same research. The clinical data will be independently entered into the EpiData electronic database by two researchers and tested by referring to the original data source when inconsistent data appears. EpiData electronic data will be exported to Microsoft Excel and then analyzed using SPSS software package (SPSS 11.5 ko for Windows). The participants will be scanned by a professional imaging technician on the same machine, and the imaging data will be checked by the same professional imaging technician.

Statistical analysis

Statistical analysis will be performed using SPSS 11.5 statistical analysis software; All statistical tests were double-sided, if P value is less than 0.05 that the examined difference is statistically significant. Measurement data of each attendance will be described by means ± standard deviation. Compare with the base value of the filter period, the paired t test was used to compare the differences before and after. The changes before and after treatment were compared by paired t test. The enumeration data of each attendance were statistically described by frequency (component ratio). X^2 test & Wilcoxon rank sum test was used to quantitatively analyze the changes before and after treatment intergroups. Expulsion analysis: The X^2 test will be used to compare the total expulsion rate between the two groups and the expulsion rate due to adverse events. Equilibrium analysis of base value: Use the t test or X^2 test to measure the equilibrium between the two groups. Effectiveness analysis: the changes in WOMAC score, X-ray and MRI examination results at each attendance were statistically described changes relative to the baseline, calculation the number of cases, mean, standard deviation, median. The changes were tested by the analysis of covariance (ANCOVA), which took the baseline data as the covariable. In addition, the changes in each group before and after treatment were compared using the paired t test. The evaluation (classification) of the effectiveness indicators was described, the number and percentage of cases were calculated, and the two groups were compared according to the hierarchy centralized structure CMH-X^2 test. Security analysis: The X^2 test was used to compare the incidence of adverse events between the two groups, making a list of adverse events occurred in this trial; Compare the relationship between

normal/abnormal changes of laboratory test results before and after the test with the occurrence of abnormal changes with the experimental drugs.

Ethics and dissemination

The protocol was designed following the principles of the Helsinki declaration. Participants will be informed of the study protocol, possible risks, and other related matters before entering the study and sign the informed consent before randomization. The results will be published in peer-reviewed academic journals and disseminated through conferences.

Discussion

Massage treatments through pressing, pinching, flexion-extension, stretching, plucking, rubbing and other bone-setting manipulation are all recommended. According to traditional Chinese medicine (TCM), massage on the epidermis of the body can stimulate and adjust the distribution of meridians, qi and blood. According to modern medicine, massage may improve systemic immune and inflammatory profiles in healthy individuals [16]. As a supplementary and alternative therapy, massage has been widely used in clinical practice and was widespread recommended by the Chinese orthopedic experts.

Although some studies shown effective and safe for all patients with KOA treatment by traditional Chinese massage or Diclofenac solution; however, as far as we know, our study will be the first randomized controlled and multicenter clinical trial. In this study, evidence-based traditional Chinese medicine massage treatment VS External Diclofenac Diethylamine Emulgel will be conducted in participants with KOA to observe the correlation between clinical manifestations and changes in X-ray and MRI, so as to further understand and identify the effective and safe in both treatment methods.

In order to avoid the bias of results and improve the reliability of clinical results, we try to keep the baseline consistency as much as possible. Participants will be screened strictly according to inclusion and exclusion criteria. All the researchers will be trained to understand the design of the study. To achieve blindness in the course of the intervention, the sealed envelopes should be attached to massage and External Diclofenac Diethylamine Emulgel before the intervention. In order to maintain the consistency of massage techniques, all Chinese massage therapists who involved in the study have achieved the strict massage training. In the study, MRI images of the affected limb were taken for MRI score of cartilage defect in both groups. all of participants will be carried out in the above five hospitals. This study also has several limitations. First of all, Chinese massage therapist and participants in the waiting list will not be blinded due to the nature of the intervention. Secondly, the long-term efficacy of massage therapy will not be observed due to the observation treatment period of the study is only 10 weeks.

Trial Status

The study protocol was approved by the Ethical Committee of Guang'anmen Hospital on 08 January 2018. The study is currently in the recruitment phase, and the first participant was included in 1 June

2018. We predict that recruitment will be completed by September 2021.

Abbreviations

KOA knee osteoarthritis; ACR: American College of Rheumatology; TCM: traditional Chinese medicine; NSAIDs : Non-Steroidal Anti Inflammatory Drugs; CRF: Case Report Form; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; CSKO (PRO scale for knee osteoarthritis based on the concept of Traditional Chinese Medicine, Chinese scale for knee osteoarthritis; MRI: Magnetic Resonance Imaging.

Declarations

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Availability of data and materials

The full protocol for the study will be available from the corresponding author. Datasets generated or analyzed during the current study will not be publicly available due to data privacy. Results from the trial will be published in peer-reviewed international journals and positive, negative and inconclusive results will be published.

Ethics approval and consent to participate

The study was approved by the ethical committees of Guang'anmen Hospital. Patient informed consent will be obtained.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

	STUDY PERIOD				
	Enrolment	Allocation	Post- Allocation		
Time Point (week)	week-1	0	Week-1	Week-5	Week-10
Enrolment					
Eligibility Screen	x				
Informed Consent	x				
Randomization		x			
Interventions					
Experimental group			x	x	x
Control group			x	x	x
Assessments					
Clinical Characteristic					
WOMAC		x		x	x
CSKO		x		x	x
Rescue medicine		x	x	x	x
Adverse events		x	x	x	x
Blinding Assessment					x
X-ray		x			x
MRI scan		x			x
Blood detection		x			x

Figure 1

Schedule of enrollment, intervention, and assessment. WOMAC, CSKO, X-Ray, MRI Scan

Supplementary Files

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- SPIRIT2013Checklist.docx