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Tuina on knee pain and physical function for patients with mild-moderate knee osteoarthritis in Shanghai: protocol for a multicenter, assessor-blinded, randomized controlled trial

Jianwen Ma
Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine

Guangxin Guo
Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine

Hongyu Yue
Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine

Chaoqun Xie
School of Acupuncture-Moxibustion and Tuina, Shanghai University of Traditional Chinese Medicine

Fangfang Xie
School of Acupuncture-Moxibustion and Tuina, Shanghai University of Traditional Chinese Medicine

Ziying Chen
School of Acupuncture-Moxibustion and Tuina, Shanghai University of Traditional Chinese Medicine

Yuanjia Gu
Shuguang Hospital, Shanghai University of Traditional Chinese Medicine

Shuaipan Zhang
Shuguang Hospital, Shanghai University of Traditional Chinese Medicine

Min Fang
Shuguang Hospital, Shanghai University of Traditional Chinese Medicine

Fei Yao (doctoryaofei@shutcm.edu.cn)
Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine

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Study protocol

Keywords: Knee osteoarthritis, Pain, Tuina, Efficacy, Randomized controlled trial

Posted Date: September 22nd, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3335099/v1

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Abstract

Background

Knee osteoarthritis (KOA) is one of the most common osteoarthritis, imposing substantial economic and medical burdens on both individuals and society. In China, Tuina has been chosen as a complementary and alternative therapy to relieve symptoms of knee pain and dysfunction. However, current evidence is insufficient to support the efficacy of Tuina therapy in addressing knee pain and improving physical function. The purpose of this trial was to investigate the efficacy of Tuina compared to celecoxib, by observing changes in outcome measures and assessing its level of effectiveness as an alternative treatment.

Methods and analysis

A total of 360 patients with KOA aged between 40 and 70 years and classified as Kellgren and Lawrence Grade I-II will be recruited from eight sub-central hospitals. The participants will be randomly assigned to either the treatment group (Tuina, Biw) or the control group (Celecoxib, Qd), with both groups undergoing a 4-week intervention phase followed by an 8-week follow-up phase. The primary outcome is the change of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale at week 4 compared with baseline. Secondary outcomes including WOMAC stiffness and function subscales, WOMAC total score, 36-item short form health survey (SF-36), timed up and go test (TUG), short physical performance battery (SPPB), gait analysis parameters, and pain medication records will be assessed at weeks 4, 8, and 12. Any adverse events occurring during the trial will be promptly recorded.

Discussion

This multicenter randomized trial aims to evaluate the effectiveness of Tuina on relieving pain and increasing physical function of KOA patients. This protocol, if proven effective, will present more compelling evidence supporting the value of Tuina and contribute to providing a promising alternative therapy for patients with mild-moderate KOA.

Trial registration number: This trial has been registered in the China Clinical Trials Registry (registration number: ChiCTR2300069416).

Article Summary

Strengths and limitations of this study

1. The design of a multicenter and large-sample trial mitigates the potential for bias and provides a more robust body of clinical evidence.
2. The study employed both subjective and objective indicators to comprehensively assess the effectiveness and safety post-intervention, while utilizing the outcomes of first-line drugs as a reference to objectively reflect the level of Tuina's efficacy.

3. The sub-center pilot incorporates hospitals at different levels in Shanghai, enabling extensive recruitment of potential or confirmed KOA patients and effectively, enhancing the reliability and validity.
4. The recruitment of patients is limited to individuals with mild to moderate KOA, excluding those with severe KOA or requiring surgical intervention.
5. Eight sub-center hospitals are all located in Shanghai, the enrollment of patients has regional limitations.

Introduction

As one of the most common musculoskeletal diseases worldwide[1], about 30% of people over the age of forty-five have radiographic evidence of knee osteoarthritis (KOA), with approximately half of experiencing obvious discomfort symptoms[2]. In China, through the large sample research statistics and previous research, the cumulative incidence of KOA is estimated to be 8.7%, and the prevalence of symptomatic KOA in women (10.3%) is higher than that in men (5.7%). The prevalence of KOA escalates with advancing age, indicating a progressively increasing disease burden and demand for elderly care within the Chinese population[3, 4]. Shanghai, being the largest city in eastern China, bears a substantial population burden and consequently experiences significant demands for medical services[5]. Previous epidemiological studies had demonstrated that the prevalence of symptomatic KOA in this region reaches up to 3.4%, with higher rates of tibiofemoral joint OA observed among urban populations compared to Caucasians[6, 7]. As urbanization expands and the population ages, the healthcare strain and socioeconomic burden associated with KOA will become more severe, necessitating urgent exploration of cost-effective treatment[8].

Strong evidence indicates that KOA could be affected by a variety of risk factors including sex, obesity, and previous knee injury[9], and it is characterized by intermittent or sustained chronic knee pain, brief morning stiffness and functional limitations related to muscle weakness[10, 11]. The most prevalent issue among patients is knee pain, which could lead to restricted lower limb movement and abnormal gait due to the onset and exacerbation of pain[12–14]. Therefore, numerous therapeutic interventions are focused on alleviating knee pain, which leading to enhance patients' quality of life and promote their physical and mental well-being through effective medical management[15–17]. According to the guidelines, oral non-steroidal anti-inflammatory drugs (NSAIDs) has been recommended to mitigate pain [18, 19]. Among them, celecoxib, the frequently prescribed medication in clinical practice, demonstrates substantial efficacy in alleviating pain and inflammation based on ample evidence[20–22]. Although previous studies have demonstrated comparable cardiovascular safety to ibuprofen or naproxen[23, 24], its use is not recommended for individuals with cardiovascular or gastrointestinal comorbidities in the context of KOA[25]. Consequently, the potential variation in side effects associated with drug therapy restricts its application.

Currently, several trials exhibited sufficient evidence that exercise therapy has significant benefits for patients with lower extremity osteoarthritis in terms of pain relief and improving limitation in function[26].

However, with regard to the age of OA patients in China and the level of basic medical condition[4], the need to develop a personalized, standardized and high-quality exercise training program for the large population of patients could be hard to achieve. Furthermore, considering concomitant factors such as excess obesity, obvious effect of exercise therapy may take a relatively high cost of time. As symptoms worsen, surgical treatment including total knee arthroplasty could be considered to bring greater pain relief and functional improvement[27], but it may also be accompanied by higher cost of treatment and an increased risk of adverse events which can raise the burden of living[28]. Thus, considering both cost and the applicable population, an effective and safe intervention for KOA is urgently needed.

Tuina, a form of non-invasive physical therapy, is based on the meridians theory of Traditional Chinese Medicine (TCM) uses appropriate manipulation by evaluating specific symptoms to treat different diseases. The efficacy of Tuina on pain relief of different diseases has been proven, such as non-specific chronic neck pain[29], tension-type headache[30], as well as chronic fatigue syndrome[31], and this therapeutic manual therapy is also helpful for the relief of anxiety and depression[32, 33]. In addition, owing to the low requirements for equipment, the process and duration of Tuina are flexible and adjustable, which to some extent reduces the potential risk of therapeutic damage brought by other physical therapies. In previous RCTs, the incidence of adverse events in Tuina therapy is generally low[34, 35], which is due to the timely communication between therapists and patients during the treatment. Different from exercise therapy, Tuina therapy can ignore risk factors including size, age, and gender to intervene. Furthermore, compared with high cost of surgery, the cost of non-surgical therapies like Tuina is lower and does not increase the medical burden of OA patients[36, 37]. The efficacy of Tuina in treating KOA has been supported by several studies[38, 39]. However, there remains a dearth of sufficient evidence regarding its impact on physical function improvement, and the evaluation of this complementary therapy's effectiveness still lacks credible high-quality evidence.

Building upon the findings of our previous studies[39, 40], we developed the multicenter, large-sample RCT with the aim of implementing this effective complementary intervention for treating knee pain and lower limb dysfunction in diverse community settings in Shanghai. Through this study, we hope results of this study will provide adequate and valid data to demonstrate the effectiveness and safety of Tuina in pain reduction in patients with KOA, which could bolster the credibility of Tuina as a complementary therapy.

Methods and analysis

Hypothesis

We conducted this RCT to hypothesize that the application of Tuina will reduce the level of pain, improve the quality of life, and improve physical function in KOA patients. The objectives of this study are twofold: (1) to validate the efficacy of Tuina in relieving pain and improving physical function in individuals with mild-moderate KOA compared to celecoxib, and (2) to investigate the intricate relationship between pain and lower extremity physical function more comprehensively.

Study design and settings

This study is a 12-week, multicenter randomized controlled trial and will be conducted in a total of eight public hospitals at various levels(Shanghai Municipal Hospital of Traditional Chinese Medicine, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai General Hospital, Shanghai Jing 'an District Hospital of Traditional Chinese Medicine, Shanghai Jiading District Hospital of Traditional Chinese Medicine, Shanghai Qingpu District Hospital of Traditional Chinese Medicine, Shanghai Jing 'an District Central Hospital, Shanghai Jiangning community health service center).

Patients who meet the inclusion criteria will be recruited and randomly assigned equally into one of two groups: the Tuina Group (TG) or the Celecoxib Group (CG). Participants in TG will receive Tuina treatment 2 times a week for 4 weeks, each treatment lasts for 30 minutes. In CG, participants will be required to take 200 mg of celecoxib orally daily for 4 weeks. At the end of the intervention, an 8-week follow-up will be conducted, and relevant outcome measures will be assessed at 8, 12 weeks of the follow-up phase. All participants will complete the assessments by the WOMAC, 36-item short form health survey (SF-36), Time up and go test (TUG), Short Physical Performance Battery (SPPB) and Gait analysis (Detailed trial process seen in *Fig. 1* and *Table 1*). All patients will be fully informed the potential benefits, potential risks and responsibilities, those who will sign the informed consents once they are included.

Participants

The trial will recruit patients who had symptomatic, radiologically confirmed KOA according to criteria from the American College of Rheumatology[41]. To precisely screen the target patients, the following criteria were developed for this clinical trial.

Inclusion criteria

All patients with symptomatic KOA will be assessed to see if they meet the following inclusion criteria:

1. Men or non-pregnant women.
2. Aged ≥ 40 years and ≤ 70 years.
3. Be consistent with the diagnostic criteria for OA of the knee[41].
4. Mild-moderate radiographic tibiofemoral osteoarthritis (Kellgren and Lawrence Grade I-II) in at least one knee;
5. WOMAC pain sub-score ≥ 3 on at least one of five questions;
6. Unilateral knee involvement.
7. Understand Chinese and speak Mandarin Chinese
8. No previous knee surgery and no accompanying other knee problems.
9. Volunteer to participate in this trial and provide written informed consent.

Exclusion criteria

Participants who meet any of the following criteria will be excluded from this trial:

1. History of trauma and surgery on knee.
2. History of other treatment in last 6 months.
3. Have tumors, tuberculosis, osteomyelitis and other diseases in knee.
4. Have severe liver and kidney dysfunction, severe cardiovascular disease, diabetes mellitus and mental illness.
5. Suffer physical pain caused by other diseases.
6. Non-steroidal drug allergy.
7. Alcohol and drug abuse.
8. Voluntary withdrawal.
9. Have joint in another intervention study.

Recruitment

We will recruit participants from eight public hospitals by recruitment posters. Patients with KOA who show interest in this trial could make a call or scan the QR code on the poster to get in touch with our trial contact person and will be informed to have a face-to-face interview in any of eight public hospitals. Upon meeting the inclusion criteria and expressing their willingness to participate in this study, participants will be requested to provide written informed consent and undergo a comprehensive baseline assessment.

Sample size calculation

The calculation of sample size was based on the hypothetical changes in the outcome measurement, WOMAC pain subscale, at week 4. According to our previous clinical trial[39], we formulate expected effects with WOMAC pain subscale as the primary outcome. We hypothesized that a 2-point improvement in WOMAC pain subscale occurred in the Tuina group. Group sample sizes of 142 achieve 90% power to detect non-inferiority using a one-sided, two-sample t-test with the significance level (alpha) of the test is 0.025 through PASS software (v.15.0.5)[42]. According to the conservative principle and the ability of each center to enroll patients, considering a dropout rate of about 20%, the study will require 360 patients in total.

Randomization and blinding

This trial adopts stratified block randomization and will be completed by an independent statistical expert team. Eligible patients will be randomly allocated on a 1:1 basis to either TG or CG by a computer-generated random sequence in R (R Project for Statistical Computing, cloud.r-project.org). Randomization will be stratified among the eight public hospitals and the random block design will be adopted in which the block sizes will be changed randomly. Random allocation hiding will be implemented through random envelopes. Two copies of the random envelope will be given to researchers and each hospital. The

randomized envelope of group information stored with the study researchers shall not be opened during the duration of the study.

Due to significant differences in intervention, this trial is an open one that neither the researchers nor the participants implemented the blind method. However, group concealment can still be implemented through blinding outcome evaluators, data monitors, and statistical analysts. Data monitors who will perform data entry, query and data management and statistical analysts will be blinded as to the allocated intervention until all statistical analyses are completed. Each part of this trial will remain separate and independent.

Intervention

Before the trial officially starts, all the physicians and therapists involved in this study will be trained in a standardized operating procedure to acquire a full understanding of this trial. We do not recommend that patients continue to receive other interventions during this trial. Medications will be permitted if necessary, and the type and dosage of medications will be recorded timely.

Celecoxib Group (CG)

Participants in CG will take 200 mg of oral celecoxib (Pfizer Inc. USA.) daily for four weeks. After randomization, the patients will be required to make weekly visits to the hospital in order to collect their medications for the upcoming week and will be reminded to take their medications by daily text message or e-mail. The whole process will be carried out under the guidance of physicians and medication records will be completed by regular tele-monitoring.

Tuina Group (TG)

Tuina treatment will be performed in the outpatient department of each pilot. The Tuina doctors involved in this study must hold the Chinese medicine practitioner license from the Ministry of Health of the People's Republic of China. In order to minimize the gap of the manipulation caused by the different doctors, we will select those who have more than five years of experience for clinical experience and familiarize them with the treatment process. They will be required to strictly adhere to established procedures. Participants in TG will receive 30-minute Tuina treatment two times a week for four weeks. The interval between two treatments for at least 24 hours. Details of the treatment process are attached in *Fig. 2.*

Outcome Measurements

Based on the study schedule, all outcome measurements will be collected at different time points as the trial progresses.

Primary outcome

The primary outcome is WOMAC pain subscale (standardized range, 0–10 cm; 0 cm = asymptomatic, 10 cm = extreme symptoms) to be assessed at baseline, week 4, 8 and 12. WOMAC is a self-reported visual

analogue scale specifically designed to assess osteoarthritis symptoms, knee pain in five states will be assessed through five items. Participants will rate these five items according to their actual situation and will get a total score to reflect the pain level of the knee joint. The higher the score, the worse the knee pain and the worse the physical condition[43].

Secondary outcomes

1. WOMAC total score and WOMAC stiffness and function subscale

WOMAC stiffness subscale which contains 2 items will be used to measure the stiffness of the patient's knee joint and the WOMAC function subscale also contains 17 items to assess knee joint physical function. The score of each item in both scales are from 0 to 10 and will be assessed at baseline, 4 weeks of treatment, 8, 12 weeks of follow-up. WOMAC total score ranges between 0 and 240 (higher scores indicate more severe symptoms). The reliability, validity and sensitivity of the knee joint assessment will be evaluated objectively through these scores.

2. Short form 36-item health survey (SF-36)

SF-36 covers eight health concepts in separate scales: physical functioning, role limitations due to physical functioning, bodily pain, role limitations due to physical health problems, general mental health, role limitations due to personal or emotional problems social functioning, energy/fatigue or vitality, and general health perceptions. The 8 scales are also scored to produce 2 summary component measures of physical and mental health and will be assessed at baseline, 4 weeks of treatment, 8, 12 weeks of follow-up[44–46].

3. Time up and go test (TUG)

The functional status of the knee joint is tested on a fixed time schedule. The study included the subject assessment through the TUG test. The test is performed so that the patient is properly positioned on the test stand. The patient sits in a steady chair, and after declaring readiness, the task is to get up, cover a distance of 3 m, and return to the chair. The tests were performed in triplicate and the mean value was calculated. Normal value for a healthy adult is 10 s(s) or less.

4. Short Physical Performance Battery (SPPB)

The SPPB is a performance-based test that includes 3 components: walking velocity, time for five repeated chair stands, and a balance test. A 0- to 4-point score is assigned to each test (4 = best), and scores are summed to yield an overall score ranging from 0 to 12 (12 = best). This test is used to evaluate lower extremity function.

5. Gait analysis

Gait analysis parameters are associated with an increased odds of KOA onset and progression[47]. In this trial, 28 retroreflective markers will be affixed to the pelvis and bilateral lower extremities. Kinematic and

kinetic data will be captured with a 16-camera motion analysis system (Vicon Vero 2.2, Vicon, UK, 100 Hz) as participants walked over an embedded 6-meter pressure distribution measurement platform (FDM-3, Zebris, Germany). Participants will complete over-ground gait analysis and these data will be recorded and held consistent within individuals across trials. 10 non-invasive wireless EMG electrodes (Noraxon Ultium, Noraxon, USA) will be used to calculate 3D kinematic and kinetic gait data. Ground reaction force data will be tested by 4-channel force plates (AMTI BP400600, AMTI, USA, 1000 Hz). Maximal knee compressive force, external knee adduction moment, AP shear force, vertical ground reaction forces, 3D moments and forces of hip, knee and ankle joints will all be collected and analyzed at the same time. And gait kinematics of the lower limbs also include total time of one gait cycle (s), velocity (cm/s), step length (cm), knee joint angles (°) during walking. All data will be processed using Visual 3D, and gait analysis will provide us with functional descriptions of knee joints by comparing the objective differences in gait data before and after the intervention.

Dropouts and adverse events

Considering the age of patients with KOA, it is possible that they have other chronic diseases. We will truthfully record the standard medication content of relevant diseases instead of discontinuing the drug medication during the course of the trial. Participants in all groups will continue taking in their individual routine dosage from baseline to follow-up. If their conditions obviously change during the study, they will be free to consult our therapist from eight hospitals to make adjustments based on actual conditions. For better implementation of standard medical therapy, researchers will try to carry out proper health education for all patients and supervise them in recording their daily medication dosage.

Any adverse events including unfavorable or unintended signs, symptoms or diseases due to oral administration of celecoxib need to be reported by participants and will be recorded during this trial. Participants who refuse to continue taking celecoxib medication could be considered a dropout in the study.

Tuina therapy is a non-invasive, safe, manual treatment and does not rely on other equipment but we won’t completely rule out the occurrence of adverse events. Common adverse events were skin breakage, bruising due to local subcutaneous hemorrhage, and soft tissue injury. Therapists are required to report any adverse events in a timely manner. And these adverse events will be recorded.

Statistical analysis

The data will be analyzed independently by professional statisticians who are blinded to group assignment and patients’ basic information. All participants who pass the screening will be considered as the intention-to-treat analysis population for efficacy analyses. The outcome of the primary analysis will be based on the primary endpoint (WOMAC pain subscale) collected from participants that have received treatments for four weeks. The outcomes of secondary analyses will compare the changes of secondary outcomes (WOMAC stiffness and function subscales, WOMAC total score, SF-36, TUG, SPPB, Gait parameters) between either two groups from baseline to four weeks after treatment. The data collected during the follow-up will also be analyzed in order to observe the duration of effect after treatment.

Differences in outcome measurements (WOMAC, SF-36, Gait parameters) will be analyzed using an independent t-test or a rank-sum test if these data follow a normal distribution with homogeneity of variance. Analysis of covariance will be used for comparison between groups, and linear mixed effects model will be used for comparison between multiple time points. Otherwise, non-normal distribution will be described by Median (P25, P75). Mann-Whitney U non-parametric test will be used for comparison between groups. Missing data will be accounted by multiple imputation with baseline variables as predictors in the imputation model and a complete-case analysis without imputation of missing data will be performed to compare the consistency of results. Continuous data will be presented as mean ± SDs for normally distributed data or median and interquartile range for skewed data. Categorical data will be presented using frequencies and proportions (as percentages). All data will be analyzed by using the statistical software SPSS (v.24.0). Values of $p < 0.05$ (two-sided) are considered to have statistical significance.

Data management

The raw data will be captured using Case Report Forms (CRFs, paper) at the designated time. Two data administrators, who are not affiliated with the research team and blinded to group allocation, will independently receive the completed CRFs and enter the raw data into an Excel database (Microsoft, Redmond, WA, USA). Simultaneously, they will input real-time data into China Clinical Trial Registry (http://www.chictr.org.cn). Both administrators must undergo comprehensive training in data monitoring. To enhance data authenticity, we have established an independent Data Safety Monitoring Board (DSMB) responsible for reviewing and monitoring trial data. The DSMB comprises experts in Tuina therapy, orthopedics, methodology, and statistics who ensure overall quality and completeness of the collected information. Committee members will conduct spot checks on raw data during meetings with evaluators to ensure adherence to protocol guidelines. They possess authority to terminate the study prematurely if necessary. Upon completion of the study period, all collected data will be locked and researchers will not have access to modify it thereafter. All CRFs will be securely preserved for a minimum of five years following article publication. In case reviewers have any concerns regarding our trial's validity or reliability, they can contact the corresponding author for access to raw data.

Quality control

To ensure consistent procedures at all the hospitals before the official start of the trial, a trial kick-off meeting was scheduled, and all staff (except statisticians) were trained on the participants and content of the trial, patient recruitment, treatment scheduling, the precautions of patient-physician communication, and outcome assessment. Uniform and standardized operating procedures are developed and provided to all hospital staff. After undergoing centralized training, the Tuina doctors in each sub-center will undergo assessment and be required to strictly adhere to the established Tuina process and time. Additionally, they are expected to provide appropriate knee joint health guidance verbally during treatment sessions. Dedicated personnel will be stationed at the sub-center hospitals to establish regular contact with the participants via telephone or e-mail, ensuring timely medication intake, providing health guidance, and maintaining accurate records of all medications and dosages

administered throughout the study period. If the patient proactively discontinues medication due to significant symptom improvement, they will provide feedback to the attending physician through the dedicated personnel, signifying the completion of intervention. The established plan will be used to evaluate primary and secondary outcomes, record relevant data, and proceed to the follow-up phase. Comprehensive review of completed cases and clinical procedures by independent monitors was required. Once they find problems or serious adverse events during the intervention, they can raise direct objections and even discontinue this trial.

Patient and public involvement

Prior to the design, the principal investigators consulted with patients with KOA in clinical departments. The number and duration of treatments were designed from clinical experience and patient feedback. We will recruit all participants from outpatient clinics at the eight hospitals described above. Patients who have previously participated in trial design consultation will not be recruited as participants. We will write a draft journal article based on the results of the trial data, and participants will receive a brief report in which changes before and after the intervention are demonstrated after this trial. Treatment costs during the course of this trial will not need to be borne by the participants.

Ethics and dissemination

This study protocol has been approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine (2023SHL-KY-16-01), and any revisions or corrections of this protocol will be discussed by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine. Changes of detailed information will be kept. The trial will not officially begin until written informed consent has been collected from all patients. After the study completed and the data analyzed, results of this trial will be presented as articles in peer-reviewed journals or at academic conferences.

Discussion

In China, Tuina, as a complementary and traditional therapy, has been utilized since ancient times. Drawing upon the principles of TCM, Tuina stimulates specific acupoints and surface muscles to promote optimal circulation of Qi and Blood around the affected joints, reaching a state of Qi and Blood flow while enhancing joint mobility. It involves external physical manipulation that enhances muscle compliance and range of motion around the knee joint in the lower limbs[48–50]. This approach effectively reduces both passive and active stiffness of the knee joint, improves lower limb movement function, which leading to alleviate pain[51]. Increasing evidence supports the efficacy and safety of non-pharmacological therapies which are readily accepted by patients[52]. It is reasonable for us to speculate that Tuina could play a role in on pain relief and the functional limitation of KOA.

The selection of press-points of Tuina treatment are mainly proximal acupoints in previous studies[53]. We referred to the results of data mining and selected the acupoints including Liangqiu (ST34), Neixiyan (EX-LE4), Dubi (ST35), and Xuehai(SP10) on the front of the thigh and Weizhong (BL40) on the back side which appeared at a high frequency in the treatment of KOA[54]. These points in TCM theory are

interpreted as tonifying Qi and Blood, promoting the circulation of meridian channels and collaterals, leading to facilitating joint function recovery. Previous RCTs have also confirmed that acupoint stimulation around the knee joint has a significant effect on KOA and improves patients' pressure-pain threshold[53, 55], which was consistent with the findings of our previous study[39].

This multicenter pilot study expands patient recruitment beyond a single hospital setting to minimize regional differences that may exist. Additionally, we adjusted our sample size based on previous findings to reduce individual treatment variations and potential bias risks. Based on our prior study design, objective outcomes were supplemented to effectively assess changes in physical function and biomechanics of the lower limbs before and after treatment.

In general, there may exist potential safety concerns during the trial implementation, including the inherent risk of untimely or missed drug administration and loss to follow-up. Participants might inadvertently forget to adhere to their prescribed celecoxib regimen due to temporary symptom improvement or pain reduction, or they may opt for alternative treatments due to perceived lack of efficacy. To mitigate these risks, we proactively addressed these issues in the early stages of trial design. Firstly, by carefully selecting patients who are theoretically suitable candidates, we will emphasize the importance and safety of regular medication intake while excluding individuals resistant to oral celecoxib therapy. Secondly, scheduled tele-monitoring and regular reminders via SMS or email will be employed to minimize loss to follow-up; additionally, our contact information will be provided for participants in case of incomplete data due to attrition. Lastly, regardless of group assignment (TG or CG), if a patient's symptoms worsen significantly and become unbearable, intervention or follow-up will be interrupted promptly with data recorded prior to withdrawal. Direct access to medical attention can be requested through multiple channels aiming at reducing barriers for patients and ensuring timely healthcare access. The fidelity of the whole intervention must be upheld while reducing the risk of bias.

To alleviate the increasing burden of chronic joint disease, pertinent guidelines and studies have proposed a stepped treatment strategy for KOA, excluding surgical intervention for end-stage or severe cases, non-surgical treatments are recommended to use based on varying stages and severity levels of KOA and the optimal timing of the various treatment options is to be discussed[56, 57]. Among them, physical therapy or non-pharmacological interventions are recommended for patients in the early stage or when symptoms are mild. In China, one major challenge faced by KOA patients is the selection of appropriate treatment options. Many individuals are concerned about potential side effects and safety risks associated with drug, leading them to avoid or reject this approach. Additionally, various constraints make it difficult for these patients to engage in personalized self-management or regular exercise. As a result, they tend to rely on short-term interventions provided by hospitals at different levels in order to obtain symptom relief.

The findings will provide valuable references and examples for urban residents' clinical treatment and community health management related to KOA, aiming at effectively alleviating knee pain and improving lower limb function. It is anticipated that implementing this multicenter study in Shanghai will offer

important insights for Tuina doctors across TCM hospitals at different levels and expand treatment options available for patients with mild-moderate KOA in the region while ensuring reasonable costs within the comprehensive national healthcare system.

Declarations

Trial status

At the time of submission, recruitment for the trial has been started. The first participant was included on 5 August 2023.

Ethics approval and consent to participate

The protocol has been approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine (2023SHL-KY-16-01). Informed consent will be obtained from all participants before they participate in the study. All procedures in this study will be in accordance with the declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This study has been partly supported by Future Plan for Traditional Chinese Medicine development of Science and Technology of Shanghai Municipal Hospital of Traditional Chinese Medicine (WL-JXXK-2021001K) and National Natural Science Foundation of China (No.82105042). The sponsor, Shanghai Medical Innovation Development Foundation, is not involved in the conduct of the trial, date collection and statistical processing. Final trial results and the publication of any reports are independent of the sponsor.

Authors' contributions

JM and GG contributed to the concept and design of the study. JM and GG established the hypothesis and wrote the original proposal. JM, HY, GG, SZ, CX, YG and ZC contributed significantly in creating the

manuscript. MF and FY performed critical revisions of the manuscript. JM and GG drafted the manuscript. All authors read and revised the final version of the manuscript and will approve the final version.

Acknowledgements

The authors would like to thank all the investigators, study staff, outcome assessors, participants, and their families for their support in this trial.

Authors' information

[1] Shanghai Municipal Hospital of Traditional Chinese Medicine, Zhijiang Middle Road 274, Jingan District, Shanghai 200071, Shanghai, China.

[2] School of Acupuncture-Moxibustion and Tuina, Shanghai University of Traditional Chinese Medicine, Cailun Road 1200, Pudong New District, Shanghai 201203, Shanghai, China.

[3] Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Zhangheng Road 528, Pudong New District, Shanghai 201203, Shanghai, China.

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Tables

*Table1: Schedule of trial recruitment, interventions and assessments. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. SF-36, 36-item short form health survey. TUG, Time up and go test, SPPB, Short Physical Performance Battery.

	Baseline	Intervention		Follow-up	
	Week -1	Week 0	Week 4	Week 8	Week 12
PATIENTS					
Recruitment	✓				
Signed informed consent	✓				
Medical history	✓				
Merger disease	✓				
Randomization		✓			
Intervention			✓		
PRIMARY OUTCOME					
WOMAC pain subscale		✓	✓	✓	✓
SECONDARY OUTCOMES					
WOMAC stiffness subscale		✓	✓	✓	✓
WOMAC function subscale		✓	✓	✓	✓
WOMAC total score		✓	✓	✓	✓
SF-36		✓	✓	✓	✓
TUG		✓	✓		
SPPB		✓	✓		
Gait analysis		✓	✓		
OTHERS					
Medication records			✓	✓	✓
Patient satisfaction questionnaire			✓		✓

Figures

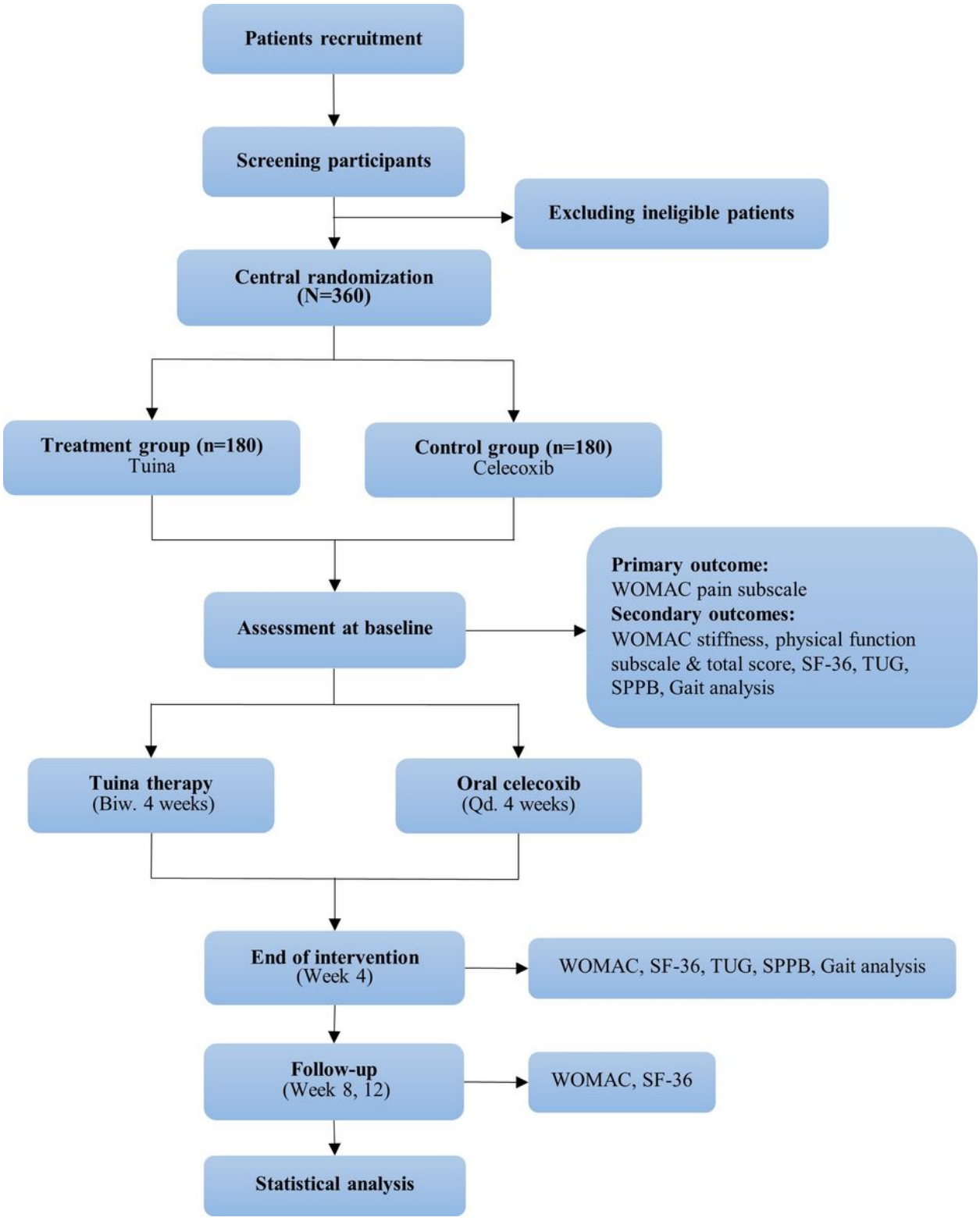


Figure 1

Study process. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. SF-36, 36-item short form health survey. TUG, Time up and go test, SPPB, Short Physical Performance Battery.

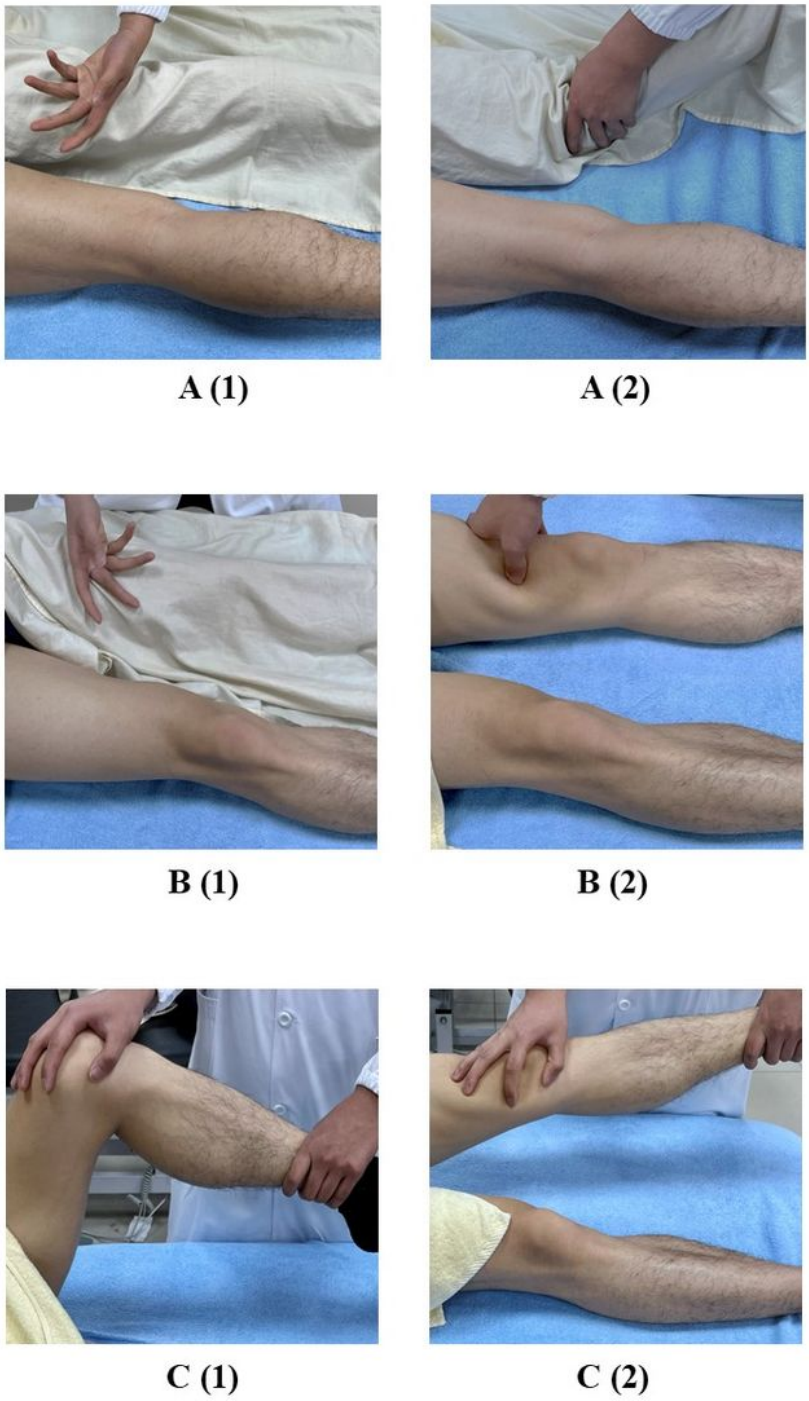


Figure 2

Details of the treatment process.

Step 1: A(1) Patient in the prone position. Roll back and forth on the posterior thigh, popliteal fossa, and posterior calf with the back of the hand; **A(2)** Point-press on Weizhong (BL40) with the thumb;

Step 2: B(1) Patient in the supine position. Roll back and forth on the anterior thigh and calf with the back of the hand; **B(2)** Point-press on Liangqiu (ST34), Neixiyan (EX-LE4), Dubi (ST35), and Xuehai(SP10) with the thumb;

Step 3: C(1-2) Press the knee joint with one hand, and hold the ankle with the other hand to give passive flexion of the lower limbs