Effectiveness of Tuina manipulation in patients with knee osteoarthritis: study protocol for a randomized controlled trial

Zhizhen Lv
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine

Qingguang Zhu
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine

Guangxin Guo
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine

Wuquan Sun
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine

Yanbin Cheng
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine

Lingjun Kong
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine

Min Fang (✉ fangmin19650510@163.com)
Institute of Tuina,Shanghai Institute of Traditional Chinese Medicine,Shanghhai 200437,China;Shanghai University of Traditional Chinese Medicine,Shanghai201203China

Zhiwei Wu
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine

Shanda Xu
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine

Xin Zhou
Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine

Shuaipan Zhang

Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine

Chongjie Yao

Shanghai University of Traditional Chinese Medicine Yueyang Hospital of Integrated Traditional Chinese Medicine and Western Medicine

---

Study protocol

Keywords: Knee osteoarthritis, Effectiveness, Randomized controlled trial, Tuina, manipulation treatment

Posted Date: November 11th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-20550/v3

Abstract

Background: Knee osteoarthritis (KOA) is a common musculoskeletal disorder. Previous studies reported that Tuina manipulation showed benificial effects in management of musculoskeletal disorders . However, there was no enough evidence to support the effectiveness of Tuina manipulation for KOA. The purpose of this study is to evaluate the effectiveness of Tuina manipulation on pain and dysfunction of patients with KOA compared with health care education.

Methods/Design: This study is a single-centre, two-arm, open-label randomized controlled trial (RCT). A total of 170 eligible KOA patients will be randomly assigned to the Tuina manipulation group or the health care education group in a 1:1 ratio. In the Tuina manipulation group, patients will receive a 30 min treatment including pain point assessment and manual therapy. The health care education group will receive 45 min of lecture and discussion. All treatments will be conducted three times a week for four weeks. The primary outcome is the Knee Injury and Osteoarthritis Outcome Score (KOOS). Secondary outcomes include the McGill Pain Questionnaire (MPQ) and 36-item Short-Form Health Survey (SF-36). The results will show the evidence of the effect of Tuina manipulation for KOA compared with health care education.

Discussion: The design and methodology of the trial is rigorous and allows the collection of valuable data to assess the effect of a specific Tuina regimen for the treatment of KOA. Therefore, the trial will provide a solid foundation for future clinical research on KOA and Tuina therapy.

Trial registration: This trial was registered with the Chinese Clinical Trial Registry on 24 February 2020 (ChiCTR2000030154), http://www.chictr.org.cn/index.aspx

Background

Knee osteoarthritis (KOA) is a disease characterized by joint pain, inflammation, stiffness and dysfunction [1]. KOA is a common musculoskeletal disorder that affects human health and brings a heavy financial burden worldwide [2]. Specific factors contributing to KOA include sex, advanced age, the use of postmenopausal hormone replacement therapy, educational attainment, and obesity [3]. Over 55 years old, the prevalence of pain and disability due to KOA is 10%, and a quarter of the affected individuals are severely disabled [4]. According to a survey, approximately 14% of American adults and 40% of Britons and Australians over the age of 65 suffer from KOA [5].

The pathophysiology of KOA has not been obviously established because it is difficult to determine the source of the pain. Studies have confirmed that cytokines such as tumour necrosis factor-α and proteases played important roles in the occurrence and development of osteoarthritis. The levels of TNF-α in the plasma and synovial fluid of patients with osteoarthritis were significantly higher than those in unaffected people, and the level of TNF-α in the synovial fluid was related to the degree of severity of the KOA lesions [6-7].

Asymmetrical narrowing of the joint space, osteosclerosis and/or cystic deformation at the lower end of the cartilage, and extra bone formation at the joint edge are the typical X-ray manifestations of KOA. MRI and CT scans can be used to achieve an early diagnosis of KOA, assist with the differential diagnosis and facilitate clinical research. MRI images of KOA are characterized by the thinning of cartilage thickness, tissue defects, meniscus injuries and degeneration, joint effusion, oedema and popliteal cysts. CT can show the stenosis of the affected joint space, subchondral bone sclerosis, cystic changes and osteophyte hyperplasia [8].

There are several different treatments than can be adopted to control KOA, such as intra-articular (IA) corticosteroid (CS) injection, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, physical therapy (PT), arthroscopy, IA hyaluronic acid (HA) injection, surgery and exercise therapy [9-12]. However, NSAIDs may induce mucosal damage in the upper digestive tract and lower digestive tract[13]. Even with the use of gastric protectants, up to three-quarters of patients who use NSAIDs suffer from small bowel damage [14]. Opioids also carry the risk of addiction [15]. These treatments can achieve beneficial effects but are associated with recurrence and side effects. The indications for the use of each treatment depends on the stage of the disease and the specific circumstances of the patient. When basic and medical treatments are not effective, patients can only undergo surgery. However, surgery is very expensive, which imposes a substantial economic burden on families and society. Therefore, to maximize the safety and minimize the cost of treatment, we need to find a treatment with few side effects and a low cost.

Tuina is a type of physical therapy that relies on the strength of the practitioner's fingers, and it is a long-standing healing art [16]. When treating KOA with Tuina, the manipulation technique should be gentle and be applied for long enough to relieve pain to achieve optimal clinical efficacy.

As a type of physical therapy, manual therapy has been recommended by many countries as a non-drug therapy in management of musculoskeletal diseases. Recent clinical studies and systematic reviews have ithat manual therapy is safe and effective for the treatment of KOA [17-19]. Compared with NSAIDs, massage therapy can improve functional pain while incurring fewer costs. However, due to differences in treatment accuracy, the use of various treatment methods, insufficient sample sizes, low methodological quality, and the differences in the control groups, the efficacy is quite controversial.

Health care education is also an effective way of intervention, it shows positive effects for KOA patients[20-22]. The study reported short-term education lecture improved pain levels, physical function, and physical and mental quality of life of patients with KOA, as well as decreased BMI of them, which based on telephone calls one year after health education lecture[23].

Previous studies showed that Tuina manipulation may improve walking ability and muscle strength of patients with KOA [24,25]. Tuina manipulation also showed potential effects on joint dysfunction of patients with KOA. In order to provide reliable clinical evidence on pain and dysfunction of Tuina manipulation for patients with KOA, the randomized controlled trial is designed to investigate the effect on pain and dysfunction of Tuina manipulation for KOA compared with health care education. The

primary outcome is the Knee Injury and Osteoarthritis Outcome Score (KOOS). Secondary outcomes include the McGill Pain Questionnaire (MPQ) and 36-item Short-Form Health Survey (SF-36).

Methods/design

Study design

This is a multicentre, blinded RCT with two parallel groups: the Tuina manipulation group and the health care education group. The research protocol was approved by the Regional Ethics Review Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine (Project No. 2019-097). It has been registered with the China Clinical Trial Registry (ChiCTR-2000030154). A total of 170 eligible patients with KOA will be randomly assigned to the two groups in a 1:1 ratio. All patients will be asked to provide written informed consent. Outcome assessments and statistical analyses will be performed by independent investigators blinded to the patient assignments. The research design is illustrated in the flow chart in Figure 1, and the research schedule is shown in Figure 2.

Participants

Eligible participants will be patients diagnosed with KOA. Patients will be notified of the trial if knee pain or dysfunction affects their daily activities at work or elsewhere. If patients express willingness to participate, the clinical trial communicator will describe the trial to them and ask them if they would like to participate. If the patient wishes to participate, an interviewer will conduct a face-to-face interview in the reception room of the hospital. Patients who meet the inclusion criteria and do not meet the exclusion criteria can join after signing the consent form.

Recruitment

We will make this trial publicly available to potential participants in the following ways: 1) posting recruitment posters in the hospital's outpatient and ward corridors; 2) posting advertisements in community centres near the hospital; 3) posting information on the hospital's official Weibo and WeChat platforms, and 4) printing advertisements in newspapers.

Inclusion criteria

Participants who meet all of the following criteria can be enrolled:

1) Fulfilment of the diagnostic criteria for knee osteoarthritis

2) Knee X-ray Kellgren and Lawrence grade 1: the joint space is possibly narrowed and may have osteophytes

3) Intensity of pain measured on the visual analogue scale (VAS) at the time of recruitment exceeding 3 points

4) Age between 40 and 65 years old, male or female

5) No massage or other related treatment received within the last 4 weeks prior to the study

6) Voluntary participation and provision of a signed informed consent form

7) Ability and willingness to comply with the interventions and follow-up assessments

8) Agreement to not receive other related treatments (including cartilage softeners) during treatment.

Exclusion criteria

Participants who meet any of the following conditions will be excluded:

1) A history of trauma and surgery in the knee or diseases such as cancer, tuberculosis, and osteomyelitis in the knee

2) Severe liver and kidney dysfunction, severe cardiovascular disease, diabetes and mental illness that could affect massage therapy

3) Inability to communicate or provide self-care due to mental or psychological disorders associated with severe mental illness or dementia

4) Physical pain caused by other diseases

5) Partial damage in the acute phase or local skin damage

6) Duration of knee joint pain or stiffness episodes less than 0.5 hours.

7) Pain attacks for less than 3 months or more than 2 years

8) Failure to adhere to treatment at the prescribed time

9) Use of massage or other related treatments within one week prior to entering the study

10) Participation in other clinical trials

11) Use of any other treatment (drug or non-drug) during the trial.

Dropout criteria

Participants who do not complete the clinical programme for the following reasons should be considered as having withdrawn from the study:

1) Patient withdrawal (poor efficacy or adverse reactions)

2) Lost to follow-up

3) Patient removal by a researcher (poor compliance, complications or serious adverse events).

The test communicator will have in-depth communication with a patient who wants to withdraw from the trial because of low effectiveness or a lack of time to promote retention.

Randomization

In this trial, the Yueyang Hospital Science and Technology Department will generate a random sequence using a random number generator (SPSS 21.0, SPSS Inc., Chicago, IL, USA). Random numbers will be placed in opaque envelopes, numbered sequentially, and sent to the therapists. The envelopes will be opened in numerical order to determine the assignment of participants during screening. After completing the baseline questionnaire, the therapist perform the physical examination and apply the exclusion criteria. Only after that has been completed will the envelope be opened, so that the study administrator, therapist, and the study participant are unaware of the group assignment until all baseline data have been collected.

Blinding

As an open-label clinical trial, both clinicians and patients will know which treatment is being administered. The clinical efficacy assessment will be conducted by the clinical assessor on the phone, and the assessor will conceal the treatment. During the data collection and analysis phase, clinical researchers, evaluators, and statisticians will not share research information with each other.

Interventions

Participants will receive 12 treatments within 4 weeks. The treatment will be carried out by a senior therapist who has studied acupuncture and massage and has been licensed for more than 10 years. Participants will be asked to rest for 15 minutes before treatment. A constant room temperature of 23 to 25°C will be maintained to ensure that the patient is comfortable and relaxed during treatment. The intervention will be performed twice a week. Each treatment will last for 20 minutes. Knee function will be assessed at baseline and 2, 4, 8, and 12 weeks after the baseline assessment.

Tuina manipulation group

In this part of the study, the therapist will use a two-step approach to relieve pain around the knee and improve knee dysfunction. The therapist will release the soft tissue around the knee by inducing general relaxation while addressing specific structural problems. The clinician will determine which approach will be most helpful for alleviating pain due to KOA and for promoting air transport (activation of blood circulation according to traditional Chinese medicine (TCM) theory). The specific scheme used will be as follows.

The specific method of massage implemented will be based on conventional acupoint tuina manipulation around the knee joint of the patient. The pain points will be identified based on the

description provided by the patient and palpation of the area by the practitioner and then treated with Tuina manipulation, 20 minutes each time, 3 times a week for 4 weeks.

Step one: Check the pain points around the knee joint

With the patient in a supine position, the examiner will identify pain points by holding the upper part of the patient's knee joint in one hand while sliding and pressing the thumb of the other hand along the inner knee, the outer knee eyes, any adductor nodules, the medial and lateral joint spaces, the femur, the tibia, and the periorbital and popliteal fossa.

To check the popliteal fossa, the patient will be placed in the prone position with the knee bent, and the practitioner will slide and press the thumb along the centre, the lower portion, the outside and the upper portion of the popliteal fossa. When inspecting the inner side of the apex patellae, the examiner will push the patella downwards with the left hand so that the apex patellae is lifted up and then press the facies medialis of the apex patellae with the fingertips of the right hand, with the thumb facing upward.

Step two: Tuina local manipulation

The patient will be placed in the supine position. The doctor will stand on the affected side, apply Tuina manipulation to a regular acupuncture point around the patient's knee joint and then press and rub the patient's pain point. The pain point is generally considered to reflect the underlying condition and is often used for pain relief. The frequency of the press and rub manipulation should be 120-140 times/min. The doctors press the acupoints, including Futu (ST32), Liangqiu (ST34), Dubi (ST35), Xiguan (LR7), Neixiyan (EX-LE4), Xiyan (EX-LE5) and Ashi points, with the thumb to achieve Deqi sensation. Then, the patient will be placed in the prone position, and the doctor will repeat the above operation.

Health care education group

In the health care education group, patients with KOA will participate in a 45-minute health care educational seminar three times a week for 4 weeks. The programme will include a 30-minute lecture and a 15-minute discussion. The content will involve the diagnosis of KOA, healthy diet, pain management, physical and mental health, and healthy lifestyle factors.

Each participant will be given an introduction about the underlying mechanisms and predisposing factors of KOA. Interventionists will draw up specification of daily routines for participants, for example: Keep the knees warm; prevent obesity; maintain a beneficial posture and abandon bad exercise posture; avoid fatigue, excessive exercise or weight lifting; choose appropriate exercise; maintain a good mental state, and inform them that chronic pain has a long process.

Allowance for concurrent treatment of patients

All KOA treatments are prohibited during the trial, including oral muscle relaxants, anaesthetics, analgesics, surgery, drug injections, acupuncture and physical therapy. They may receive any treatment

that is not related to knee pain. Any changes to concurrent treatments will be recorded at each visit.

Primary outcome measurements

KOOS

The knee injury and osteoarthritis outcome score (KOOS) has been widely used in research and has been shown to be efficient and reliable when use to measure knee pain [26]. We used the KOOS (0-100 scale, 0 for extreme knee problems, 100 for no problems) as our primary outcome at baseline and at the end of the intervention to measure the clinical results. The KOOS scale is an extension of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a self-administered 42-question survey covering five patient-related domains: pain, other disease-specific symptoms, daily functional activities, motor and recreational functions, and knee-related quality of life. The scale is an effective, reliable, and responsive method of measuring results with good test reliability and structural validity for total joint replacement. We used other KOOS subscale scores as the primary outcome. We will measure the outcome at these five time points (baseline, two, four, eight and twelve weeks) and compare. In this trial, we will compare the mean and standard deviation of the two groups at each time point. then, the change in values from baseline until the time point will be included in the comparison.

Secondary outcome measurements

MPQ

The McGill pain questionnaire (MPQ) is a very common scale that measures and evaluates various pain [27-28]. The MPQ contains 4 groups of 20 pain descriptions. Each group of words is arranged in increasing order with regard to the severity of pain. Dimensions one to ten are sensory, 11 to 15 are affective components of pain, 16 are pain evaluations, and 17 to 20 are miscellaneous. The test subject selects a word to indicate the degree of pain in each group (they must select a word).

SF-36

The SF-36 questionnaire assesses the association between health-related quality of life and various factors [29]. It is widely used in the field of quality of life, clinical trials and health policy. It consists of 36 questions, divided into Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP): General Health (GH), Vitality, Social Function (SF), Role-Emotional, (RE), Mental Health (MH), General Health (GH) and eight other aspects. For each domain, the score ranges from 0 to 100, with higher scores reflecting a better quality of life. The SF-36 will be evaluated using repeated longitudinal analysis. Same as primary outcome, secondary outcome will be measured at these five different time points (baseline, two, four, eight and twelve weeks).the method of aggregation and the metric for comparison is the same as KOOS.

Safety evaluation

Treatment safety will be assessed by researchers monitoring patient symptoms before and after treatment. In this trial, the following events will be defined as adverse events (AEs): (1) severe pain; (2) syncope; (3) deterioration in walking function; (4) hospitalization; and (5) life-threatening changes, all of which will be carefully recorded in the case report form. In the case of any AEs, whether or not they are related to the treatment, treatment will be stopped immediately. The patient will be treated, and the AEs will be reported to the responsible unit and the ethics committee to determine if the patient should withdraw from treatment.

Follow-up

To assess the short-term efficacy, long-term efficacy, and safety of the interventions, we will track participants for 2 months after the trial. During the 2 months of unsupervised follow-up, no participants will receive special treatment other than regular knee care. At weeks 8 and 12, the evaluators will investigate the recurrence of knee pain over the telephone. Patients will also be able inform the assessor of their clinical signs and mood changes by email, text message or WeChat at the relevant time. During the follow-up period after the trial, any health issues will be assessed, and the committee will be notified.

Data collection and monitoring

The assessor will record the clinical results in the case report form (CRF), including the assessment of the treatment effect, the changes in physiological function and details of AEs. The completed CRFs will be reviewed by a four-person steering committee composed of the heads of the four research centres. Then, the CRFs will be submitted to the data stewards, who are independent of the research team and do not know the group allocation of the participants. The stewards will enter the data into an Excel database. All data administrators will have data analysis qualifications and unified training. To ensure the accuracy of the data, the two data administrators will independently enter the information and check the accuracy of the entered data. If there is a problem with the information on a CRF, the data administrator will complete the requisite form, and then the data administrator can modify the data according to any revisions provided by the steering committee. After confirming that the database is correct, the steering committee, data stewards, and statisticians will lock the database.

Health economics

All costs associated with this test will be recorded. These costs mainly include medical costs for the direct treatment of KOA, such as inpatient bed fees, outpatient registration fees, Tuina treatment fees, daily care and testing fees, and in addition, the cost of treatment for any AE will be recorded and included in the health cost evaluations.

Sample size calculation

The expected efficacy rate of Tuina manipulation is 70%, and the efficacy rate of health care education based on the literature is 45%. The sample size was calculated with a significance level of 0.05 and

power of 0.90, with consideration of a maximum dropout tolerance of 10%. Finally, 170 patients are needed for the trial, with 85 patients in each group.

Data analysis

Demographic and baseline data will be analysed with standard descriptive statistics. Between-group differences will be tested using repeated measures analysis of variance. The acceptable significance level for all analyses will be $P<0.05$. The complete analysis set, including dropouts, will be analyzed through an intention-to-treat (ITT) population analysis. Statisticians who are independent of the research team and are blinded to group allocation will perform the data analysis. Data analysis will be performed with SPSS software (for Microsoft Windows® SPSS, Inc., SPSS 21.0 KO, Chicago, Illinois, USA).

Quality control

To improve the reliability of the results of this study, we designed quality control procedures with regard to the following aspects: (1) baseline homogeneity: this study limits the age of participants to between 40 and 65 years, and we will assess people with similar living habits; (2) Tuina manipulation: in this study, all researchers will be trained to fully understand the design and protocol of the trial, the use of the CRF, and the manipulation technique. To avoid operational differences, two experienced doctors who will have received specialized standardized training before the trial will perform all treatments in accordance with the standard operating procedures. In addition, during the treatment, except for that needed to identify pain points, communication between the therapist and the patient is prohibited; (3) Pain points: considering the importance of pain point identification for accurate treatment evaluation, the pain threshold at the tender points will be measured after each treatment to evaluate whether there is a significant difference in stimulus and pain perception after each treatment, which will help rule out the bias of using the pain points; (4) data collection and completeness: Yueyang Hospital of Integrated Traditional Chinese and Western Medicine Data Monitoring Team will be responsible for controlling bias and identifying problems in the project. Detailed records of changes will be kept. Meanwhile, a qualified clinical trial expert will monitor the therapists after every course of treatment, and regular board meetings will be held to ensure the quality of the study process.

Discussion

Knee pain is one of the most challenging public health problems in the world. Given its prevalence, there is a need to identify effective methods of treating knee joint disease. Tuina is an important aspect of Chinese medicine and has contributed to the health of the Chinese people for more than a thousand years. A large body of scientific evidence supports this treatment for knee pain, but its efficacy has not been determined. Therefore, it is important to provide strong evidence of the effectiveness of massage therapy for the treatment of KOA.

This trial is a comparative study of the efficacy and safety of massage (intervention) and health care education (control) for pain relief and functional recovery in KOA patients. For high-quality RCTs, proper

control is critical. Both pain intensity and motion function are subjective, and we will use validated scales and questionnaires to assess these clinical outcomes. The KOOS will be used as the primary outcome, as it measures knee pain and the impairment of daily function. The secondary outcomes are the MPQ, which measures the intensity of pain in general and the emotional effect of pain, and the SF-36, which measures health-related changes in quality of life.

The A-Shi point in Chinese medicine refers to a point on the surface of the body. When it is lightly pressed, it will reproduce the specific pain being treated. Its position indicates the exact location where the Qi and blood are blocked. Manipulation of the A-Shi point promotes the free movement of the Qi and improves blood circulation in the area, eliminating obstacles and relieving pain. Studies have shown that one mechanism by which Tuina acts is by activating the piezo electric channel as a physical stimulus, after which the membrane potential changes due to the flow of charged ions and generates an analgesic effect[30]. Strength training around the joint muscles and low-intensity aerobic exercise can relieve pain. Maintaining joint mobility and improving joint function can control the progression of KOA. Tuina is a treatment that uses manipulation by a doctor to achieve muscle stimulation and improve joint function. The RCT design and methodological rigor of the trial will allow the collection of valuable high-quality data that can be used to assess the efficacy of Tuina manipulation and health care education for the treatment of KOA. The trial will provide a solid foundation for the clinical treatment of KOA and future research on Tuina and massage therapy.

Study limitation

One of the primary methodological difficulties inherent to studies evaluating physical interventions is blinding of participants. In this study, Tuina manipulation and health care education are different forms of physical therapy, which hardly be blinded for the participants and therapists.Therefore, the quality of the blinding method should be monitored to control the questionnaire measurement credibility, which is composed of administrator, evaluators and the data analysts.

Trial status

Participant recruitment started in March 2020 and is expected to end in February 2021. This trial was registered in the Chinese Clinical Trial Registry on 24 February 2020. The registration number is ChiCTR2000030154

Abbreviations

AE: adverse event; CRF: case report form; CT: computerized tomography; ITT: Intention-to-Treat; KOA: knee osteoarthritis; KOOS: Knee Injury and Osteoarthritis Outcome Score; MPQ: McGill pain questionnaire; MRI: magnetic resonance imaging; NSAIDs: nonsteroidal anti-inflammatory drugs; RCT: randomized controlled trial; SF-36: 36-item Short-Form Health Survey; SPSS: Statistical Package for Social Sciences; TCM: traditional Chinese medicine; TNF-α: tumour necrosis factor-α; WOMAC: Western Ontario and McMaster Universities Arthritis Index

Declarations

Funding

This study is supported financially by the Shanghai Further Accelerate the Three-year Action Plan for the Development of TCM of Shanghai (ZY(2018-2020)-CCCX-2004-02), the Major Disease Clinical Skills Upgrading Project of Shanghai Shen-kang Hospital Development Center (16CR1023A), the National Major and Difficult Diseases Collaborative Pilot Project of Traditional Chinese and Western Medicine–Osteoarticular Degenerative Disease (ZY(2018-2020)-FWTX-2005), the Outstanding Young Medical Talents of Shanghai Municipal Commission of Health and Family Planning (2018YQ04), the Chinese Traditional Medicine Association Young Talent Project (QNRC2-A01), and the Chinese Medicine Research Tasks of Shanghai Health Planning Committee (2018LP040). The funders had no role in the design of the study; analysis, collection, and interpretation of the data; or the writing of and decision to publish the manuscript. All this funding applies to this study.

Authors' contributions

ZL and GG participated in the protocol writing and design of the trial, and LK drafted the manuscript. QZ will perform the Tuina treatments. WS recruited and screened qualified participants in the outpatient department, and MF was responsible for the study. YC is responsible for coordinating the treatment of patient ZW, who participated in the design of the trial and helped prepare the manuscript. SX participated in evaluating treatment efficacy and collecting clinical data. XZ participated in the strict revision of the manuscript. SZ participated in evaluating treatment efficacy and collecting clinical data. CY participated in the strict proofreading of the manuscript. All authors have read and discussed the final manuscript, and all approved the manuscript for publication.

Ethics approval and consent to participate

This study will be conducted in accordance with the guidelines and principles of the Declaration of Helsinki. The protocol was approved by the Ethics Review Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, which is affiliated with Shanghai University of Traditional Chinese Medicine (reference 2019-097) and is registered with the Chinese Clinical Trial Registry (ID: ChiCTR-2000030154). Informed consent from all study participants will be obtained before clinical trial assessors begin collecting any data. All participants will provide their written consent. No one except investigators will have access to the final data.

Availability of data and material

The datasets analysed in the whole study can be obtained from the corresponding authors upon reasonable request.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Tuina Department, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200437, China. [2]Institute of Tuina, Shanghai Institute of Traditional Chinese Medicine, Shanghai 200437, China. [3]Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China.

References

1. White AG, Birnbaum HG, Janagap C, et al. Direct an indirect costs of pain therapy for osteoarthritis in an insured population in the United States. J Occup Environ Med. 2008;50:998–1005.
2. Ong KL, Runa M, Lau E, et al. Cost-of-illness of knee osteoarthritis: potential cost savings by not undergoing arthroplasty within the frst 2 years. Clinicoecon Outcomes Res. 2019;5(11):245-255.
3. Callahan LF, Shreffler J, Siaton BC, et al. Limited educational attainment and radiographic and symptomatic knee osteoarthritis: a cross-sectional analysis using data from the Johnston County (North Carolina) Osteoarthritis Project. Arthritis Res Ther. 2010;12(2):46.
4. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis. 2001;60:91–7.
5. Le TK, Montejano LB, Cao Z, et al. Health care costs in US patients with and without a diagnosis of osteoarthritis. J Pain Res. 2012;5:23-30.
6. David D McErlain, Veronica Ulici, Mark Darling, et,al. An in vivo investigation of the initiation and progression of subchondral cysts in a rodent model of secondary osteoarthritis.Arthritis Research & Therapy (Online). 2012;14(1):26.
7. S Botha-Scheepers, I Watt, E Slagboom, et,al. Innate production of tumour necrosis factor α and interleukin 10 is associated with radiological progression of knee osteoarthritis. Ann Rheum Dis. 2008;67(8):1165-1169.
8. W Zhang, M Doherty, G Peat, et al. EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. Ann Rheum Dis. 2010;69(3):483-489.
9. Bozic KJ, Stacey B, Berger A, et al. Resource utilization and costs before and after total joint arthroplasty. BMC Health Serv Res. 2012;12:73.
10. Cohen JR, Bradley AT, Lieberman JR. Preoperative interventions and Charges before total knee arthroplasty. J Arthroplasty. 2016;31(12):2730–2735.
11. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis:an update with relevance for clinical practice. Lancet.2011;377(9783):2115 -2126.

12. Sadr K, Pulido P, McCauley J, et, Osteochondral Allograft Transplantation in Patients With Osteochondritis Dissecans of the Knee. Am J Sports Med. 2016;44(11):2870-2875.
13. Lanas Á, Carrera-Lasfuentes P, Arguedas Y, et al. Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. Clin Gastroenterol Hepatol. 2015;13:906-912.
14. Wallace JL. NSAID gastropathy and enteropathy: distinct pathogenesis likely necessitates distinct prevention strategies. Br J Pharmacol. 2012;165:67-74.
15. Da Costa Bruno R, Nüesch Eveline, Kasteler Rahel, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. The Cochrane database of systematic reviews. 2014;9:
16. Goats GC. Massage–the scientific basis of an ancient art: Part 1: the techniques. Br J Sports Med. 1994;28:149–52.
17. Ali A, Kahn J, Rosenberger L.Development of a manualized protocol of massage therapy for clinical trials in osteoarthritis. Trials. 2012;13:185.
18. Ali A, Rosenberger L, Weiss TR, et al.Massage Therapy and Quality of Life in Osteoarthritis of the Knee: A Qualitative Study. Pain Med. 2017;18(6):1168-1175.
19. Perlman A, Fogerite SG, Glass O, et al. Efficacy and Safety of Massage for Osteoarthritis of the Knee: a Randomized Clinical Trial. J Gen Intern Med. 2019;34(3):379-386.
20. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012;64(4):465-74.
21. Fernandes L, Hagen KB, Bijlsma JW, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis. 2013;72(7):1125-35.
22. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014;22(3):363-88.
23. de Rezende MU, Hissadomi MI, de Campos GC, et al. One-Year Results of an Educational Program on Osteoarthritis: A Prospective Randomized Controlled Trial in Brazil. Geriatr Orthop Surg Rehabil. 2016;7(2):86-94.
24. Zhu QG, Fang M, Gong L, et al. Gait analysis of patients with knee osteoarthritis before and after Chinese Massage treatment. Journal of Traditional Chinese Medicine, 2015;35(4):411-416.
25. Zhu QG, Li JH, Fang M, et al. Isokinetic muscle strength evaluation of patients of knee osteoarthritis before and after Chinese Massage. Journal of Traditional Chinese Medicine, 2016;36(3):314-320.
26. Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) dvalidation and comparison to the WOMAC in total knee replacement. Health Qual Life Outcome. 2003;1:
27. Ferreira VT, Guirro EC, Dibai-Filho AV, et al. Characterization of chronic pain in breast cancer survivors using the McGill Pain Questionnaire. J Bodyw Mov Ther. 2015;19(4):651-5.
28. Hansen RB, Frost CØ, Sonne NM, et al. Exploring the Patients' Perception of Background and Breakthrough Pain: A McGill Pain Questionnaire Inquiry in Patients with Bone Cancer Pain. J Palliat

Med. 2019,22(8):881-883.

29. Lam CL, Tse EY, Gandek B, et al. The SF-36 summary scales were valid, reliable, and equivalent in a Chinese population. Clin Epidemiol. 2005;58:815-
30. Song PF, Lin ZG, Zhu QG, et al. Possible mechanism underlying analgesic effect of Tuina in rats may involve piezo mechanosensitive channels within dorsal root ganglia axon. J Tradit Chin Med. 2018; 38(6):834-841.

Figures

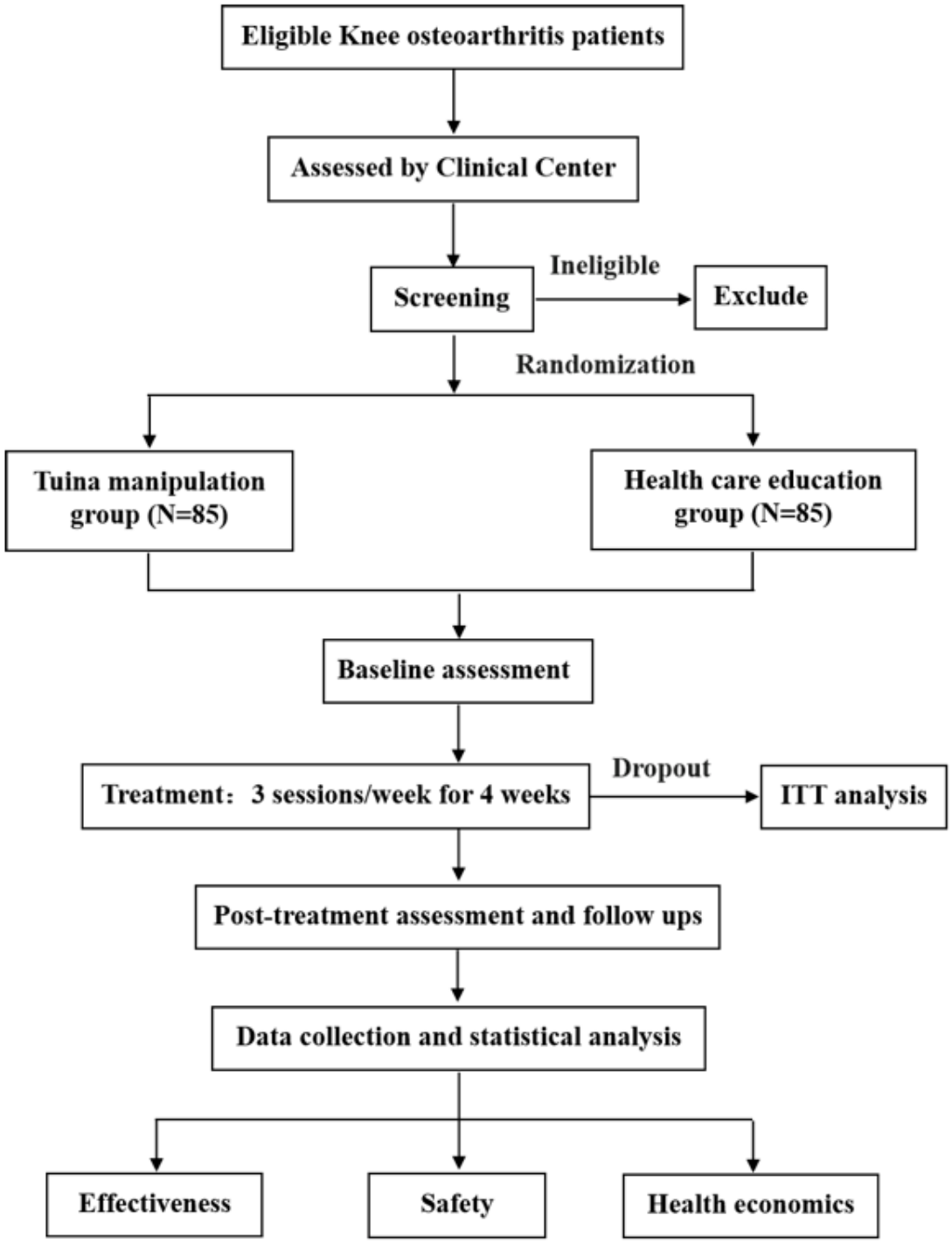

Figure 1

Trial flow chart. This study is a single-center, randomized, health education-controlled, open-label trial. It is expected that 170 eligible KOA patients will be randomly assigned to a Tuina manipulation group or a health care education control group at a 1: 1 ratio. Patients in the Tuina manipulation group will receive two-step Tuina treatment including pain point examination and relaxation manipulation. Tuina manipulation treatment includes 12 treatments, each lasting about 20 minutes, 3 times a week for a total

of 4 weeks. Patients in the health care education group will receive lectures. After collecting data, statisticians will analyze the effectiveness, safety, and health economy of Tuina manipulation compared to health care education. The complete analysis set, including dropouts, will be analyzed through an intention-to-treat (ITT) population analysis.

Time	W-1	W0	W1	W2	W3	W4	W8	W12
Period assessment	Screening	Baseline	Intervention				Follow-up	
Patients diagnosis								
Inclusion confirmed	√							
Informed consent	√							
Disease history	√							
Treatment history	√							
Comorbidity	√							
X-ray	√					√	√	√
Physical examination	√			√		√	√	√
Randomization		√						
Intervention								
Tuina manipulation group（n=75）			12 sessions of Tuina manipulation treatment					
Health care education group（n=75）			12 sessions of health care education					
Outcomes								
KOOS		√		√		√	√	√
MPQ		√		√		√	√	√
SF-36		√		√		√	√	√
Data collection and statistical analysis								
Adverse event			√	√	√	√	√	√
Causes of dropout			√	√	√	√	√	√
Safety analysis			√	√	√	√	√	√
Health economics						√	√	√
Analysis	√	√	√	√	√	√	√	√

Figure 2

Study schedule data collection showing time points for enrollment and assessment. The informed consent and examination will be conducted after recruitment. After that, we will randomly match KOA patients into two groups, one group will receive Tuina manipulation treatment and the other will receive health care education. Clinical results will be performed at two time points, including: baseline and end of session of study. During the study, adverse events will be recorded on the case report form. KOOS Knee Injury and Osteoarthritis Outcome Score, MPQ McGill pain questionnaire, SF-36 36-item Short-Form Health Survey, W-1 screening before enrollment, W0 baseline assessment, W2 assessment after the sixth treatment, which is in the second week, W4 assessment after the 12th treatment, which is in the fourth week, W8 assessment 8 weeks after the first treatment, W12 assessment 12 weeks after the first treatment.

Supplementary Files

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

- SPIRIT.doc
- KOOSKNEESURVEY.pdf