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STUDY PROTOCOL

Effect of Shi-Style Steaming and Bathing Decoction in Patients with Knee Osteoarthritis: Study Protocol for a Randomized Placebo-Controlled Trial

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Purpose: To prove more accurately that Chinese herbal bath therapy may be a safe, effective, simple alternative treatment modality for knee OA, we designed a randomized, double-blind, placebo-controlled trial to explore the effectiveness of SSBD for the relief of pain, daily activities, and quality of life in patients with knee OA.

Patients and Methods: A single-center, 52-week, randomized controlled trial of SSBD versus placebo is being performed. A total of 200 patients with symptomatic knee OA will be randomly allocated to the SSBD treatment or placebo intervention group for 4 weeks. The two groups of patients are allowed to steam and bathe their knees once every other day, using one packet of SSBD each time, for 30 minutes, 3 times a week, for a total of 4 weeks. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale at 4 weeks is the primary outcome measure, and the secondary outcomes include WOMAC stiffness and function scores, the Lysholm knee scale score, quality of life, the Brief Pain Inventory score, the Patient's Global Impressions of Improvement Scale score and the Clinical Global Impressions of Severity scale score. The safety of the herbal medications will also be evaluated.

Conclusion: We will discuss whether SSBD has greater advantages in terms of efficacy, safety, and patient overall perception than does placebo control in middle-aged and elderly patients with knee OA. The findings may provide new and valuable information about the efficacy and safety of Chinese herbal bath therapy in the treatment of knee osteoarthritis.

Keywords: balneotherapy, traditional Chinese medicine, complementary and integrative medicine, randomized placebo-controlled trial, knee osteoarthritis

Introduction

Knee osteoarthritis (OA) is a degenerative joint disease that typically results from wear and tear and progressive loss of articular cartilage.[1] It can cause pain, joint stiffness, joint swelling, loss of joint function and other clinical manifestations,[2] and results in heavy personal and social burdens for middle-aged and older adults.[3] OA affects an estimated 302 million people worldwide and is an enormous economic loss to individuals and society.[4] Despite its high prevalence, the exact etiology and pathogenesis of OA are poorly understood and no effective disease-modifying treatment for OA is currently available.[5,6] Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are commonly used to treat knee OA but often fail to relieve symptoms and may cause serious adverse effects.[7,8]

In recent decades, many clinical studies and reviews have evaluated the efficacy of balneotherapy in the treatment of Knee osteoarthritis.[9,10] The available evidence from these growing numbers of clinical trials and reviews suggests that balneotherapy is effective for pain relief and the functional improvement of Knee osteoarthritis.[11,12] As a complementary and alternative therapy, herbal bath therapy has been developed over thousands of years in China for relieving knee

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osteoarthritis pain and alleviating knee dysfunction, but the necessary quantitative evidence to estimate treatment effects is still lacking. Inappropriate water temperature settings may be the cause of the expected negative consequences, which could burn the skin. These Chinese medicines have been used for thousands of years in China, and no negative side effects, such as skin allergies, have been reported from prior use. Shi-style steaming and bathing decoction (SSBD) is the most famous external treatment technique in Shanghai "Shi's Traumatology", a school of Chinese medicine that has been passed down and used for hundreds of years.[13,14] To evaluate more accurately if Chinese herbal bath therapy may be more accurately that Chinese herbal bath therapy may be a safe, effective, simple alternative treatment modality for knee OA, we designed a randomized, double-blind, placebo-controlled trial to explore the effectiveness of SSBD for the relief of pain, daily activities, and quality of life in patients with knee OA.

Material and Methods

Study Setting

This is a single-center, double-blind, placebo-controlled, randomized clinical trial that will be organized and implemented by the Shuguang Hospital Affiliated with Shanghai University of Traditional Chinese Medicine (TCM) in China. The trial was registered at ClinicalTrials.gov on 19 August 2022. (identifier ChiCTR2200062818).

Eligibility Criteria

Inclusion Criteria

(1) Patients aged ≥ 50 years. (2) Patients who met the diagnostic criteria of the American College of Rheumatology for symptomatic knee OA[15] (recurrent knee pain in the past month, morning stiffness ≤ 30 minutes in duration, crepitus on motion, or a definite osteophyte identified on knee radiographs). (3) Patients with a score of 40 or greater on at least 1 of the 5 questions in the WOMAC pain subscale (range 0 to 100 each, higher indicating more pain) at baseline. (4) Patients who voluntarily participated in the trial and signed the informed consent form.

Exclusion Criteria

(1) Patients with serious primary diseases, such as those of the cardiovascular, hepatic, renal or hematopoietic systems, or mental disorders. (2) Skin lesions or skin diseases at the treatment site. (3) Paresthesia of the skin temperature. (4) Patients who are participating in other drug clinical trials or have participated in other clinical trials within 3 months.

Sample Size

Sample size calculations were conducted by biostatisticians from the Department of Epidemiology and Health Statistics, Shanghai University of TCM. The total score of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was the primary outcome for sample size calculations. As reported by early experimental study data, the improvement rate in the total WOMAC score in the experimental group was 35%, whereas that in the control group was 16%.[16] The sample size calculation formula:[14] $n=(U_{\alpha}+U_{\beta})^2\ 2P\ (1\text{-}P)\ /(P_1\text{-}P_0)^2$. The positive rate P1 of the experimental group was 35% and the positive rate P0 of the control group was 16%, $\alpha=0.05$ (two-tailed hypothesis tests), and $1\text{-}\beta = 0.90$. Considering a dropout rate of 10%, the estimations indicated that a sample size of 100 individuals was required for each group.

Recruitment Strategies and the Informed Consent Process

The combinations of posters and flyers within the hospital and social media advertising are employed. Referrals from doctors and nurses from other affiliated hospitals of Shanghai University of TCM are also important ways to obtain candidates. A study physician explains all the study procedures to potential participants and answers their questions. All individuals who agreed to participate provide informed consent form. After providing informed consent, the study physician screen the participants to confirm that potential participants meet the eligibility criteria. A flowchart for participant identification, inclusion, study design, interventions, assessments, and follow-up is shown in Figure 1.

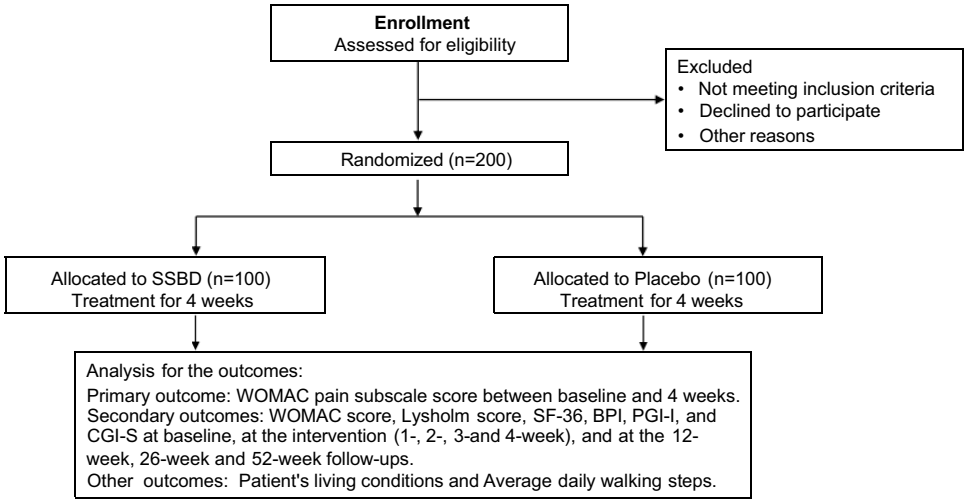

Figure 1 Study flow chart. Abbreviations: BPI, The Brief Pain Inventory; CGI-S, Clinical Global Impressions of Severity scale; PGI-I, Patient's Global Impressions of Improvement; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; SSBD, Shi-style steaming and bathing decoction; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Randomization

Participants with knee OA who meet the study eligibility criteria are randomly assigned to the trial group or control group in a 1:1 ratio. An independent study statistician randomizes assignments using a computer-generated randomization sequence that will be placed in sequentially numbered sealed, opaque envelopes. Adequate allocation concealment methods will be used in this trial. The study staff members and the patients were blinded to the treatment assignments during the enrollment and intervention. The blinded outcome assessors and data analysts cannot access the data until the data collection is completed. According to the emergency unblinding policy, when a patient needs emergency treatment due to an adverse event, and when the emergency treatment is related to the actual situation of receiving the study drug, the principal investigator and the project director may decide to initiate emergency unblinding and read the corresponding emergency letter. The researcher should fill in the corresponding records with the date, reason, and process of unblinding.

Ethics Approval

The study design and procedures were approved by the Chinese Ethics Committee of Registering Clinical Trials, (Reference number: ChiECRCT20220077). The study protocol has been modified based on expert opinion and the version number currently in use is version 2.0, which was revised on 8 April 2022. The trial will be conducted in accordance with the Helsinki Declaration.

Intervention Measures

Eligible participants will be randomized into two groups. Participants in the intervention group will be administered the Shi-style Decoction by steaming and bathing their sick knees for 4 weeks. SSBD is composed of Cassia Twig 20 g, Manchurian Wildginger 10 g, Arisaema Consanguineum 20 g, Clematis Root 20 g, Dahurian Angelica Root 20 g, Chinese Pyrola Herb 20 g, Pricklyash Peel 10 g, Rhubarb 20 g. After the above herbs were boiled with 3000 mL of water, the plants were poured into the foot soaking bucket together with the residue, cold water was added to reduce the temperature of the liquid to approximately 50°C, the sick knee was first placed on the top of the bucket, the steam was fumigated into the knee (while paying attention to avoid scalding), and when the water temperature dropped to 40°C, the knee was submerged in the herbal liquid. A towel soaked in the herbal liquid was used to wipe and cover the knee for 30 minutes, a thermometer was used to monitor the temperature of the herbal liquid throughout the whole process, and the temperature of the herbal liquid was not lower than 40±2°C.

The control group will receive a placebo containing a food coloring agent and a small amount of Manchurian Wildginger and Pricklyash Peel, which have the same color and smell as the intervention group. The steaming and bathing process will also be the same as that in the intervention group.

The above herbs were obtained from the Chinese Medicine Pharmacy of Shuguang Hospital affiliated to Shanghai University of TCM. To ensure that the herbal medication used in the intervention group and the placebo used in the control group were completely consistent, we also commissioned Shanghai Traditional Chinese Medicine Pharmaceutical Technology Co., Ltd, to powder the herbal medication and placebo and wrap it in a nonwoven bag so that the patients in the two groups could not notice the difference when they received the treatment herbs or placebo or after boiling. The dispensing and withdrawal of herbal medications and placebos are the responsibility of the research coordinator, and are stored and managed by the research pharmacy. Every patient is given only a 1-week quantity of herbal medications and placebos at each visit during treatment. The old packaging is collected at the weekly visit, and the herbal medications will be dispensed for the following week.

The two groups of patients are allowed to steam and bathe their knees once every other day for 30 minutes, 3 times a week; for a total of 4 weeks. The study coordinator will inform the participants of the correct method of the application and precautions, and each included patient will be given an electronic wristband to record the average number of walk steps taken during the intervention. Participants will receive free health talks and health guidance from professional physicians at the research center, and research staff will also maintain close contact with patients by phone or via a social media app to ascertain and improve patient adherence. All participants in the two groups are encouraged to perform their usual physical activities. The use of painkillers, muscle relaxants and other drugs is prohibited during the intervention period. If there are special circumstances that require the use of the above drugs, the application should be truthfully recorded in the case report form.

Outcome Measures

Follow-up assessments with questionnaires and outcome measurements of knee OA will be focused on pain, physical function, quality of life, and patient global assessment of the knee based on the core domain set recommended by the Outcome Measures in Rheumatology Group and the Osteoarthritis Research Society International.[17] All participants are evaluated at baseline, at the intervention (1-, 2-, 3-and 4-week), and at the 12-week, 26-week and 52-week follow-ups. The specific endpoints, study process and outcome evaluation are presented in Table 1.

Table 1 The Specific Endpoints, Study Process and Outcomes Evaluation

	Study Period								
	Enrolment	**Allocation**	**Intervention**				**Follow-Up**		
Timepoint	***−7-0 Day***	***0 Day***	***1 Week***	***2 Week***	***3 Week***	***4 Week***	***12 Week***	***26 Week***	***52 Week***
Enrolment:									
Eligibility screen	×								
Informed consent	×								
Random allocation		×							
General information		×							
Interventions:									
SSBD			×	×	×	×			
Placebo			×	×	×	×			

(*Continued*)

Table 1 (Continued).

	Study Period								
	Enrolment	**Allocation**	**Intervention**				**Follow-Up**		
Assessments:									
*WOMAC-Pain**	×	×	×	×	×	×	×	×	×
WOMAC-Physical Function		×	×	×	×	×	×	×	×
WOMAC - Stiffness		×	×	×	×	×	×	×	×
Lysholm		×	×	×	×	×	×	×	×
SF-36		×				×	×	×	×
BPI		×	×	×	×	×	×	×	×
PGI-I			×	×	×	×	×	×	×
CGI-S		×	×	×	×	×	×	×	×
Average daily walking steps		×	×	×	×	×	×	×	×
Safety Observation:									
Adverse event			×	×	×	×			

Notes: *WOMAC Pain is the primary outcome at 4 weeks; the other collection times are secondary outcome variables.
Abbreviations: BPI, Brief Pain Inventory; CGI-S, Clinical Global Impressions of Severity; PGI-I, Patient's Global Impressions of Improvement; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; SSBD, Shi-style Steaming and Bathing Decoction; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Primary Outcome

The primary outcome measure of this study is the change in the WOMAC pain subscale score between baseline and 4 weeks. The WOMAC is a self-administered questionnaire consisting of 24 items divided into 3 subscales: pain (score range, 0–500), stiffness (0–200), and function (0–1700), with higher scores indicating more severe disease.[18,19] The WOMAC is widely used in the evaluation of hip and knee OA and has been extensively validated, translated and linguistically validated in more than 60 alternative-language forms.[20] In addition, WOMAC scores are also assessed at 1-, 2-, 3-and 4-week during the intervention period for both groups of patients as well as at the 12-week, 26-week and 52-week follow-ups as secondary outcomes.

Secondary Outcomes

1. The Lysholm knee scale is a patient-reported instrument that consists of subscales for pain, instability, locking, swelling, limp, stair climbing, squatting, and the need for support and was designed to assess ligament injuries of the knee. Scores range from 0 (worse disability) to 100 (less disability).[21]
2. Quality of life is assessed by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), which is designed for use in clinical practice and research, health policy evaluations, and general population surveys.[22] The SF-36 includes one multi-item scale that assesses eight health concepts: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Scores range from 0 to 100, with higher scores indicating better health.[23,24]
3. The Brief Pain Inventory (BPI) is a self-reported scale that measures the severity of pain and the interference of pain on function.[25] The Brief Pain Inventory of Severity (BPI-Severity) items include worst pain, least pain, average pain, and pain right now. The severity item ratings range from 0 (no pain) to 10 (pain as severe as one can imagine). The brief pain inventory-interference (BPI-Interference) item ratings range from 0 (does not interfere) to 10 (completely interferes).[26]
4. The Patient's Global Impressions of Improvement (PGI-I) scale and the Clinical Global Impressions of Severity scale (CGI-S) will be used to evaluate the global disease severity and global improvement of patients. Disease

severity is assessed by the same evaluator throughout the study using the CGI-S item on a scale ranging from 1 (normal) to 7 (most extremely ill). For the PGI-I, the following categorizations were made: "improved" (scores 1 and 2), "stable" (scores 3, 4, and 5), or "worsened" (scores 6 and 7).[27]

5. Patient's living conditions and daily exercise records. In addition, the floor on which the participants lived and whether there is an elevator will be also recorded. Each participant will be given an electronic wristband to track their daily walking steps.

Safety Assessments

Participants are monitored during the study intervention at each visit for the occurrence of adverse events. All adverse events are recorded on an adverse event case report form during the treatment and evaluated for relevance to the intervention and severity. Adverse events will be reported to other relevant parties, including the institutional review board.

Data Management and Monitoring

The study data include random grouping data, clinical baseline data, intervention symptom and sign changes, follow-up data, and statistical analysis data. Two research assistants entered the data into an Excel sheet, proofread and corrected the input errors with each other, checked the accuracy of the raw data with the case report form, locked the data, and then performed statistical analysis.

This trial is under the supervision, direction, and management of the research team from Shanghai University of TCM. We have established an independent data monitoring committee (DMC) consisting of researchers with expertise in orthopedics, rheumatology, TCM, clinical trials, and statistical design. The DMC is responsible for monitoring the project, subject safety, and adequacy of the data quality. A summary of enrollment progress, adverse events, and protocol deviations will be provided to the DMC every three months. The participants' medical records will be kept entirely at the project's research center. All patient privacy data are stored in encrypted protection, and are used only for project research and may not be used for other purposes.

Statistical Analysis

The data will be collected and analyzed according to the intention-to-treat principle. To estimate the missing value of the main variable, the last observation carried forward (LOCF) method is used to carry forward the missing part of the test data. Normality testing will be applied to the results; when the data are not normally distributed, an equivalent nonparametric test will be adopted. The results are presented as the number of patients, means, standard deviations, medians, and 95% confidence intervals for continuous variables and as the frequency or percentage for classified variables. The primary and secondary outcome measures will also be compared between treatment groups at each time point using paired t tests. Analysis of variance with repeated measures will be applied to analyze changes in outcomes at baseline, posttreatment, and follow-ups between and within groups. IBM SPSS statistics software, version 22.0 (Armonk, NY: IBM Corp). will be used for the statistical analyses and the significance value for all tests is set at $P < 0.05$.

No interim analysis will be conducted. When the patient falls off or the patient's compliance is poor, the reasons for the fall off and poor compliance will be entered into the case report form in detail. The case of a patient who fell off, patient compliance, and adverse reactions shall be statistically described, compared, and evaluated between the groups. Participants will still be able to receive guidance and assistance from experts in the study hospital after completing the trial. If damage occurs during the study, after the expert advisory committee determines that the participant has indeed suffered damage due to the study, the sponsor will assume corresponding responsibilities in accordance with relevant laws and regulations and give corresponding compensation for the damage related to the trial. The study results will be disseminated through peer-reviewed journal publications and conference presentations, and will be shared with relevant medical institutions. The datasets created or analyzed in this study are not publicly available due to the privacy of persons who participated in the trial, but are available upon reasonable request from the corresponding author.

Patient and Public Involvement

Patients or the public were involved in dissemination plans of our research, but were not involved in the design, or conduct of the study protocol.

Discussion

Bath therapy is a common non-pharmacological treatment for OA that is characterized as a non-invasive treatment and is low-cost and effective.[28] Often combined with massage, exercise, physical therapy and rehabilitation, balneotherapy is widely used in the treatment of osteoarthritis of the knee.[29,30]

Randomized controlled trials[31] and Systematic evaluation and meta-analysis[32,33] have demonstrated the clinical efficacy of balneotherapy in improving osteoarthritis of the knee. In addition, mud-bath therapy and Neydharting mud-pack provide beneficial effects on the quality of life, painful symptoms and functional capacities in patients with knee OA even in the follow-up studies lasting over time.[34,35] The OARSI guideline recommends balneotherapy and spa therapy for patients with multiple-joint OA and the relevant co-morbidities.[36] However, their effectiveness in patients with knee osteoarthritis only is uncertain due to poor methodological quality, which requires further validation in more large and well-designed randomized controlled trials.

Herbal bath therapy has been used for thousands of years in China, especially for treating chronic muscle and skeletal disorders including knee OA, and its experience and therapeutic effects have been tested and refined in Asian countries.[37] However, high-quality, rigorously designed and well-controlled randomized controlled studies that can truly demonstrate the efficacy and safety of herbal medicinal baths are still lacking.[38] The primary objective of this 52-week randomized controlled trial is to provide clinical evidence for the safety and long-term efficacy of SSBD in the treatment of older patients with knee OA compared with placebo.

The patient experience is now globally recognized as an independent dimension of health-care quality.[39] The objective evaluation of patient-centered outcomes, including function, symptoms, and quality of life, is becoming increasingly important.[40] Validated measures of patient-reported outcomes with standardized questionnaires are thus critical to clinical and research outcome assessment.[41] The PGI-I and CGI-S have been used to investigate the efficacy of pharmacological treatments for psychiatric and medical conditions where subjective symptoms predominate, including pain, fatigue, and mood.[42] Since knee OA pain is also a subjective symptom, the PGI-I and CGI-S are adopted in this study to assess patients' overall perception of their condition at the endpoint and improvement from baseline.

Compared with those in European and American countries, most residents of China, especially in metropolises such as Shanghai, live in multi-stories dwelling buildings and lack the necessary elevators. To better determine the impact of the living environment and exercise on knee OA, we also investigated and recorded the living conditions of the participants and issued electronic bracelets to record their daily walking steps. Thus, successful completion of the proposed study will contribute to the evidence base on whether Chinese herbal bath therapy can be used as a simple, safe, inexpensive, effective and durable treatment for patients with knee OA, simultaneously providing physicians and patients with additional options to improve clinical decision-making in this field of clinical practice.

Trial Status

This trial is currently enrolling patients. We started recruitment in March 2023, and it was expected to be completed in March 2025. All items from the World Health Organization Trial Registration Data Set are shown in Table S1.

Abbreviations

BPI, Brief Pain Inventory; CGI-S, Clinical Global Impressions of Severity; DMC, data monitoring committee; LOCF, last observation carried forward; NSAIDs, Nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PGI-I, Patient's Global Impressions of Improvement; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; SSBD, Shi-style steaming and bathing decoction; TCM, traditional Chinese medicine; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Data Sharing Statement

The datasets created or analyzed in this study are not publicly available due to the privacy of persons who participated in the trial, but are available upon reasonable request from the corresponding author.

Consent for Publication

Not applicable.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

Declarations

The ethics of this trial research scheme were reviewed and approved by the Chinese Ethics Committee of Registering Clinical Trials with approval number ChiECRCT20220077. After careful discussion and modification by the project team, the study plan of this project was registered on the website of the Chinese Clinical Trial Registry (https://www.chictr.org.cn/) and further improved and modified according to the modification suggestions provided by the expert team, with approval number ChiCTR2200062818. Each participant voluntarily signed the informed consent form prior to the start of the study.

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Disclosure

The authors declare that they have no competing interests in this work.

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