Trials

STUDY PROTOCOL

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Radial extracorporeal shock wave therapy for pain and function in adults with knee osteoarthritis: protocol for a placebo-controlled, randomized clinical trial

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Abstract

Background Knee osteoarthritis (KOA) is the most common degenerative joint disease. It is characterized by pain, stiffness, reduced joint motion, and muscle weakness. It also has the potential for long-term disability. Radial extracorporeal shock wave therapy (rESWT) is a noninvasive therapeutic modality widely used for the treatment of musculoskeletal disorders. However, the role of rESWT in the treatment of knee osteoarthritis remains controversial in previous clinical trials. This trial will investigate the efficacy of rESWT in improving the symptoms, function, and bone metabolic status of participants with knee osteoarthritis.

Methods The study is a randomized, double-blind, controlled trial. Thirty participants with knee osteoarthritis will be randomized to receive either rESWT or sham rESWT on the affected knee once per week for 4 weeks. All participants will undergo professional physiotherapy once a week during the treatment period. The primary outcome is the visual analogue scale score for pain. Secondary outcomes include the Western Ontario and McMaster Universities Osteoarthritis Index score, knee range of motion, the 10-m walk test results, and bone metabolism biochemical indicators. Outcomes will be measured at baseline (T0), 5 weeks post-intervention (T1), and 8 weeks post-intervention (T2).

Discussion This study will investigate the effects of rESWT on pain, physical function, and bone metabolism biochemical indicators in participants with knee osteoarthritis, which is expected to reduce the pain of participants, improve the function of participants, and improve bone metabolism biochemical indicators. The information obtained will enhance our understanding of rESWT for the treatment of knee osteoarthritis and may be used to standardize clinical treatment protocols for knee osteoarthritis.

Trial registration Chinese Clinical Trial Registry ChiCTR2300069997. Registered on 30 March 2023.

Keywords Knee osteoarthritis, Radial extracorporeal shock wave therapy, Rehabilitation, Manual physical therapy, Bone metabolism biochemical indicators

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Introduction

Background and rationale {6a}

Knee osteoarthritis (KOA) is a common degenerative joint condition that affects more than 500 million people worldwide [1]. Its etiology is complex with risk factors including higher age, female sex, obesity, history of knee injuries, and jobs that require prolonged standing [2]. Its clinical manifestations include pain, stiffness, reduced joint motion, muscle weakness, and carries a risk of disability in the long term [3].

The treatment of KOA is currently based on health education, exercise, and weight loss, supplemented by nonsteroidal anti-inflammatory drugs, corticosteroid intra-articular injection, hyaluronic acid intra-articular injection, and platelet-rich plasma intra-articular injection [4–9]. Some participants with KOA adhere poorly to exercise therapy due to factors such as severe pain and cardiopulmonary dysfunction. While drug therapy can provide partial pain relief, it often falls short of delivering optimal results due to limited options, drug resistance, and drug safety concerns [10]. Importantly, no studies have shown that drug therapy can reverse the progression of KOA [11]. In addition, intra-articular drug injections can relieve pain and improve function, but they are an invasive treatment [12]. Eventually, some patients with late-stage KOA undergo joint replacement surgery; however, artificial joints have a limited lifespan and there is a risk of adverse outcomes [13]. Therefore, the treatment of KOA needs to focus on other safe and reliable therapies based on education, exercise, and weight loss.

Radial extracorporeal shock wave therapy (rESWT) is a non-invasive form of physical therapy in which a device is placed against the skin and pulses of energy are delivered to the damaged tissue at a given pressure and frequency [14]. rESWT can promote healing through mechanical transduction, and its biological roles include analgesia, tissue regeneration, wound healing, angiogenesis, and bone remodeling [15, 16]. Growing evidence suggests potential benefits of rESWT to treat musculoskeletal disorders [17, 18]. Studies have shown that rESWT can achieve good results in treating calcific tendonitis of the rotator cuff, carpal tunnel syndrome, plantar fasciitis, and lateral epicondylitis [19–22]. However, the role of rESWT in the treatment of KOA remains controversial in previous clinical studies [23–25]. Therefore, higher quality evidence is needed to evaluate the effectiveness of rESWT in the treatment of KOA.

The primary aim of this study is to determine whether the integration of rESWT with physiotherapy offers better pain relief and functional improvement in participants with KOA compared to only physiotherapy. Additionally, we aim to explore the effects of rESWT on relevant bone metabolism biochemical indicators in these participants.

Objectives {7}

The objective of this study was to evaluate the effectiveness of rESWT therapy by comparing pain relief, functional recovery, and improvement in biochemical markers of bone metabolism in participants who received physical therapy alone with those who received physical therapy combined with rESWT.

Trial design {8}

This study is a randomized, controlled, double-blind trial followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines [26]. It follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guidelines [27]. Figure 1 is a flow diagram designed for the study.

Methods: participants, interventions, and outcomes

Study setting {9}

This trial will be conducted with 30 participants with KOA to evaluate the effects of rESWT treatment. The experimental site is the Rehabilitation Center of Shengjing Hospital of China Medical University. The experimental group will receive rESWT treatment combined with physiotherapy, and the control group will receive a combination of sham rESWT treatment and physiotherapy. rESWT and physiotherapy administered once a week. The entire treatment course will last for 4 consecutive weeks.

Eligibility criteria {10}

Participants will be recruited from the Shengjing Hospital of China Medical University in Shenyang, Liaoning Province, China. Following an evaluation of the inclusion and exclusion criteria, participants will be requested to provide their signatures to an informed consent form before commencing the trial. Participant recruitment was initiated in April 2023. The study is expected to be completed in October 2025.

If the following criteria are met, the participants will be considered for inclusion: (1) age 45–75 years; (2) knee pain in the past 3 months; (3) Kellgren-Lawrence (K-L) grade = II or III [28]; (4) signed informed consent to participate in the study.

If any of the following criteria are met, participants will not be included: (1) acute knee trauma, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, and other types of knee joint disease; (2) cardiopulmonary insufficiency, cognitive dysfunction, poor compliance, and inability to tolerate the test; (3) intra-articular drug injection treatment or surgery of the affected knee within 6 months; (4) contraindications for extracorporeal shock wave therapy which include abnormal coagulation

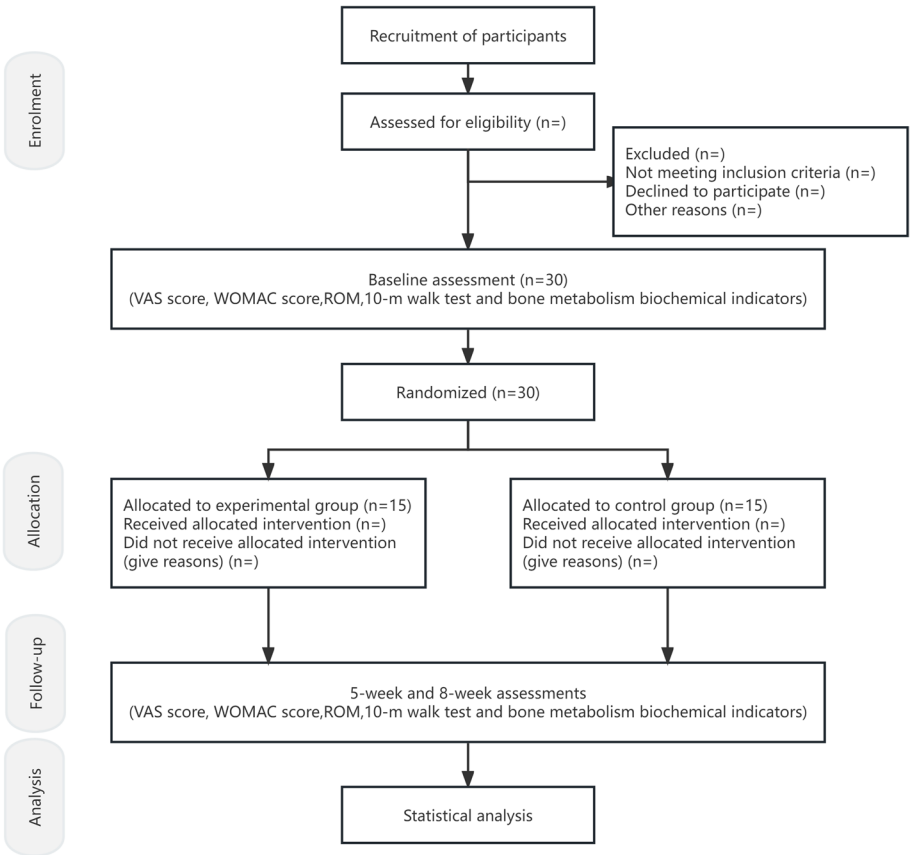

Fig. 1 Flow diagram designed for the study

mechanism, deep venous thrombosis of the lower limbs, treatment of local peripheral tumors, infection, and metal implantation.

Who will take informed consent? {26a}

Informed consent signed by the participant himself/herself.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable, no biological specimens collected.

Interventions

Explanation for the choice of comparators {6b}

Participants in the control group will be managed by the same physiotherapist as experimental group who will follow the same rESWT protocol; however, the pneumatic pressure will be set at 1.5 bar, corresponding to a minimum positive energy flux density of 0.02 mJ/mm^2 [29]. Participants will hear a sound similar to a regular rESWT but cannot see the instrument panel.

Intervention description {11a}

All participants will receive professional physiotherapy treatment, including manual physiotherapy and reinforcing exercises, once a week. The experimental group will receive rESWT treatment combined with physiotherapy, and the control group will receive a combination of sham rESWT treatment and the same physiotherapy as the experimental group. The entire intervention will last 4 weeks. Throughout the treatment, all participants will be prohibited from receiving any additional treatments, such as oral pain medications, knee cavity injections, and knee surgery.

rESWT

Participants in the experimental group will receive rESWT therapy, all of which will be provided by an experienced therapist. The equipment used will be a Swiss DolorClast Master Extracorporeal Shock Wave Therapy Instrument with a standard blue handle (10 mm), which will be performed once a week for 4 consecutive weeks (total of four sessions). Under non-anesthetic conditions, the participant will be positioned supine on the treatment

bed with the knee flexed at 90° and the skin exposed. The therapist will identify the knee pain points by palpation. They will mark the pain points as well as the patellofemoral and tibiofemoral boundaries, being careful to avoid important nerves or blood vessels. The coupling agent will be evenly applied to the marks and shockwave probe, and the shockwave probe will be pressed against the skin for treatment. The first half of the pulses will be evenly distributed at the pain points, whereas the rest will be moved back and forth along the patellofemoral and tibiofemoral boundaries. The frequency will be 8 Hz, the number of pulses will be 2000, and the pneumatic pressure will be 1.5–3.0 bar, corresponding to 0.12–0.23 mJ/mm^2, representing a moderate intensity energy flux density. During the treatment, the energy flux density will be gradually increased from low to high, the energy flux density will be increased as much as possible within the pain tolerance range of the participant, and the treatment intensity is selected individually [29, 30]. During treatment, rESWT may cause the following adverse reactions: local hematoma, petechial and spot bleeding at the treatment site; increased pain response at the treatment site; local numbness, acupuncture, decreased sensation at the treatment site, etc. For any adverse event during the study, the researcher should truthfully fill in the adverse event record form to record the occurrence time, severity, duration, measures taken, and outcome of the adverse event. The principal investigator of the research unit, the ethics committee, the sponsor, etc. must be reported within 24 h. All adverse events should be followed until they are properly resolved or stable.

Physiotherapy procedures

All participants will receive the same physiotherapy procedures one time per week, each lasting approximately 40–50 min for a total of 4 weeks. Physiotherapy will be delivered by physiotherapists with clinical experience in musculoskeletal physiotherapy and trial interventions who are not involved in the implementation of rESWT. Physical therapists will receive a 3-day training to standardize shockwave therapy and physical therapy protocols. Training will be provided by a qualified and experienced musculoskeletal physiotherapist. Before beginning each physiotherapy procedure, the therapist will conduct a detailed consultation and physical examination and choose personalized, targeted training according to the specific problems of the participant. The training consists of two parts: manual physiotherapy and reinforcing exercises. Physiotherapy focuses on the knees. If the participant's lumbar, hip, and ankle areas are believed to cause associated symptoms of pain and limited movement, the therapist will implement a targeted training regimen to alleviate these symptoms. The optional training schemes are presented in Table 1 [31]. Throughout the treatment, participants will be regularly queried about their well-being, including the presence of severe pain or any discomfort. Any necessary adjustments or discontinuations will be promptly addressed, with participants

Table 1 Physiotherapy procedures protocol for two groups

Physiotherapy	Prescriptions	Duration or targeted repetitions
Manual physiotherapy	1 Soft tissue mobilization in a position of knee extension	2 min
	2 Small amplitude lateral to medial or medial to lateral patellofemoral glides using the palm of the hand	2 min
	3 Small amplitude superior to inferior patellofemoral glides	2 min
	4 Small amplitude knee extension mobilizations	2 min
	5 Small amplitude tibiofemoral external rotation in knee extension	2 min
	6 Soft tissue mobilization in a position of knee flexion	2 min
	7 Small amplitude internal tibiofemoral rotation	2 min
	8 Small amplitude knee flexion with wedge	2 min
Reinforcing exercise	9 Static quadriceps set with extension mobilization	10 s holds × 10 reps
	10 Repeated knee extension challenges	3 s holds × 10 reps Rest for 1 min and repeat
	11 Repeated knee flexion challenges	3 s holds × 10 reps Rest for 1 min and repeat
	11 Alternative technique: repeated challenges to knee flexion with a towel or strap	3 s holds × 10 reps Rest for 1 min and repeat
	12 Quadriceps and hip flexor stretch	30–60 s holds × 3 reps
	13 Double-leg mini squat	3 s holds × 10 reps
	14 Terminal knee extensions	3 s holds × 10 reps
	15 Calf stretch	30–60 s holds × 3 reps

maintaining detailed records of their treatment experiences throughout the process.

Criteria for discontinuing or modifying allocated interventions {11b}

During the treatment, the energy flux density will be gradually increased from 0.12 mJ/mm^2, the energy flux density will be increased as much as possible within the pain tolerance range of the participant, and the treatment intensity is selected individually. Throughout the course of the trial, participants could withdraw at any time, withdraw informed consent, and request that their own data not be used.

Strategies to improve adherence to interventions {11c}

At the end of each session, therapist and participant agree on a time for the next session. Two days before the agreed time, the researcher contacted the participant through the contact information left by the participant in advance and informed the participant to proceed with the treatment 2 days later.

Relevant concomitant care permitted or prohibited during the trial {11 d}

Throughout the treatment, all participants will be prohibited from receiving any additional treatments, such as oral pain medications, knee cavity injections, and knee surgery.

Provisions for post-trial care {30}

Patients were asked not to apply hot packs on the day of treatment to avoid swelling. Avoid strenuous exercise for 48 h after treatment to avoid affecting the treatment effect.

Outcomes {12}

Subjective and objective outcome measures will be selected to evaluate treatment efficacy. The results will be documented at baseline (T0), 5 weeks post-intervention (T1), and 8 weeks post-intervention (T2).

Primary outcome measure

The visual analogue scale (VAS) of pain intensity is a well-established and validated self-report measure [32, 33]. It consists of a 10-cm straight line, one end of which indicates "no pain at all" and the other end of which indicates "worst pain imaginable" or "pain to the extreme." Participants will be asked to mark the corresponding position on the line to represent the intensity of pain they experienced. The VAS has demonstrated good validity and reliability in assessing pain levels in participants with osteoarthritis of the knee [34].

Secondary outcome measure

The WOMAC score can be used to assess symptoms in participants with KOA and is a valid disease-specific self-report questionnaire [35]. The questionnaire consists of 24 questions in three areas: 5 questions about the severity of knee pain, 2 questions about stiffness, and 17 questions about physical functional limitations. All items are measured on a Likert scale ranging from 0 (asymptomatic) to 4 (extreme symptoms) for an overall range of 0–96, with higher scores indicating more severe symptoms [36].

The knee ROM will be measured in the prone position with the hip and knee joints extended. With the fibular tuberosity of the knee joint as the axis of the protractor, the fixed arm will be placed parallel to the long axis of the femur and the mobile arm will be placed parallel to the long axis of the fibula. The participant will be instructed to actively flex the knee in the sagittal plane, and possible compensatory movements will be avoided during measurement. Three measurements will be obtained and averaged to an accuracy of 1° [37, 38].

A 10-m walk test, which can be used to assess a participant's walking time over short distances, has good reliability and validity [39, 40]. In this test, the 10-m distance is determined by bonding dark bands at the start and end points. The participant will be asked to walk the entire distance at a comfortable pace. Participants perform three repetitions with a 30-s gap between each test, and the mean values are recorded in "seconds" to the nearest 0.01 s.

Biochemical indicators of bone metabolism are associated with the progression of knee injury [41]. Bone metabolism biochemical indicators respond rapidly to treatment and can, therefore, play an important role in the development and monitoring of disease-modifying therapies [42–44]. Bone-specific alkaline phosphatase (BALP) originates in osteoblasts and is an extracellular enzyme of osteoblasts that hydrolyzes phosphatase during osteogenesis. BALP is considered to be one of the most accurate markers of bone formation. Quantitative determination and dynamic observation of serum BALP can be used as an effective parameter to monitor changes in bone formation [45]. Osteocalcin (OC) is a specific non-collagenous bone matrix protein synthesized and secreted by non-proliferative osteoblasts. It reflects the specific biochemical index of bone formation and can maintain the normal mineralization rate of bone, inhibit the mineralization rate of cartilage, and inhibit the formation of abnormal hydroxyapatite crystals in bone [46]. Type I procollagen amino-terminal peptide (PINP) is mainly synthesized by osteoblasts, and its content in serum reflects the ability of osteoblasts to synthesize osteocollagen, which is a specific and sensitive indicator of osteoblast activity [47]. β-Collagen degradation

products (β-CTX) are specific products produced by the degradation of osteoclasts during bone resorption, reflecting the bone resorption activity of osteoclasts. The increased degree of β-CTX is consistent with the increased degree of osteoclast activity and is an important biochemical marker of bone resorption [48].

Participant timeline {13}

Figure 2 shows the schedules of enrolment, interventions, and assessments.

Sample size {14}

The sample size is determined based on the change in the score from baseline to post-intervention in previous study: the VAS score of participants receiving rESWT is expected to decrease by 2.2 points, whereas the VAS score of participants in the control group is expected to decrease by 0.7 points [23]. Assuming an SD of 1.1 and a bilateral significance level of 0.05, 24 participants (12 per group) are required to achieve 90% power. Considering the potential dropout rate, 30 participants (15 per group) will be recruited.

Recruitment {15}

Recruitment strategies include the following: (1) recruitment from the hospital outparticipant clinic; (2) posters/flyers in hospital areas and community areas; (3) advertisements on social media networks; (4) radio.

Assignment of interventions: allocation

Sequence generation {16a}

We will randomly assign participants to the experimental and control groups using block randomization with block sizes of 4 and 6 in a 1:1 ratio.

Concealment mechanism {16b}

The allocation will be concealed in sequentially numbered, sealed, opaque envelopes to ensure concealment.

Implementation {16c}

The randomization process will be overseen by a researcher who is not involved in recruitment, assessment, or trial implementation.

	Enrolment	Allocation	Post-allocation							
TIMEPOINT	**-t1**	**0**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**
ENROLMENT:										
Eligibility screen	X									
Informed consent	X									
Ethical approval and trial registration	X									
Allocation		X								
INTERVENTIONS:										
rESWT + physical therapy			←	—	—	→				
Sham rESWT + physical therapy			←	—	—	→				
ASSESSMENTS:										
Basic characteristics Information		X								
VAS score		X					X			X
WOMAC score		X					X			X
ROM		X					X			X
10-m walk test		X					X			X
Bone metabolism biochemical indicators		X					X			X

Fig. 2 The schedules of enrolment, interventions, and assessments

Assignment of interventions: blinding

Who will be blinded {17a}

The therapists delivering the intervention will remain blind to the treatment allocation, and participants will be instructed to maintain confidentiality regarding their group assignment.

Procedure for unblinding if needed {17b}

In case of emergency, such as a severe adverse event, the researchers may unblind to ensure appropriate medical care for the participant. Upon unblinding, the participant will be immediately withdrawn from the trial, and the researchers will document detailed information regarding the unblinding, including the time, reason, and rescue measures.

Data collection and management

Plans for assessment and collection of outcomes {18a}

The evaluation and collection of the outcomes will be carried out by the professional rehabilitation physicians, who will receive a 3-day training to standardize the credibility of the evaluation results prior to the evaluation.

Plans to promote participant retention and complete follow-up {18b}

At the end of each session, therapist and participant agree on a time for the next session. Two days before the agreed time, the researcher contacted the participant through the contact information left by the participant in advance and informed the participant to proceed with the treatment 2 days later.

Data management {19}

The gathered data will be documented in the case report to ensure completeness, accuracy, and punctuality. Two researchers will enter the study data into Excel and cross-check the data. Therefore, the electronic data will be properly stored for sole use by the researchers involved. The data will be anonymized.

Confidentiality {27}

Paper case report forms and questionnaires will be organized sequentially and securely stored in a filing cabinet to maintain confidentiality. The Medical Ethics Committee of Shengjing Hospital of China Medical University will be responsible for overseeing the gathering and handling of data and has the option to terminate this trial if a serious adverse event occurs. All procedures in this study will adhere to the medical data confidentiality standards.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable, no biological specimens collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The primary endpoint of this study is the comparison of VAS scores between groups after 5 weeks of treatment and 8 weeks of treatment. Linear regression analysis will be employed to compare the groups, with the baseline VAS score serving as a covariate. To evaluate secondary outcomes, we will utilize similar methods: for continuous outcomes, we will apply linear regression; for binary outcomes, logistic regression; and for count outcomes, Poisson regression. When analyzing data from multiple time points, mixed-effects regression models will be constructed. These models will account for the non-independence of observations from the same participant by treating the participant as a random effect. In cases where continuous data exhibits skewness that cannot be addressed through transformation, non-parametric methods such as median regression will be utilized. To address missing data during follow-up, sensitivity analyses using imputation techniques will be conducted. Finally, we will adhere to standard principles for RCTs and perform intention-to-treat analyses using two-group comparisons.

Interim analyses {21b}

Due to the short intervention time and small sample size, an interim analysis will not be performed.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Not applicable, no subgroup analysis will be performed in this study.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

We will use intentionality analysis to address compliance issues. To deal with the missing data, we will employ multiple interpolation techniques, which help preserve statistical power.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

Full open access is not yet available, but we may grant access to the full agreement on a case-by-case basis.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5 d}

The study will be coordinated by researchers at China Medical University's Shengjing Hospital. The principal investigator will have overall responsibility for the study, providing guidance and supervision. The project manager will be responsible for day-to-day project management, monitoring that all elements of the research are implemented in accordance with the protocol and in compliance with ethical principles. For example, they will oversee data monitoring, supervise researchers, conduct adverse event interviews, communicate with participants, and maintain communication with various contributors and stakeholders of the research. There is a dedicated statistician for data monitoring and adverse event screening. Communication between researchers will take place weekly through meetings and emails.

Composition of the data monitoring committee, its role and reporting structure {21a}

The Ethics Committee has determined that this trial does not require a data monitoring board, as no drug use is involved.

Adverse event reporting and harms {22}

The intervention is non-invasive and no major adverse events are expected. However, if participants experience severe psychological distress during this trial, participants will have a period of recovery and can opt out of the trial if they continue to feel unwell. Each adverse event and serious adverse event will be recorded in the participant's clinical record and in the main study file. Each adverse event will be evaluated by PI, after which appropriate action will be taken based on its severity.

Frequency and plans for auditing trial conduct {23}

If necessary, the Ethics Committee will conduct monitoring, auditing, and inspection at the site of this trial study.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Any changes made after the start of the trial will be reported to the trial registry, ethics committee for approval, and the version number and date of each update will be used to monitor the history of these changes.

Dissemination plans {31a}

This study will provide a comprehensive research report to the funding agency and submit the findings to a peer-reviewed journal for publication.

Once this research is completed, the results will be shared in a number of ways to ensure that the findings benefit both the scientific community and the public.

1. For participants and the public: We will prepare easy-to-understand abstracts and provide them to the public through multi-platform, so that the public can understand the therapeutic effect of rESWT for knee osteoarthritis, and provide new means for participants to alleviate the disease.
2. For medical professionals: We will share our research findings with rehabilitation physicians/therapists through workshops and seminars. This helped them to understand the effectiveness of rESWT for participants with knee osteoarthritis and to further promote this non-invasive treatment.
3. For the scientific community: We will publish the results of our research in scientific journals so that researchers around the world can benefit from our research.

By sharing our research findings widely, we hope to ultimately improve the lives of people with knee osteoarthritis.

Discussion

As a non-invasive treatment, rESWT has shown its unique safety and reliability and has been widely used in the clinical treatment of musculoskeletal system diseases (50). rESWT has a synergistic effect with other treatments, which further increases the application scope of rESWT. This protocol combines rESWT with physical therapy. Clinical scale, physical function test, and biochemical indexes of bone metabolism were used to evaluate the therapeutic effect. We hypothesized that participants who received physiotherapy combined with rESWT will get greater pain relief, better functional recovery, and better bone metabolic biochemical indicators than participants who received only physiotherapy alone.

However, this study has some limitations. First, this trial will be conducted in one center, which may limit its generalizability. In addition, this study lacks a long-term follow-up assessment, which is also a shortcoming.

Despite these limitations, we hope that this study will demonstrate the efficacy of rESWT in KOA and provide evidence for further widespread use in the future.

Trial status

Recruitment for the trial starts in April 2023 and is expected to continue recruitment until October 2025. This is protocol version 3, December 6, 2024.

Abbreviations

KOA	Knee osteoarthritis
rESWT	Radial extracorporeal shock wave therapy
VAS	Visual analogue scale
ROM	Range of motion
WOMAC	Western Ontario and McMaster universities osteoarthritis index
CONSORT	Consolidated standards of reporting trials
SPIRIT 2013	Standard protocol items: recommendations for interventional trials 2013
BALP	Bone-specific alkaline phosphatase
OC	Osteocalcin
PINP	Type I procollagen amino-terminal peptide
β-CTX	β-Collagen degradation products

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08844-4.

Additional file 1: Informed consent form.

Additional file 2: SPIRIT checklist.

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Authors' contributions {31b}
PR, ZW, and XL contributed to the conception and design of the study. PR drafted the protocol. ZL, SX, XY, and FZ are principal and associate investigators on the study. All authors have read and approved the final protocol.

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Data availability {29}
The datasets used and analyzed during the study will be available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate {24}
This study was approved by the Medical Ethics Committee of Shengjing Hospital of China Medical University, Number: 2023PS571 K, and will adhere to the guidelines set forth in the Declaration of Helsinki. The study is also registered with the Chinese Clinical Trial Registry. The results will be showcased at both domestic and global conferences and disseminated through peer-reviewed scientific publications. The participants will provide their informed consent to participate in the study.

Consent for publication {32}
Not applicable, personal and clinical details of participants will not be provided in this study and will not be provided in the reporting of trial results.

Competing interests {28}
There are no financial and other competing interests for principal investigators for the overall trial.
Patient and public involvement.
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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