Efficacy of the combination therapy of platelet-rich plasma and hyaluronic acid on improving knee pain and dysfunction in patients with moderate-to-severe KOA: a protocol for a randomised controlled trial

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ABSTRACT

Introduction 54% of patients with moderate-to-severe knee osteoarthritis (KOA) still reported persistent pain and functional loss after conservative treatment according to guidelines. As an emerging treatment, platelet-rich plasma (PRP) has been proven to significantly relieve pain and improve activity function in patients with mild-to-moderate KOA, either used alone or in combination with hyaluronic acid (HA). However, it is still unclear of its efficacy in moderate-to-severe KOA. This study aims to evaluate the clinical efficacy of PRP and the combination therapy of PRP and HA in patients with moderate-to-severe KOA and to explore the potential synergistic effect of PRP and HA.

Methods and analysis This triple-blind randomised controlled trial will involve a total of 162 participants with moderate-to-severe KOA from two study centres. Participants will be allocated randomly into three groups: the HA group, the PRP group and the combination (PRP+HA) group and, respectively, receive HA (2.5 mL)+saline (3 mL)/PRP (3 mL)+saline (2.5 mL)/PRP (3 mL)+HA (2.5 mL) intra-articular injection each week for 4 consecutive weeks. All of the injections will be performed under the guidance of ultrasound. The primary outcome is the change of Western Ontario and McMaster Universities Osteoarthritis Index from baseline to 6 months, and secondary outcomes include the change of ultrasound images (suprapatellar bursa effusion and synovitis), Timed Up and Go test and 12-Item Short-Form Health Survey. All outcomes will be evaluated at baseline and 1-month, 3-month and 6-month follow-ups. Data will be analysed on intention-to-treat principles and a per-protocol basis.

Ethics and dissemination This protocol was approved by the Medical Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (reference number (2021)–02-231-02). The study results will be submitted to a peer-reviewed journal.

Trial registration number ChiCTR2100050974.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To the best of our knowledge, this is the first randomised controlled trial that investigates the clinical effect of combination therapy of platelet-rich plasma (PRP) and hyaluronic acid in patients with moderate-to-severe knee osteoarthritis.
⇒ This study exhibits high methodological quality because it is randomised, triple-blinding (participants, interventionist and assessors blinding), with allocation concealment, and an intention-to-treat approach.
⇒ To improve the accuracy and safety of intra-articular injection, all injections are conducted under the guidance of ultrasound.
⇒ The procedures for the preparation of PRP are operated by experienced technicians. Platelet count will be performed before and after preparation to ensure the homogeneity of platelet concentration.
⇒ The main limitation of this study is that there are only two centres involved in this study whereas multicentre clinical trials will provide more robust evidence.

INTRODUCTION

Knee osteoarthritis (KOA) is the leading cause of disabilities in middle-aged and elderly.1 As a result of progressive deterioration of the articular cartilage and menisci, there is no curative therapy for KOA currently.2 Thus, protecting cartilage and slowing down the progression of degeneration to inhibit pain and improve activity function are important strategies for the clinical treatment of KOA.3,4 Moderate-to-severe KOA refers to grade III–IV KOA according to the Kellgren-Lawrence classification with consistent knee pain.5 54% of patients with moderate-to-severe KOA still

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report persistent pain after conservative treatment, with functional loss and decreased quality of life. These patients eventually have to face surgery, while a considerable number of them are ineligible for surgery due to comorbidities or refusal. Therefore, there is still a critical need for further research on conservative treatment of moderate-to-severe KOA.

With the concept of regenerative therapies gaining attention, platelet-rich plasma (PRP) was recommended as an alternative injection for KOA by guidelines. Prepared by centrifugation of blood, PRP contains a high concentration of platelets and can directly stimulate natural healing cascades and tissue regeneration at the treated site by releasing platelet-derived factors. Systematic reviews suggested that PRP is a safe treatment which can alleviate pain symptoms and improve knee function in patients with KOA up to 12 months. But severe KOA was barely seen in these studies and imaging evidence for chondrorepair was lacking. Regarding the limited evidence, the efficacy of PRP in moderate-to-severe KOA is needed to be evaluated in high-quality randomised controlled trials (RCTs).

Similar to that of PRP, the evidence of intra-articular hyaluronic acid (HA) injection also indicates less improvement in advanced KOA than in early KOA. However, some studies showed that HA, as a major component of synovial fluid, provides an appropriate matrix and supportive scaffold material for chondrorepair, while PRP is also proved to increase HA production in native synoviocytes. Therefore, it was hypothesised that PRP and HA may have a potential synergistic effect on KOA. Studies on mild-to-moderate patients have shown that combination therapy is superior to HA or PRP as monotherapy, supporting the synergistic of the combination. However, evidence verifying the combined use of HA and PRP in severe KOA remains weak due to a lack of high-quality RCTs.

Therefore, we hypothesise that the combination of PRP and HA may be a new method for treating moderate-to-severe KOA. We plan to conduct an RCT to evaluate the clinical efficacy of PRP and the combination of PRP and HA in patients with moderate-to-severe KOA, meanwhile exploring the potential synergistic effect of combination therapy.

METHODS AND ANALYSIS

Study design

A two-centre, triple-blind, RCT, registered on the clinical trial platform. The principal study centre is the Third Affiliated Hospital of Sun Yat-sen University, the other is the Sixth Affiliated Hospital of Sun Yat-sen University. The study protocol is in accordance with the recommendations set forth in Standard Protocol Items: Recommendations for Interventional Trials (figure 1).

Patient and public involvement

Neither patients nor the public was involved in the design, conduct, report or dissemination of this trial. Once the trial has been published, participants will be informed of the results by telephone.

Participants

All of the participants are recruited from October 2022 in patients with KOA who visit the rehabilitation department of the two research centres. Patients will be first enrolled according to their basic information, medical history, imaging results and Visual Analogue Scale (VAS). Those who are willing to cooperate with treatment and sign informed consent after understanding the trial and purpose will be involved in this study and be allocated randomly into three groups: the HA group, the PRP group and the combination (PRP+HA) group.

Personal information (name, telephone number, profession, schooling level), anthropometric data (age, height, weight and body mass index) and clinical history of the disease will be collected at baseline. All of the participants will be evaluated four times: at baseline, 1-month, 3-month and 6-month follow-ups (table 1). Participants’ personal data will be coded in a database, to which only the researcher in charge of randomisation will have access.

Inclusion criteria

Aged 50–80 years; diagnosed as KOA for at least 6 months according to American College of Rheumatology criteria; with pain of at least 40 mm on a 100 mm VAS reported 1 month after conservative treatment of KOA recommended by guidelines (including non-pharmacological treatment, oral nonsteroidal anti-inflammatory drug (NSAID) or intra-articular injection of glucocorticoids; graded III and IV according to Kellgren-Lawrence radiological classification on X-ray image; able to cooperate with knee ultrasound examination; able to listen, speak, read and write in Chinese; capable of understanding the study requirements and willing to cooperate with the study instructions.

Exclusion criteria

Accompanied by other inflammatory arthritis (such as gout, reactive arthritis, psoriatic arthritis, seronegative spinal arthritis), rheumatic or autoimmune diseases; previous or anticipated knee surgery in the next 1 year; severe genu valgus or varus deformity (valgus angle >30° or varus angle >20°) or previous trauma; intraarticular injection in the last 4 weeks; oral corticosteroid used in the last 2 weeks or NSAID used in the last 2 days; anticoagulant or antiplatelet drugs used in the last 10 days; haemoglobin <100g/L, platelet count <150×10⁹/L; history of infectious diseases such as HIV positive; recently suffered from febrile diseases; with haematopoietic or skeletal cancer; accompanied by coagulation dysfunction; pregnant or lactating women; unstable vital signs; unable to complete or withdraw from the treatment regimen.

For those participants whose two knees are both eligible, intervention will be conducted on the more severe one.
If the two knees are of equal severity, only the right knee will be included.

Sample size calculation

The main outcome measure of this study is the change of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score from baseline to 6 months after treatment, evaluated by the significance test of difference. According to the previous study, the decrease of WOMAC score from baseline to 12 months in patients with KOA without distinction of severity was 272.25±443.50 points in the HA group, 396.00±414.75 points in the PRP group and 592.25±332.00 points in the combination group.21 22 We anticipated that similar results will be achieved in patients with moderate-to-severe KOA 6 months after treatment. Considering the power of 90% and alpha value of 5% (two-tailed), each group will have at least 49 participants to detect the significance. Inclusive of a potential 10% dropout rate, a total of 162 participants will be needed in this trial. The calculation is performed using PASS V.15.0 software (Kaysville, Utah, USA).

Randomisation

The block randomisation method will be used in this trial. Use SPSS statistical software (V.21.0) to generate a randomisation list based on the seeds number of 210000 and the block length of 6 to allocate participants into the three groups at a ratio of 1:1:1. The randomisation will be sealed in opaque envelopes and properly kept by a relevant person who has no contact with any participants. Another researcher will assign random numbers to enrolled participants according to the sequence of passing screening. At the first treatment appointment, a research nurse will telephone the envelope keeper just before administration of the first injection to reveal the participant’s group allocation.

Blinding

This study is a triple-blind randomised trial with participants, interventionists and evaluators blinded. No one except the study nurse and the researcher in charge of allocation can have access to the grouping information before the study ends. Before treatment, all the participants will be asked to extend their forearms into a

Figure 1  Flowchart illustrating the process of the study. BESS, Balance Error Scoring System; HA, hyaluronic acid; PRP, platelet-rich plasma; SF-12, 12-Item Short-Form Health Survey; TUG, Timed Up and Go test; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
sheltered window, and the research nurse will puncture the antecubital veins. 20 mL of venous blood will be drawn from each participant from the PRP group and the combination group, respectively, while participants in the HA group will only receive punctures without blood collection. The operation will not be visible to the participants. The research nurse will then prepare the injections in a separate room, wrap syringes with white paper to occlude the contents, attach a label of the corresponding participant’s name and give the syringe to the interventionists to perform the injection.

Interventions and measurements will all be implemented in separate locations by different independent researchers.

**Intervention**

**Drug administration**

PRP group: every participant will receive an intra-articular injection of 3 mL PRP and 2.5 mL saline each week for 4 consecutive weeks.

HA group: every participant will receive an intra-articular injection of 2.5 mL sodium hyaluronate (ARTZ, Seikagaku Corporation, Japan) and 3 mL saline each week for 4 consecutive weeks.

Combination (PRP+HA) group: every participant will receive an intra-articular injection of 3 mL PRP and 2.5 mL HA each week for 4 consecutive weeks.

**PRP preparation**

Step 1: Take three 10 mL EDTA anticoagulant blood collection tubes, draw 30 mL of the participant’s autologous whole blood and count the platelet concentration. Centrifuge at a speed of 500 G in the same direction for 8 min.

Step 2: Transfer the upper layer of plasma obtained by the first centrifugation into a sterile centrifuge tube with a pipette. After homogeneous mixing, count the platelet concentration (a) and plasma volume (b). Centrifuge the mixed plasma in the same direction at 1900 G for 12 min to concentrate platelets from plasma.

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**Table 1** Schedule of the study protocol according to the Standard Protocol Items: Recommendations for Interventional Trials checklist

<table>
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<th>Time point</th>
<th>Screening (−T1)</th>
<th>Baseline (T0)</th>
<th>Beginning of intervention (T1)</th>
<th>End of intervention (T2)</th>
<th>1-month follow-up (T3)</th>
<th>3 months follow-up (T4)</th>
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BESS, Balance Error Scoring System; HA, hyaluronic acid; PRP, platelet-rich plasma; SF SF-12, 12-Item Short-Form Health Survey; TUG, Timed Up and Go test; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
Step 3: Discard the upper layer of platelet-poor plasma, leaving the lower layer of plasma with a volume of $a \times b / (1000 \times 10^9)$. Disperse and homogeneously mix the platelet pellet which is precipitated at the bottom of the plasma with a sterile pipette, then count the platelet concentration again (by this time it may be approximate $1000 \times 10^9/L$, an error of $\pm 200 \times 10^9/L$ is allowed in this study), and finally get the standard PRP. Withdraw 3 mL PRP with a disposable syringe (5 mL) for injection. The PRP will not be activated before injection (figure 2).

All of these procedures will be operated by experienced technicians of the Transfusion Department of the two study centres, equipped with special collection, preparation and treatment rooms, strictly observing the principles of sterility.

The preparation of PRP will be completed within 30 min after the peripheral autologous whole blood is drawn. And the injection will be performed within 5–10 min after preparation.

**Injection procedure**

All of the injections will be guided with an S-Series (Sonosite, Seattle, America) sonography device and an HFL 38x high-frequency linear array probe (6–13 MHz). The participant will lie supine with the knee flexed at a 20–30° angle laid on a pillow. The probe will be placed crosswise above the patella of the lower segment of the femur to reveal the suprapatellar bursa. After conventional sterilising, the needle will be inserted into the suprapatellar bursa from the skin lateral superior to the patella, in-plane with the probe. PRP or HA will be injected when there is no abnormal aspiration. If there is effusion in the suprapatellar bursa, aspirate the fluid before injection (figures 3–4).

**Outcome measures**

**Primary outcomes**

The WOMAC$^{22, 23}$ will be applied at baseline, 1-month, 3-month and 6-month follow-ups. The change of WOMAC score at 6 months follow-up compared with the score at baseline will be used as the primary outcome measure. The WOMAC questionnaire consists of three subscales: pain (5 items), stiffness (2 items) and physical function (17 items). Each item is recorded with a 100 mm VAS. The total score is 2400. Higher scores indicate severer problems.

**Secondary outcomes**

1. The change of WOMAC score at 1 and 3 months follow-ups compared with the score at baseline.
2. Sonography will be used to measure the diameter of suprapatellar bursa effusion, and grading of synovi-
   
   **Figure 2**  Preparation of PRP: (A) the collected whole blood; (B) whole blood separated into three layers after the first centrifugation; (C) transfer the upper layer and superficialuffy coat to an empty sterile tube; (D) platelet pellet concentrated from plasma after a second centrifugation; (E) the platelet pellet; (F) PRP for injection. PRP, platelet-rich plasma. RBC, red blood cell.

   **Figure 3**  Ultrasound-guided intra-articular injection.

   **Figure 4**  Ultrasound image at injection: $\downarrow$ shows the needle, * shows the suprapatellar bursa, $\Delta$ shows the femoral cortical.
ti in each group at 1-month, 3-month and 6-month follow-ups.

1. Diameter of suprapatellar bursa effusion: Measure the longitudinal diameter of the suprapatellar bursa to reflect the level of effusion: the participant is in a supine position with the tested knee flexed at 30°. Place the ultrasound probe on the longitudinal and horizontal axis of the suprapatellar bursa and show the effusion, measure the length of its longitudinal axis.

2. Grading of synovitis (grade 0–3): Synovitis will also be examined at the suprapatellar area, graded according to the following criteria: grade 0 is normal; grade 1 is mild synovial thickening with smooth inner layer; grade 2 is moderate synovial thickening with less villous protrusions in inner synovium; grade 3 is severe synovial thickening with multiple villi-like protrusions.

3. Timed Up and Go test (TUG)25: TUG will be used to assess the objective physical function at 1-month, 3-month and 6-month follow-ups. The participant sits in a standard chair with armrests. After instructed, stand up from the chair and walk towards the finish line 3 metres away at a normal pace, then return to the chair and sit down. The researcher responsible for assessment will time the process.

4. 12-Item Short-Form Health Survey (SF-12) score26: The SF-12 will be used to assess the impact of health status on participants’ daily lives at 1-month, 3-month and 6-month follow-ups. The score ranges from 1 to 47 points. A higher score indicates a higher quality of life and less affected by the disease.

Co-intervention assessments
Participants will be suggested not to receive other interventional treatments targeted at KOA during the study period. Therapeutic modalities that used to deal with pain in any part of the body (including analgesics, physical therapies, etc) during the study period will be recorded in detail. Other intra-articular injection treatments (such as glucocorticoid) and surgical treatment at knee joints are forbidden.

Safety assessments
Close attention will also be paid to adverse events. Any adverse events occurring during the trial will be recorded in the case report form (CRF), including the timing of occurrence, symptoms, intensity, duration, treatment measures and outcome. Researchers will analyse the relationship between the adverse events and the intervention, record in detail, sign and date.

Statistical analysis
Both intention-to-treat analysis and per-protocol analysis will be conducted in this study. Conclusions will be initially based on the results of intention-to-treat analysis, while results of per-protocol analysis will provide supporting evidence. Per-protocol is defined as completing a whole session of treatment. Mean imputation will be used to address missing data caused by loss to follow-up and non-responses if the missing is judged to be random. The last observation carried forward method will be used in the analysis of all outcomes among patients who made at least one follow-up visit but did not complete the whole study. Unless otherwise specified, measurement data will be described in mean, SD, median, quartile, minimum and maximum.
maximum; counting data will be described in frequency and percentages. Significance testing will be applied to analyse the outcome measures and the significant level set at \( \alpha = 0.05 \) on two sides.

Analysis of outcomes: The mixed effect model will be used to analyse the differences between groups, including differences in change of WOMAC scores, degree of synovitis, suprapatellar bursa effusion, time of TUG, BESS score, SF-12 score, trochlear cartilage thickness, cartilage abrasion and cartilage clarity, with month and centre as covariates.

A step-up Hochberg procedure analogous to Dunnett procedure will be used to control the overall type I error in multiple comparisons. The comparisons will be first conducted between the combination group and the HA group (C1), and between the PRP group and the HA group (C2), respectively, using a Hochberg procedure to adjust the critical value. If the larger of the two \( p \) values is smaller than the two-sided 0.05 type I error level, then both hypotheses will be rejected and step up to compare the combination group with the PRP group (C3) at a significance level of 0.05. Otherwise, the null hypothesis corresponding to the larger \( p \) value will be retained and the smaller one will be compared with \( \alpha/2 = 0.025 \). If the smaller one of the two \( p \) values is under 0.025, then C3 will be conducted at a level of 0.025. Otherwise, all of the three null hypotheses will be retained.

In addition, stratified analyses will be used to explore differences in the efficacy of each treatment between moderate and severe patients according to radiographic disease severity (Kellgren-Lawrence grades III for moderate and IV for severe).

All of the Statistical analysis will be performed using SPSS (V.21.0).

Quality assurance

The project manager will take the responsibility for quality assurance. Before the study, all researchers will accept a series of unified standardised training, including the trial protocol, CRF filling, data collection and entry, standard of physical and laboratory examination, etc. During the study, the project manager will conduct casual checks on each part from time to time to ensure that the study protocol is strictly adhered to and the research data are correctly filled in. Ultrasound-guided injection, pain and functional evaluation will be, respectively, performed by specific researchers. The protocol will not be altered during the study time frame.

Data integrity and management

All data obtained during the trial will be compiled and stored electronically. Names will be encoded to keep personal information confidential. Data integrity and validity will be verified at the time of data entry (double-check). The project manager will regularly monitor the study database to supervise the progression of the study and make a third check for the data.

Withdrawal

Participants will be removed in the following condition when: severe complications (eg, intra-articular infection) or knee joint trauma occurs; comorbidities mentioned in the exclusion criteria newly develop during the study; participants receive other intra-articular injection treatment (such as glucocorticoid) and surgical treatment; participants withdraw informed consent at the beginning of the trail. If a participant withdraws or is removed from the study, the reason and date of discontinuation will be recorded. If the withdrawal happens after the whole session of injection, the participant will be asked to finish the last assessment on leaving the study, and the data will be recorded as a result to carry forward.

DISCUSSION

We present this prospective RCT to compare the efficacy of PRP-HA combination and that of PRP and HA as monotherapy in patients with moderate-to-severe KOA, thus determining whether there is a synergistic effect between PRP and HA that can improve the clinical symptoms and protect the cartilage. Chen et al have revealed that PRP combined with HA can promote chondrogenesis both in vitro and in animal models. A case series found that three patients with severe KOA who received PRP combining HA injection reported symptomatic relief and showed joint space widening on X-ray images at 8–13 months after injection. Published clinical studies also showed that the combination of PRP and HA can significantly result in better clinical outcomes compared with monotherapy of each for mild and moderate KOA. But for moderate and severe KOA, the efficacy is still remaining to be verified by high-quality RCTs.

This study exhibits high methodological quality because it is randomised, triple-blinded (participants, interventionist and assessors blinding), allocation concealment and analysing with an intention-to-treat analysis approach. To assure the blinding, a research nurse will specialise in fake blood collection, injection preparation and syringes occluding. The interventions and assessments will be conducted in separate rooms by independent researchers. Besides, we calculated the sample size based on the data of previous studies, providing enough statistical power to discover the possible differences between the main results of the study.

In published studies, the preparation method and concentration of PRP are not consistent, which may lead to controversial results. A study showed that PRP with platelet concentration of \( 1000 \times 10^9/L \) demonstrated the best proliferation effect on mouse chondrocytes and exerted the greatest therapeutic effect on clinical treatments of human KOA. Therefore, in this study, the preparation procedure of PRP will be under strict control and the platelet concentration will be unified at \( 1000 \times 10^9/L \). Meanwhile, the ultrasound-guided injection will be adopted to ensure the accuracy of injection location, thus improving the reliability of the research result.
The choice of outcome measures are carefully considered and may reflect the effectiveness of the interventions from different aspects. The primary outcome measure, WOMAC, is a validated patient-report measure recommended by Osteoarthritis Research Society International (OARSI), consisting of three subscales (pain, stiffness and physical function) which can fully reflect the participants’ subjective feelings. Sonography will be used for demonstration of the structural modification. TUG represents abilities related to ambulatory transitions, leg strength and balance, which is recommended by OARSI as a preferred indicator for objective measure of physical function in KOA because of its excellent discriminative ability. And SF-12 evaluates the quality of life.

Direct measurement of changes in cartilage after PRP-HA injection is rarely seen in previous clinical trials. Sonography is innovatively introduced in this study to evaluate thickness, abrasion and clarity of intra-articular cartilage and the level of synovitis to observe the effects of combination therapy and monotherapy on cartilage and synovial membrane.

The results of this study can provide objective evidence for the effect of PRP-HA combination therapy in moderate-to-severe KOA, and fill the gap in guidelines on the individualised injection regimen for moderate-to-severe KOA. The limitation of this study is that there are only two centres involved in this study whereas multi-centre clinical trials will provide more robust evidence.

Ethics and dissemination

This protocol was approved by the Medical Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (reference number (2021)–02-231-02). A written consent will be obtained from each participant. The study results will be submitted to a peer-reviewed journal and presented at conferences, both nationally and internationally.

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Acknowledgements A special acknowledgement to Professor Li Ling, the statistician who gave selfless, earnest and valuable guidance from study design to statistics method to this study. We also appreciate Peihua Cao who helped with the statistical analysis.

Contributors LF is the project manager of the study and is responsible for the study design. She coordinated the trial and will be responsible for participants’ enrolment. YM and JZ contributed to the study design and the manuscript drafting, and also will take responsibility for assessment. LH contributed to sample size calculation and future statistical analysis. JH and XL contributed to the study design and will take charge of injections and platelet-rich plasma (PRP) preparation, respectively. LG contributes to the illustration and explanation of the PRP preparation process. ZW contributes to the revision of the manuscript.

Funding This work is supported by Funding by Science and Technology Projects in Guangzhou, grant number 202206010195.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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