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KNEE

Intra-articular injections of platelet-rich plasma decrease pain and improve functional outcomes than sham saline in patients with knee osteoarthritis

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Abstract

Purpose To compare the long-term clinical efficacy provided by intra-articular injections of either Pure Platelet-rich Plasma (P-PRP) or sham saline to treat knee osteoarthritis (KOA).

Methods This prospective, parallel-group, double-blind, multi-center, sham-controlled randomized clinical trial recruited participants with KOA from orthopedic departments at nine public hospitals (five tertiary medical centers, four secondary medical units) starting January 1, 2014, with follow-up completed on February 28, 2021. Participants were randomly allocated to interventions in a 1:1 ratio. Data were analyzed from March 1, 2021, to July 15, 2021. Three sessions (1 every week) of P-PRP or sham saline injected by physicians. The primary outcome was the Western Ontario and McMaster Universities Arthritis Index (WOMAC) at 3, 6, 12, 24, 60 months of follow-up. Secondary outcomes included the International Knee Documentation Committee (IKDC) subjective score, visual analogue scale (VAS) score, intra-articular biochemical marker concentrations, cartilage volume, and adverse events. Laboratory of each hospital analyzed the content and quality of P-PRP.

Results 610 participants (59% women) with KOA who received three sessions of P-PRP ($n=308$, mean age 53.91 years) or sham saline ($n=302$, mean age 54.51 years) injections completed the trial. The mean platelet concentration in PRP is 4.3fold (95% confidence interval 3.6–4.5) greater than that of whole blood. Both groups showed significant improvements in IKDC, WOMAC, and VAS scores at 1 month of follow-up. However, only the P-PRP group showed a sustained improvement in clinical outcome measurements at month 24 ($P<0.001$). There were statistically significant differences between the P-PRP and sham saline groups in all clinical outcome measurements at each follow-up time point ($P<0.001$). The benefit of P-PRP was clinically better in terms of WOMAC-pain, WOMAC-physical function and WOMAC-total at 6, 12, 24, and 60 months of follow-up. No clinically significant differences between treatments were documented in terms of WOMAC-stiffness at any follow-up. A clinically significant difference favoring P-PRP group against saline in terms of IKDC and VAS scores was documented at 6, 12, 24 and 60 months of follow-up. At 6 months after injection, TNF-α and IL-1β levels in synovial fluid were lower in the P-PRP group ($P<0.001$). Tibiofemoral cartilage volume decreased by a mean value of 1171 mm^3 in the P-PRP group and 2311 mm^3 in the saline group over 60 months and the difference between the group was statistically significant (intergroup difference, 1140 mm^3, 95% CI − 79 to 1320 mm^3; $P<0.001$).

Conclusions In this randomized clinical trial of patients with KOA, P-PRP was superior to sham saline in treating KOA. P-PRP was effective for achieving at least 24 months of symptom relief and slowing the progress of KOA, with both P-PRP and saline being comparable in safety profiles.

Keywords Platelet-rich plasma (PRP) · Osteoarthritis · Knee · Pain · Saline

Introduction

Available therapies for patients with mild to severe knee osteoarthritis (KOA) are limited. There is an urgent need for disease-modifying osteoarthritis treatment, which targets the biochemical process of KOA that improves symptoms and inhibits structural disease progression.

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Platelet-rich plasma (PRP) is an autologous, whole blood product that provides a release of growth factors and proteins release from the α-granules found in platelets. Based on the abundance of leukocytes, PRP could be classified into leucocyte-poor PRP (P-PRP) with a low concentration of leukocytes and leucocyte-rich PRP with a high concentration of leukocytes. P-PRP was effective for the treatment by inhibiting the development of synovitis and cartilage matrix loss in the affected joints [3]. Several studies have shown the use of this biological therapy as clinically effective in osteoarthritis of the knee [6, 14]. Although PRP has been a promising biologic treatment option, there is no solid evidence in the literature to back up its real usefulness for the management of KOA. The purpose of this study was to evaluate the efficacy of intra-articular P-PRP injections on symptoms and joint structure in patients with KOA. The hypothesis of our study was that in patients with KOA, three intra-articular injections of P-PRP would decrease pain and improve knee function at 60 months follow-up compared with sham saline injections.

Methods

Design overview

The study conducted a prospective, parallel-group, randomized, double-blind, multi-center, sham-controlled trial. Recruitment started on Jan 1, 2014, and follow-up was completed on February 28, 2021. Patient written and verbal informed consent was obtained from all participants by the research assistant during a face-to-face inclusion visit.

Participants

All participants were outpatients. Patient screening was performed in the outpatient orthopedic department of nine hospitals, where nine experienced physicians of each hospital evaluated patients' eligibility for enrollment in this study through history collection, imaging examination and laboratory tests.

Participants meeting all of the following criteria were eligible for the study: (1) age between 18 and 80 years; (2) knee pain on most days in the last month; (3) unilateral symptoms; (4) damage to articular cartilage seen on weight-bearing radiographs or MRI; (5) ability to provide informed consent. Participants were excluded from the study if they: (1) have Kellgren and Lawrence grade 4 tibiofemoral OA on X-ray (indicating severe disease); (2) recent intra-articular injection of glucocorticoid in the past 3 months or hyaluronic acid in the past 6 months; (3) knee instability; (4) bilateral symptomatic lesions; (5) have a body mass index (BMI) > 40 kg/m^2; (6) systemic disorders such as rheumatoid arthritis, diabetes, hematological diseases (coagulopathies), osteoporosis, immunodeficiencies, or infections; (7) pregnancy, (8) use of a nonsteroidal anti-inflammatory medication in the past 1 week.

Randomisation

Nonclinical staff performed the randomization. Enrolled participants were randomized into two treatment groups according to a 1:1 allocation ratio through a computer-generated simple randomization system: intra-articular injections of P-PRP group or normal saline group. Treatment assignments (placed in sequentially numbered opaque envelopes) were assigned by a biostatistician who was not involved in the clinical care of the patients. Only the study nurse knew the condition of the group assignment.

Blinding and intervention protocol

Participants were not known which group they were allocated to until the 2-year evaluation. To keep the participants blinded to their assigned treatments, all of them underwent a 5 mL peripheral blood draw for whole blood analysis and a 50 mL blood draw for the P-PRP preparation. Blood from participants in the saline group was disposed. The study nurse prepared the P-PRP in another room and placed a patient label over the syringe and needle base to occlude the contents. P-PRP was prepared by the same model of the specialised automated centrifuge and sterile disposable kit in all hospitals. 1 mL of the plasma was sent to the laboratory for platelets and leukocytes counting analysis. The syringe was given to the injecting physician who did not know whether the syringe had saline or P-PRP.

The skin of the injection site was prepared. To analysis the intra-articular environment enzyme-linked immunosorbent assay (ELISA), approximately 1 mL of synovial fluid was aspirated under ultrasound guidance before each injection. All P-PRPs were analyzed for P-PRP content… Then, P-PRP or saline was injected into the joint. The treatment consisted of three injections at 1-week intervals. Nonsteroidal anti-inflammatory drugs and chondroprotective supplements were prohibited from being taken during the duration of the trial.

The whole blood, synovial fluid and P-PRP samples were analysed in each hospital's laboratory. Details were described in the supplement.

P-PRP preparation method

50 mL of whole blood were pre-donated in a 60-mL syringe containing sodium citrate. Two centrifugations were consequently performed with a hematology centrifuge. The first centrifugation was performed at 3200 rpm

for 5 min, and the second centrifugation was performed at 3300 rpm for 3 min. This yielded approximately 5 mL of P-PRP for use. The whole blood and platelet-rich plasma samples were sent to a central laboratory.

The mean platelet count in whole blood was $193.5 \pm 52.1 \times 10^9$/L, and that in P-PRP was $832.1 \pm 269.3 \times 10^9$/L. On average, the mean platelet concentration was 4.3 times (95% confidence interval 3.6–4.5) greater in P-PRP than in whole blood. On average, the numbers of leukocytes were $6.3 \pm 2.1 \times 10^9$/L and $0.35 \pm 0.46 \times 10^9$/L in whole blood and P-PRP, respectively. Growth factor concentrations included platelet-derived growth factorAB 49.6 ng/mL (standard deviation 25.5), vascular endothelial growth factor 1.2 ng/mL (1.0), insulinlike growth factor 166.2 ng/mL (25.3), transforming growth factor β1 119.4 ng/mL (80.4), and fibroblast growth factorbasic 116.5 pg/mL (89.2).

Outcomes

Primary outcome in the study was the Western Ontario and McMaster Universities Arthritis Index (WOMAC; range 0–96, optimum score 0). A lower WOMAC score means more favorable ratings for pain, range of motion, and knee function. The mean differences between treatment groups were compared with the minimum clinically important difference (MCID) reported in the literature for each score: 6.4 for overall WOMAC score, 1.5 for WOMAC pain score, 0.6 for WOMAC stiffness subscore, 4.6 for WOMAC function score [1]. The WOMAC score was a responsive and valid tool for patients with KOA [15].

Secondary outcomes included the International Knee Documentation Committee subjective score (IKDC; range 0–100, optimum score 100; MCID, 11.5) [13], knee pain (visual analogue scale 0–10; MCID, 1.37) [16], intra-articular biochemical marker concentrations (levels of TNF-α and IL-1β), tibiofemoral cartilage (evaluated by MRI), and adverse events.

Participants were assessed at baseline and 3, 6, 12, 24, and 60 months after the randomisation. Adverse events and serious adverse events were recorded and categorized into index knee or other sites. Participant's synovial fluid was extracted under ultrasound guidance before injection and at 6 and 12 months of follow-up. MRI scans of the study knee were performed at baseline and final follow-up. Quantitative MRI assessments were described in the supplement.

All of the participants provided written informed consent before this study, and the study was approved by the Local Ethics Committee, the First Affiliated Hospital of Soochow University (2013-098).

Statistical analysis

To determine the adequate sample size, a power analysis was performed for the primary outcome of the WOMAC total score over 60 months. The minimal clinically important difference of WOMAC total score was 6.4. From a pilot study, a standard deviation of 22.3 points was found. With a power of 90% ($\beta = 0.1$), a false-positive rate of 5% ($\alpha = 0.05$), and the estimated 20% dropout rate, 322 participants per group ($n = 644$ total) were required.

Results and analyses were performed by the primary research team. Data distributions were explored visually using histograms and assessments for normality were carried out using quantile–quantile plots, percentile–percentile plots, and the Shapiro Wilk test. Normally distributed data were summarised as means and standard deviations, non-normally distributed data as medians and interquartile ranges, and categorical variables as frequency and percentages.

Mixed models to evaluate the difference between the groups in the change of WOMAC scores were described in the supplement.

Results

From January 2014 to February 2016, 644 participants were screened and were randomized to receive P-PRP ($n = 322$) or sham saline ($n = 322$). The final date of follow-up was February 28, 2021. Of the 322 patients in the P-PRP group, 14 patients lost to follow-up. Of the 322 patients in the sham saline group, 20 patients lost to follow-up. Hence, 308 patients in the P-PRP group and 302 patients in the sham saline group were available for analysis. The baseline characteristics of participants were shown in Table 1. There were no statistically significant differences between the two groups with regard to age, gender, BMI, smoking history, and K–L grade ($P > 0.05$).

In the P-PRP group, 322, 319, 317 patients were evaluated for synovial fluid at baseline, 6- and 12-month follow-up, respectively. In the saline group, 322, 318, and 315 patients were evaluated for synovial fluid at baseline, 6- and 12-month follow-up, respectively. 644 patients who received P-PRP ($n = 322$) or saline ($n = 322$) injections were evaluated for MRI at baseline. At 60-month follow-up, 308 patients in the P-PRP group and 302 patients in the saline group were evaluated for MRI.

We asked patients if they received additional treatment at each follow-up time point. The additional treatment patients received included surgery, injections, physiotherapy, acupuncture, and chiropractor. Patients who underwent surgery and injections were excluded from the study. Patients who received physiotherapy, acupuncture, and chiropractor were still included in the study. 74 participants in the P-PRP group

Table 1 Baseline characteristics of patients included ($n=610$) in statistical analysis

Variable	P-PRP group ($n=308$)	Saline group ($n=302$)	P value
Age, mean (SD)	53.9 (5.0)	54.5 (5.1)	n.s
Sex, (M:F), *n*	123:185	127:175	n.s
BMI, mean (SD)	27.5 (3.2)	27.9 (3.6)	n.s
Injected knee, (left:right), *n*	117:191	129:173	n.s
Smoking history, *n* (%)	91 (29.6%)	75 (24.8%)	n.s
K–L classification, *n*			
Grade 1	89	95	
Grade 2	136	129	
Grade 3	83	78	
VAS Score, mean (SD, 95% CI)	4.83 (0.9, 4.7–4.9)	4.9 (1.1, 4.8–5.1)	n.s
WOMAC score, mean (SD, 95% CI)			
Pain	10.7 (1.8, 10.5–10.9)	10.4 (2.1, 10.1–10.6)	n.s
Stiffness	3.6 (1.6, 3.4–3.8)	3.6 (1.7, 3.4–3.8)	n.s
Physical function	39.1 (9.6, 38.0–40.1)	38.6 (10.6, 37.4–39.8)	n.s
Total	53.4 (11.6, 52.1–54.7)	52.6 (10.8, 51.4–53.8)	n.s
IKDC subjective score, mean (SD, 95% CI)	47.1 (8.8, 46.1–48.1)	47.7 (12.3, 46.3–49.1)	n.s

P-PRP pure platelet-rich plasma, *SD* standard definition, *CI* confidence interval, *M* male, *F* female, *BMI* body mass index, *VAS* visual analogue scale, *WOMAC* Western Ontario and McMaster Universities Arthritis Index, *K–L* Kellgren–Laurence grade, *IKDC* International Knee Documentation Committee

and 83 in the sham group received additional treatments. These treatments were similar and balanced in the 2 groups (eTable 1 in Supplement).

Primary outcome

For the within-group comparison of WOMAC scores, both groups showed statistically significant improvements from their respective baseline scores at the 3-month follow-up ($P<0.001$) (Table 2 and Fig S2A, S2B). However, this significant amelioration was only sustained in the P-PRP group and the improvement maintained for up to 48 months ($P<0.001$). For the intergroup comparison, the PRP group consistently showed better overall WOMAC outcome measures with statistical and clinical significance throughout the study duration (Table 2). No correlation was found between demographic factors or the level of articular degeneration and the WOMAC outcome.

Secondary outcomes

For the within-group comparison of IKDC scores, both groups showed statistically significant improvements from their respective baseline scores at 3-month follow-up ($P<0.001$) (Table 2 and Fig S2C). However, these statistically significant improvements were sustained for up to 48 months in only the P-PRP group ($P<0.001$). For the intergroup comparison, the P-PRP group showed statistically and clinically significant difference than the saline group in the IKDC scores at 6, 12, 24 and 60 months of follow-up (Table 2). A similar trend was also noted in the VAS score. There were no significant effects of demographic factors or the level of articular degeneration on the IKDC and VAS score (Fig. 1).

Six months after all injections, ELISA showed TNF-α and IL-1β levels in synovial fluid were unchanged in the saline group ($P>0.05$). TNF-α and IL-1β levels in the P-PRP group were lower than those before the first injection ($P<0.001$) (Fig. 2). After 12 months, the P-PRP group didn't show inhibition of TNF-α and IL-1β ($P>0.05$).

Tibiofemoral cartilage volume decreased by a mean value of 1171 mm^3 in the P-PRP group and 2311 mm^3 in the saline group over 60 months and the intergroup difference was statistically significant [intergroup difference, 1140 mm^3 (95% CI − 79 to 1320 mm^3), $P<0.001$; Table 3].

No major complications such as fever, infection, deep vein thrombosis, hematoma, tissue hypertrophy, marked muscle atrophy, adhesion formation, or others were occurred in the P-PRP group. In 3 cases, mild pain was present during the first 1 or 2 days. Only one case presented severe pain with swelling after the injection, which spontaneously resolved after 1 week.

No correlation was found between demographic factors or the level of articular degeneration and the secondary outcomes.

Discussion

The main finding of this study was that better clinical results were achieved with P-PRP and the efficacy of P-PRP injection lasted for at least 24 months. Sham saline group had

Table 2 Primary and secondary outcomes among P-PRP and saline groups at different follow-up times

Variable	PRP group ($n=308$)	Saline group ($n=302$)	Between group difference	P value
WOMAC score, pain, mean (SD, 95% CI), months				
3	5.4 (2.7, 5.1 to 5.7)	8.3 (2.7, 8.0 to 8.6)	− 2.9 (− 3.3 to − 2.4)	< 0.001
6	3.8 (2.4, 3.5 to 4.0)	9.5 (2.5, 9.2 to 9.8)	− 5.7 (− 6.1 to − 5.3)	< 0.001
12	3.6 (2.7, 3.3 to 3.9)	10.2 (2.6, 9.9 to 10.5)	− 6.6 (− 7.1 to − 6.2)	< 0.001
24	4.7 (3.2, 4.3 to 5.0)	11.5 (2.6, 11.2 to 11.7)	− 6.8 (− 7.2 to − 6.3)	< 0.001
60	12.3 (2.9, 11.9 to 12.6)	13.7 (2.4, 13.4 to 13.9)	− 1.4 (− 1.8 to − 1.0)	< 0.001
WOMAC score, stiffness, mean (SD, 95% CI), months				
3	2.3 (1.4, 2.1 to 2.4)	3.2 (1.6, 3.0 to 3.4)	− 1.0 (− 1.9 to − 0.7)	< 0.001
6	1.9 (1.3,1.7 to 2.0)	3.4 (1.8,3.2 to 3.6)	− 1.6 (− 1.8 to − 1.3)	< 0.001
12	1.8 (1.3, 1.7 to 2.0)	3.9 (1.8, 3.8 to 4.1)	− 2.1 (− 2.4 to − 1.9)	< 0.001
24	2.0 (1.5, 1.9 to 2.2)	4.4 (1.6, 4.3 to 4.6)	− 2.4 (− 2.7 to − 2.2)	. < 0.001
60	3.7 (1.8, 3.5 to 3.9)	5.67 (1.4, 5.5 to 5.8)	− 2.0 (− 2.2 to − 1.7)	< 0.001
WOMAC score, physical function, mean (SD, 95% CI), months				
3	29.0 (10.1, 27.8 to 30.1)	32.5 (10.9, 31.3 to 33.8)	− 3.6 (− 5.2 to − 1.9)	< 0.001
6	23.6 (9.0, 22.6 to 24.6)	35.4 (10.8, 34.2 to 36.6)	− 11.8 (− 13.4 to − 10.2)	< 0.001
12	22.3 (8.7, 21.4 to 23.3)	38.9 (11.0, 37.7 to 40.2)	− 16.6 (− 18.2 to − 15.0)	< 0.001
24	24.0 (9.4, 23.0 to 25.1)	41.9 (10.9, 40.7 to 43.2)	− 17.9 (− 19.5 to − 16.3)	< 0.001
60	37.5 (11.27, 36.20 to 38.73)	49.8 (9.6, 48.8 to 50.9)	− 12.4 (− 14.0 to − 10.7)	< 0.001
WOMAC score, total, mean (SD, 95% CI), months				
3	36.6 (12.9, 35.2 to 38.1)	44.0 (11.4, 42.7 to 45.3)	− 7.4 (− 9.3 to − 5.4)	< 0.001
6	29.2 (11.7, 27.9 to 30.5)	48.3 (11.2, 47.1 to 49.6)	− 19.1 (− 21.0 to − 17.3)	< 0.001
12	27.7 (11.3, 26.5 to 29.0)	53.1 (11.4, 51.8 to 54.4)	− 25.4 (− 27.2 to − 23.5)	< 0.001
24	30.7 (12.1, 29.4 to 32.1)	57.8 (11.2, 56.5 to 59.1)	− 27.1 (− 28.9 to − 25.2)	< 0.001
60	53.4 (13.3, 52.9 to 54.9)	69.1 (9.9, 68.0 to 70.3)	− 15.8 (− 17.6 to − 13.9)	< 0.001
IKDC subjective score, mean (SD, 95% CI), months				
3	56.0 (9.8, 54.9 to 57.1)	50.9 (12.8, 49.5 to 52.4)	5.0 (3.2 to 6.8)	< 0.001
6	61.1 (9.0, 60.1 to 62.1)	48.1 (12.7, 46.6 to 49.5)	13.1 (11.3 to 14.8)	< 0.001
12	61.6 (9.2, 60.6 to 62.6)	45.5 (12.3, 44.1 to 46.9)	16.1 (14.4 to 17.9)	< 0.001
24	59.8 (10.2, 58.6 to 60.9)	42.2 (12.3, 40.8 to 43.6)	17.6 (15.8 to 19.4)	< 0.001
60	49.5 (10.9, 48.2 to 50.7)	37.2 (12.1, 35.8 to 38.6)	12.3 (10.4 to 14.1)	< 0.001
Visual analogue scale score, mean (SD, 95% CI), months				
3	2.2 (1.5, 2.0 to 2.4)	3.4 (1.3, 3 to 3.6)	− 1.25 (− 1.5 to − 1.0)	< 0.001
6	1.3 (1.1, 1.2 to 1.4)	4.3 (1.1, 4.1 to 4.4)	− 2.9 (− 3.1 to − 2.8)	< 0.001
12	1.2 (1.2, 1.1 to 1.4)	4.6 (1.1, 4.5 to 4.7)	− 3.4 (− 3.5 to − 3.2)	< 0.001
24	1.6 (1.5, 1.4 to 1.8)	5.1 (1.0, 5.0 to 5.2)	− 3.5 (− 3.7 to − 3.3)	< 0.001
60	4.9 (1.7, 4.7 to 5.1)	6.2 (0.9, 6.1 to 6.4)	− 1.4 (− 1.6 to − 1.2)	< 0.001

better clinical scores at 3-month evaluation compared to baseline and then deteriorated over time. MRI analysis demonstrated that there were significant differences between the PRP and placebo groups at 60 months of follow-up. These findings supported the use of P-PRP for alleviating knee pain and slowing cartilage volume loss in patients with KOA.

In recent years, an increasing number of reports have investigated the benefit of PRP injections for KOA and found the potential to improve knee function and reduce pain [5, 8, 10]. The duration of clinical efficacy of PRP was controversial in these studies. Gobbi et al. [11] reported clinical benefits and efficacy were limited by time, and the approximate duration of efficacy was 2 years. Another report pointed out the clinical effectiveness only continued for 1 year [9]. However, these reports were mid-term follow-up study with no control group. The advantages of the present study were a comparison of P-PRP with sham saline in a 60-month follow-up. The trial indicated that, with regard to the duration of the benefits patients obtained, the improvement in clinical scores was stable for up to 24 months in the P-PRP group. At 60 months, clinical scores in the P-PRP group showed a decrease trend but still statistically and clinically better than those in the saline group. Similar to our study, a long-term follow-up study conducted by Di Martino et al. found that the effects of PRP remained stable for up to 24 months [7].

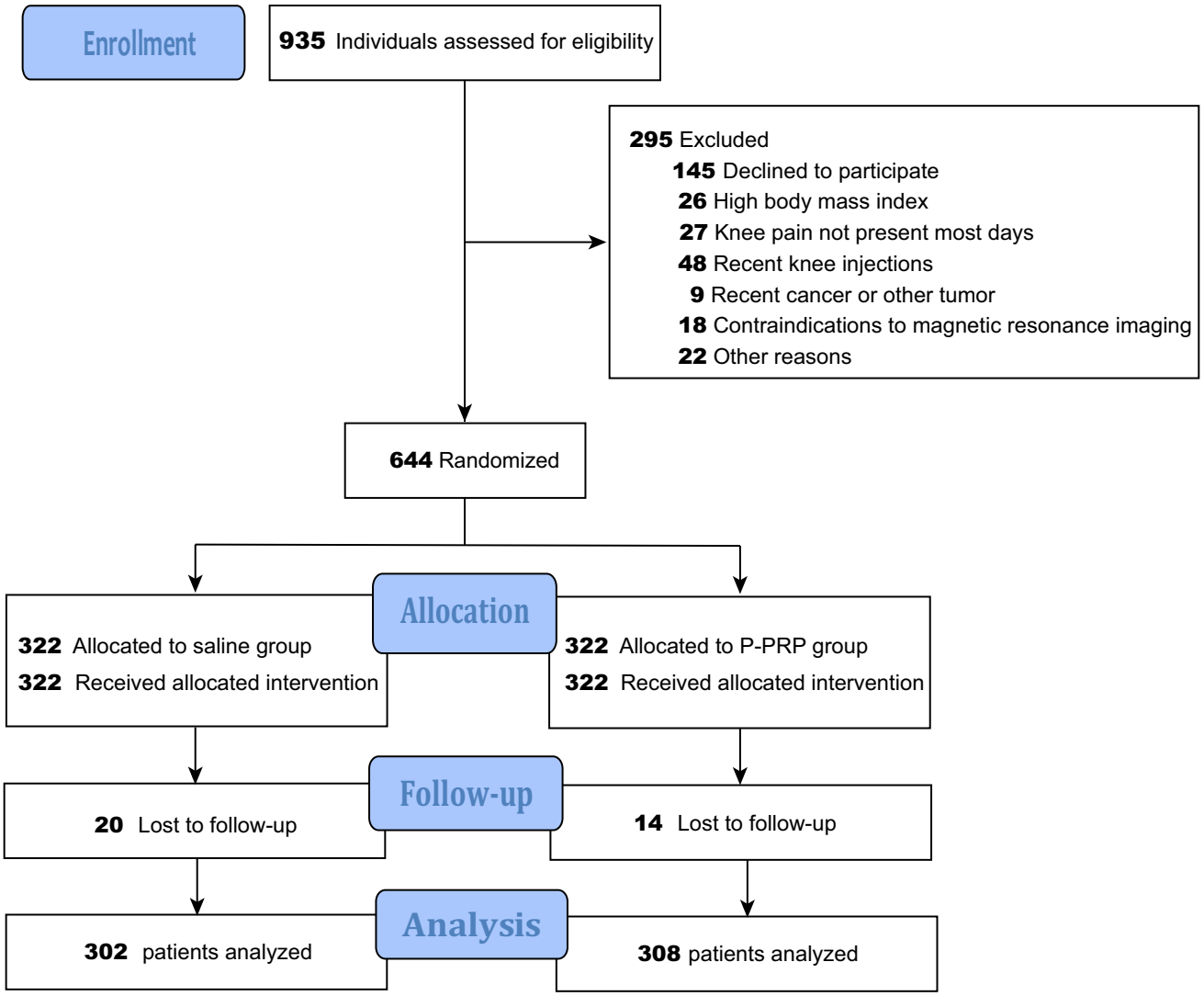

Fig. 1 Flowchart of the clinical trial

Another notable finding is that P-PRP could significantly decrease the cartilage volume loss compared with the placebo over 5 years. Therapies that not only relieve symptoms but also modify structure are a critical and unmet need for knee OA. Increasing cartilage thickness or prevention of cartilage loss could be thought of as a disease-modifying quality, and was one of the criteria required for an agent to qualify as a disease-modifying OA drug [4]. There are many animal studies available on PRP and cartilage. Angelo et al. recently published a comprehensive preclinical review of the disease-modifying effects of PRP. They found Intra-articular PRP injections showed disease-modifying effects in most studies, both at the cartilage and synovial level. Nevertheless, the overall low quality of the published studies warrants further preclinical studies to confirm the positive findings, as well as high-level human trials to demonstrate if these results translate into disease-modifying effects when PRP is used in the clinical practice to treat OA [2]. There were a limited number of clinical studies evaluating the condition of cartilage change after the treatment of PRP. Articular cartilage ought to be assessed in long-term clinical studies of similar therapeutics. Hart et al. conducted a prospective study of 50 patients to assess whether PRP could promote tibiofemoral cartilage regeneration [12]. They reported there was no significant cartilage regeneration at 12 months but the thickness of the cartilage decreased in no cases. In the present study, there was a significant reduction in the rate of tibiofemoral cartilage loss in the P-PRP group (6.7%) compared to the saline group (13.0%) over 60 months. Consequently, P-PRP could slow the progression of KOA. P-PRP was different from leukocyte-rich PRP used by many other authors. It is controversial whether leukocytes should be removed from PRP.

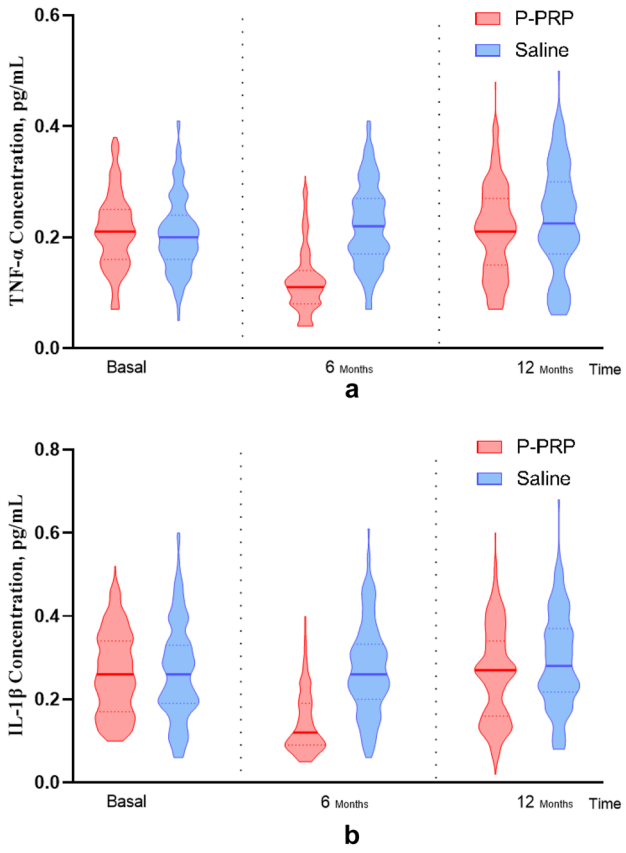

Fig. 2 Mean values of intra-articular **A** TNF-α and **B** IL-1β before treatment, at 6-month and 12-months follow-up time points, demonstrating a trend toward decreased TNF-a and IL-1βwithin 6 months and raised again at 12 months (Violin plot showing median value and quartiles)

Leukocytes had been proved to impair and be detrimental to the overall effects of PRP because of the release of reactive oxygen species, other lytic enzymes, and metalloproteinases. They would contribute to an early inflammatory response within the joint environment and a delayed healing response [18]. On the contrary, P-PRP could inhibit the inflammatory response by neutralizing nuclear factor-κB activity [17]. In the present study, the levels of TNF-α and IL-1β significantly decreased after P-PRP injection. IL-1β and TNF-α were highly expressed in the cartilage and synovium of KOA patients and reflected the degree of inflammation of the joint environment. These positive results showed that P-PRP improved the environment of cartilage regeneration.

Strengths and limitations

The strong points of the study were the comparison of P-PRP group with placebo and the long-term follow-up. Control group showed a significant improvement for all clinical outcomes at the 3-month follow-up. This phenomenon strongly suggested a positive placebo effect, as well as avoiding investigator bias. Second, the imaging and inflammatory biomarkers changes were analyzed, which allowed a better understanding of the effect and mechanism of P-PRP. Third, all measurements were independently performed by trained observers who were blinded to the group allocation, characteristics of participants, and the information of images.

This study has several limitations. First, the generalizability of the results to other platelet-rich plasma blood products was limited. Alternative PRP blood interventions differ in dose, timing, and number of injections and in the composition of platelets and leukocytes. Second, patients with different grades of cartilage degeneration (Kellgren grades 0–3) were included in this trail. This may affect the results because patients with more advanced KOA tend to have less benefit from PRP injection. Third, the blinding of treatment was removed at 2 years of follow-up, which might affect the results evaluated at the following follow-up points. Forth, 93 participants sought additional treatment during the 60-month follow-up, which may have influenced the results. However, these therapies appeared balanced across the 2 groups.

Table 3 Change in tibiofemoral cartilage volume between the PRP and the NA group over 60 months

	PRP group		NS group		Absolute between-group difference	*P* value
	Baseline	Change at 60 mo[a]	At baseline	Change at 60 mo[a]		
Tibiofemoral cartilage volume, mm^3	17,325 (15 558 to 18 429)	− 1171 (− 963 to − 793)	17,762 (14 637 to 17 441)	− 2311 (− 1004 to − 835)	1140 (− 79 to 1320)	< 0.001
Annual percentage change in tibiofemoral cartilage volume[b], %	− 1.4 (− 3.0 to − 1.2)		− 2.6 (− 3.0 to − 2.4)		1.3 (− 0.4 to 1.5)	< 0.001
P value	0.020		< 0.001			

[a]The within-group change and between-group difference were calculated in participants with baseline data of the outcome

[b]Calculated as 100 × [(follow-up cartilage volume − baseline cartilage volume)/baseline cartilage volume]/exact time between 2 scans in years. This formula requires complete data at both time points, therefore participants

Conclusions

In this randomized clinical trial of patients with KOA, P-PRP was superior to sham saline in treating KOA. P-PRP was effective for achieving at least 24 months of symptom relief and slowing the progress of KOA, with both P-PRP and saline being comparable in safety profiles.

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Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval All of the participants provided written informed consent before this study, and the study was approved by the Local Ethics Committee, the First Affiliated Hospital of Soochow University (2013-098).

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