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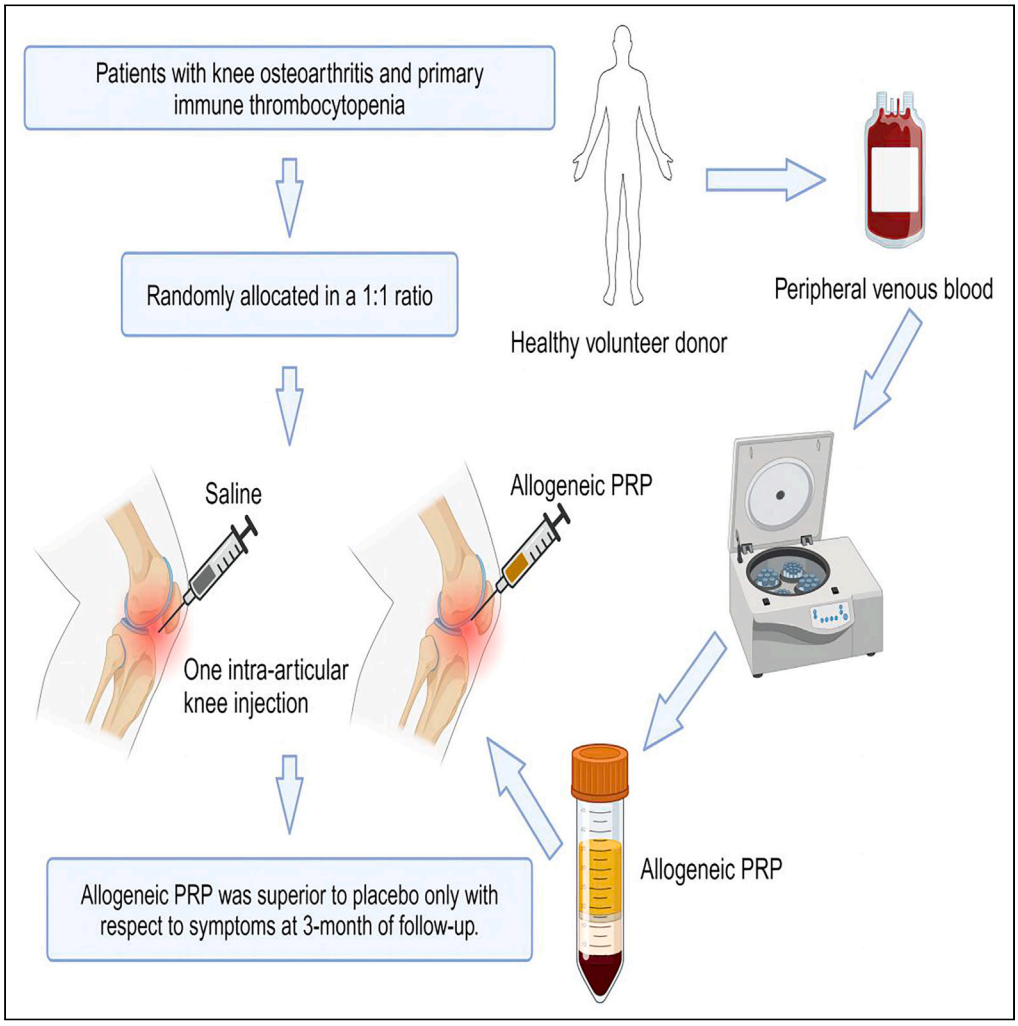

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Highlights

Allogeneic PRP might be a promising non-surgical therapy for KOA in patients with ITP

At 12 month, allogeneic PRP injection was not more effective than placebo injection

None of the structural outcomes revealed significant improvements between the two group

Allogeneic PRP was superior to placebo only with respect to symptoms at 3-month

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Allogeneic platelet-rich plasma for knee osteoarthritis in patients with primary immune thrombocytopenia: A randomized clinical trial

Xiaohang Zhu,[1,9] Lingying Zhao,[2,3,8,9] Nicoletta Riva,[4] Ziqiang Yu,[2,3] Miao Jiang,[2,3] Feng Zhou,[1] Alexander Gatt,[4,5] Peter V. Giannoudis,[6,7] and Jiong Jiong Guo[1,3,8,10,*]

SUMMARY

The treatment of painful KOA in adult patients with ITP has not been well studied yet. We conducted a prospective, double-blind, randomized, placebo-controlled trial to evaluate the efficacy of intra-articular allogeneic PRP injections on symptoms and joint structure in patients with KOA and ITP. 80 participants were randomly allocated in a 1:1 ratio to allogeneic PRP group or saline group. The primary outcome was the WOMAC total score at 12 months post-injection. The number of patients in each group who achieved MCID of primary outcome showed a statistically significant difference only at 3-month (27/39 vs. 5/39, $p = 0.001$) and 6-month (15/39 vs. 3/38, $p = 0.032$). The difference in WOMAC total score exceeded the MCID only at 3 month (mean difference of −15.1 [95% CI -20.7 to −9.5], $p < 0.001$). Results suggest that allogeneic PRP was superior to placebo only with respect to symptoms at 3-month of follow-up.

INTRODUCTION

Knee osteoarthritis (KOA) is one of the most common causes of knee pain and dysfunction. Currently, there is no successful cure for KOA, and most research has focused on pain relief and prevention of functional decline.[1,2]

Autologous platelet-rich plasma (PRP) is a safe blood product containing a myriad of growth factors and cytokines with the potential to alter biological processes implicated in OA pathogenesis and symptoms.[3,4] Although the evidence to support the clinical benefits of PRP is limited,[1,5] PRP is increasingly used to treat KOA.[6,7] Meanwhile, the production process and equipment for PRP are continuously being optimized, leading to a reduction in the cost of PRP production. Currently, the cost of a single PRP treatment is not expensive, and most patients can afford it. Possibly due to the different PRP preparation methods and blood samples, some clinical studies reported different outcomes of PRP treatment in OA.[8,9]

An autoimmune condition known as chronic primary immune thrombocytopenia (ITP) causes a low chronic platelet count as a result of increased platelet destruction and decreased platelet production.[10,11]

Recent systematic reviews concluded that platelet dysfunction may affect the efficacy of PRP.[12] Therefore, for patients with ITP, autologous PRP might not be an optimum solution. Conversely, the peripheral venous blood used for the preparation of allogeneic PRP comes from healthy donors and is not affected by the autologous platelet count. Allogeneic PRP has been reported to be safe and effective in treating several orthopedic diseases, such as OA, rotator cuff dysfunction, and refractory wounds.[13–16] Thus, it might be a promising non-surgical therapy for KOA in patients with ITP. Although several clinical trials have shown that allogeneic PRP could relieve pain and recover articular function,[15,16] the results are not convincing because they lack adequate blinding and a control group. Therefore, it is necessary to conduct a well-designed clinical trial to evaluate the efficacy of allogeneic PRP.

Therefore, this study aimed to evaluate the efficacy of intra-articular allogeneic PRP injections on symptoms and joint structure in patients with KOA and ITP.

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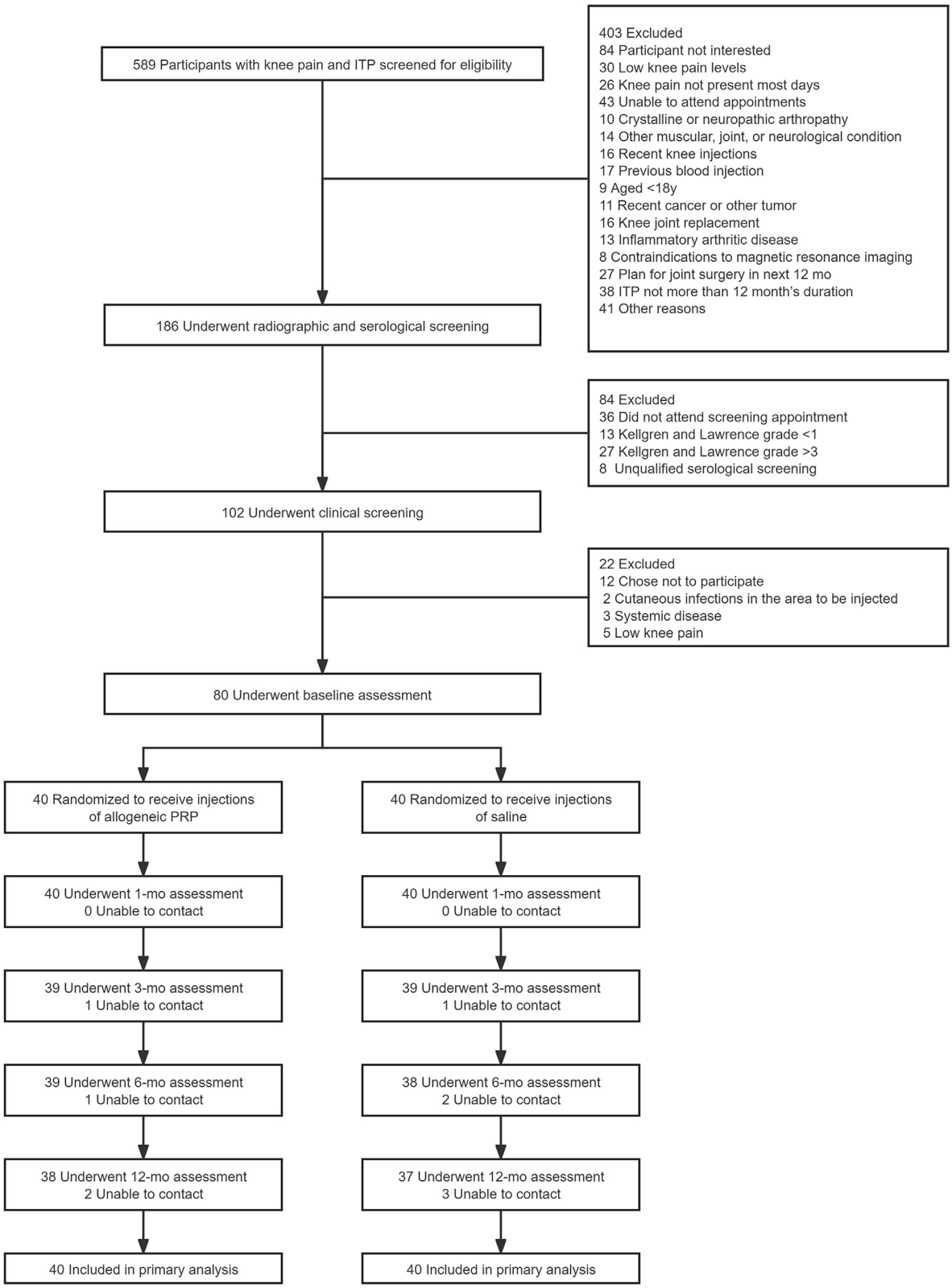

Figure 1. This flowchart shows recruitment, randomization, and follow-up of patients in the trial

Table 1. Baseline participant characteristics

Characteristics	Allogeneic PRP (*n* = 40)	Placebo (*n* = 40)
Age mean (SD), y	64.1 (6.2)	63.9 (6.6)
Sex No. (%)		
Male	17 (39.5)	18 (45.9)
Female	23 (60.5)	22 (54.1)
Body mass index, mean (SD)[a]	29.8 (4.3)	29.8 (4.7)
Kellgren and Lawrence grade of radiographic severity, No. (%)[b]		
1	7 (17.5)	4 (10.0)
2	16 (40.0)	18 (45.0)
3	17 (42.5)	18 (45.0)
Knee alignment, mean (SD), degrees[c]	180.6 (3.9)	180.8 (4.1)
Symptom duration, median (IQR), y	4.5 (2.0–10.0)	5.0 (2.0–11.5)
Side No. (%)		
Left	18 (45.0)	16 (40.0)
Right	22 (55.0)	24 (60.0)
Current pain medication use, No. (%)[d]	27 (71.1)	30 (75.0)
Nonsteroidal anti-inflammatory drugs	18 (47.4)	21 (52.5)
Topical anti-inflammatory drugs	12 (31.6)	9 (22.5)
Oral opioids	1 (2.6)	3 (7.5)
Treatment expectation, No. (%)[e]		
No effect	0 (0)	1 (2.5)
Improvement		
Minimal	6 (15.0)	7 (17.5)
Moderate	22 (55.0)	21 (52.5)
Large	7 (17.5)	5 (12.5)
Complete recovery	5 (12.5)	6 (15.0)
WOMAC score, mean (SD)[f]		
Pain subscale	10.6 (3.0)	10.9 (3.2)
Stiffness subscale	4.5 (2.1)	4.5 (2.2)
Function subscale	36.6 (10.4)	36.5 (11.8)
Total subscale	51.4 (13.5)	51.9 (14.6)
Overall knee pain score, mean (SD)[g]	6.0 (0.9)	6.0 (1.0)
Lysholm score, mean (SD)[h]	60.9 (10.6)	60.9 (11.6)
SF-36[i] Physical, mean (SD)	27.4 (8.9)	27.4 (9.8)
SF-36 mental, mean (SD)	36.5 (11.6)	36.7 (12.1)
Medial tibial cartilage volume, mean (SD), mm^3[j]	1542 (505)	1346 (492)
Presence of knee effusion, No. (%)[k]	19 (47.5)	15 (37.5)

Abbreviations: PRP, platelet-rich plasma; SD, standard deviation.

[a]Calculated as weight in kilograms divided by height in meters squared.

[b]The Kellgren and Lawrence system grades radiographic osteoarthritis disease severity from 0 to 4. Grade 2 indicates the presence of osteophytes and possible joint space narrowing; grade 3, multiple osteophytes, definite joint space narrowing, sclerosis, and possible bony deformity.

[c]Measured as anatomical axis from standing radiograph with 180° indicating neutral alignment; <180°, varus alignment; and >180°, valgus alignment.

[d]Defined as taken at least once per week over the prior month.

[e]Treatment expectation was assessed by a 5-point Likert scale with participants asked "What effect do you think injections of allogeneic platelet-rich plasma will have on your knee?"

[f]Measured on an 96-point numeric rating scale for knee pain and function, Ranges from 0 to 96; higher scores indicate worse pain.

[g]Measured on an 11-point numeric rating scale for average knee pain in the past week. Score range is 0 (no pain) to 10 (worst pain possible); higher scores indicate worse pain.

[h]Measured on an 100-point numeric rating scale for knee pain and function, Ranges from 0 to 100; lower scores indicate worse pain.

[i]The Assessment of SF-36 is a 36-item questionnaire regarding health-related quality of life. The SF-36 range is 0–100, with higher scores indicating better quality of life.
[j]A single rater (blinded to the group and time point) measured medial tibial cartilage volume from sagittal magnetic resonance images (MRI) by manually drawing disarticulation contours around the cartilage boundaries on each section. These data were resampled by bilinear and cubic interpolation for the final 3-dimensional rendering. The cartilage plate volume was determined by summing the pertinent voxels within the resultant binary volume.
[k]Graded from MRI images and scored by a single rater (blinded to the group) using the MRI Osteoarthritis Knee Score effusion subscore, with 0 indicating normal; 1, small; 2, medium; and 3, large. Presence of knee effusion was defined as a score of 2 or 3.

RESULTS

Figure 1 summarizes participant flow. A total of 589 patients were evaluated, and 509 patients were deemed to be ineligible at the screening visits (either initial evaluation, radiographic and serological screening, or clinical screening). Finally, 80 patients were recruited and randomized into the two groups (40 patients in each group). The first patient was enrolled on July 30, 2021 and the 12-month follow-up was completed on October 25, 2022 (Supplement Information, Figure S1). Baseline participant characteristics and Participants' treatment expectations (no effect, improvement, and complete recovery) were comparable between groups (Table 1). For the outcomes assessment at 12 months, the follow-up rate was 95% in the PRP group (2 patients lost to follow-up) and 93% in the placebo group (3 patients lost to follow-up).

In each group, all participants received one injection. Concomitant interventions were comparable between groups (Table S3 in Supplement Information). The James Blinding Index indicated successful blinding beyond chance (mean, 0.73 [95% CI, 0.68 to 0.77] for participants and 0.76 [95% CI, 0.70 to 0.79] for the individuals administering the injections).

At baseline, the mean WOMAC total score was 51.7 in the allogeneic PRP groups and 51.9 in the placebo group.

Primary outcome

At 12 months, allogeneic PRP injection was not more effective than placebo injection on the primary outcome (Table 2; Figure 2). The mean WOMAC total score was 45.1 points in the PRP group vs. 51.0 in the placebo group, corresponding to a difference of −5.9 points (95% CI, −11.9 to 0.05, $p = 0.049$). While the difference between the two groups was statistically significant, it did not reach the predefined MCID, thus it was not considered clinically relevant. Meanwhile, a sensitivity analysis was done after multiple imputations and the results did not change (Supplement Information, Tables S7 and S8)

Secondary outcomes

Secondary outcomes were generally in the same direction as the primary outcome (Table 2; Figure S2 in supplement Information). The mean WOMAC total score was 45.6 in the PRP group vs. 51.7 in the placebo group at 1 month (mean difference of −6.1 [95% CI -12.0 to −0.3], $p = 0.040$), 36.4 in the PRP group vs. 51.4 in the placebo group at 3-month (mean difference of −15.1 [95% CI -20.7 to −9.5], $p < 0.001$) and 41.0 in the PRP group vs. 51.2 in the placebo group at 6-month (mean difference of −10.3 [95% CI -16.0 to −4.6], $p = 0.001$). The WOMAC total score showed a clinically significant difference between the two groups only at 3-month follow-up, since it was the only difference that exceeded the MCID. This finding was supported by a statistically significant difference in all three WOMAC subscales at this time point. The number of patients in each group who achieved MCID levels of WOMAC total score showed a statistically significant difference only at 3 month and 6 month (Table S9 in Supplement Information)

The other secondary outcomes that measured symptoms (overall knee pain score, Lysholm score, physical and mental components of the 36-Item Short-Form General Health Survey [SF-36]) were statistically significantly different between the two groups at 3- and 6-month follow-ups. However, the change in secondary outcomes only exceeded the MCID at 3 month. In the two groups, the mean clinical scores significantly improved from baseline to the 3-month follow-up, followed by a decline at the 6- and 12-month follow-ups.

More participants in the allogeneic PRP group than in the placebo group reported reduced painkillers to use at 12-month follow-up (PRP group, 25/38 [65.8%] vs. placebo group, 9/37 [24.3%]; Risk ratios [RR], 2.71 [95% CI, 1.47 to 4.99]; $p = 0.023$) (Table 3). The number of participants in the allogeneic PRP group who were willing to have a second injection was statistically significantly greater than in the placebo group (PRP group, 27/38 [71.1%] vs. placebo group, 13/37 [35.1%]; RR, 2.02 [95% CI, 1.25 to 3.28]; $p = 0.037$).

At a 12-month follow-up, none of the structural outcomes evaluated at the magnetic resonance imaging (MRI) scan revealed statistically significant improvements (Table 3 and Figure 3). At the 12-month follow-up, there was no evidence that the Kellgren and Lawrence grade (K-L grade), body mass index (BMI), or age significantly moderated the effects of allogeneic PRP on the primary outcome (supplement Information, Tables S5 and S6).

Adverse events

Adverse events were minor and transient. There were no PRP-related severe adverse events. Overall, 10.0% of patients (4 of 40) in the allogeneic PRP group and 7.5% of patients (3 of 40) in the placebo group reported mild knee pain, swelling, and stiffness after injection (immediate adverse events) that did not require treatment and resolved within 48 h. Meanwhile, more patients in the PRP group than in the placebo group reported delayed adverse events (Table S3 in Supplement Information).

Table 2. Primary and secondary outcomes

	Allogeneic PRP (n = 40)	Placebo (n = 40)	Difference (95% CI)	p value
Number of patients assessed at each time-point, n (%)				
• 1-month follow-up	40 (100%)	40 (100%)		
• 3-month follow-up	39 (97.5%)	39 (97.5%)		
• 6-month follow-up	39 (97.5%)	38 (95.0%)		
• 12-month follow-up	38 (95.0%)	37 (92.5%)		
Primary outcome				
WOMAC total score at 12-month, mean (SD)[a,b]	45.1 (12.1)	51.0 (13.9)	−5.9 (−11.9 to 0.05)	0.049
Secondary outcomes				
WOMAC score, mean (SD)[a,b]				
• Pain subscale at 1-mo	10.0 (2.9)	10.9 (3.0)	−0.9 (−2.2 to 0.4)	0.186
• Pain subscale at 3-month	8.1 (2.9)	10.6 (2.8)	−2.5 (−3.8 to −1.2)	0.000
• Pain subscale at 6-month	8.8 (3.3)	10.6 (3.1)	−1.7 (−3.2 to −0.3)	0.020
• Pain subscale at 12-month	9.9 (3.1)	10.8 (3.3)	−0.9 (−2.4 to 0.6)	0.218
• Stiffness subscale at 1-mo	3.9 (2.0)	4.5 (1.8)	−0.5 (−1.4 to 0.3)	0.228
• Stiffness subscale at 3-month	3.0 (1.9)	4.4 (1.8)	−1.3 (−2.2 to −0.5)	0.002
• Stiffness subscale at 6-month	3.6 (1.9)	4.4 (1.7)	−0.8 (−1.6 to −0.02)	0.044
• Stiffness subscale at 12-month	3.8 (1.9)	4.3 (1.6)	−0.5 (−1.3 to 0.3)	0.238
• Function subscale at 1-mo	31.7 (12.3)	36.4 (11.6)	−4.7 (−10.0 to 0.6)	0.080
• Function subscale at 3-month	25.3 (10.7)	36.5 (11.6)	−11.2 (−16.3 to −6.2)	0.000
• Function subscale at 6-month	28.5 (10.6)	36.3 (11.3)	−7.8 (−12.7 to −2.8)	0.003
• Function subscale at 12-month	31.3 (11.4)	35.8 (11.4)	−4.5 (−9.8 to 0.7)	0.090
• Total score at 1-mo	45.6 (12.9)	51.7 (13.3)	−6.1 (−12.0 to −0.3)	0.040
• Total score at 3-month	36.4 (11.8)	51.4 (13.1)	−15.1 (−20.7 to −9.5)	0.000
• Total score at 6-month	41.0 (11.8)	51.2 (13.3)	−10.3 (−16.0 to −4.6)	0.001
Overall knee pain score, mean (SD)[b,c]				
• 1-mo	5.2 (1.7)	5.8 (1.2)	−0.6 (−1.3 to 0.02)	0.058
• 3-month	3.7 (2.0)	5.8 (1.2)	−2.1 (−2.8 to −1.4)	0.000
• 6-month	4.6 (1.7)	5.7 (1.3)	−1.1 (−1.8 to −0.4)	0.003
• 12-month	5.1 (1.8)	5.7 (1.5)	−0.6 (−1.4 to 0.2)	0.127
Lysholm score, mean (SD)[d,e]				
• 1-mo	66.5 (11.8)	61.3 (11.6)	5.2 (−0.01 to 10.4)	0.051
• 3-month	71.7 (11.2)	61.9 (11.8)	9.9 (4.7–15.1)	0.000
• 6-month	68.4 (11.9)	61.7 (12.1)	6.7 (1.3–12.1)	0.016
• 12-month	66.8 (12.1)	61.7 (12.2)	5.1 (−0.5 to 10.7)	0.071
SF-36[b,f] Physical, mean (SD)				
• 1-mo	31.1 (8.9)	27.3 (9.4)	3.8 (−0.2 to 7.9)	0.065
• 3-month	39.1 (11.1)	27.3 (8.8)	11.8 (7.3–16.3)	0.000
• 6-month	33.2 (8.8)	27.3 (8.0)	6.0 (2.1–9.8)	0.003
• 12-month	30.5 (8.7)	27.6 (7.6)	2.9 (0.9–6.7)	0.130
SF-36 mental, mean (SD)				
• 1-mo	40.6 (10.5)	36.5 (11.8)	4.2 (−0.8 to 9.1)	0.098
• 3-month	46.6 (10.4)	36.7 (11.5)	9.9 (5.0–14.9)	0.000
• 6-month	43.3 (11.1)	37.0 (11.6)	6.6 (1.5–11.8)	0.013
• 12-month	40.7 (10.8)	37.1 (10.9)	3.6 (−1.4 to 8.5)	0.161

Abbreviations: PRP, platelet-rich plasma; SD, standard deviation; CI, confidence intervals.

[a]Measured on an 96-point numeric rating scale for knee pain and function, Ranges from 0 to 96; higher scores indicate worse pain. The minimum clinically important difference (MCID) is 11.5.
[b]A negative within-group change indicates improvement. For difference, in change between groups, a negative difference favors the allogeneic platelet-rich plasma group.
[c]Measured on an 11-point numeric rating scale for average knee pain in the past week. Score range is 0 (no pain) to 10 (worst pain possible); higher scores indicate worse pain. The MCID is 1.8.
[d]Measured on an 100-point numeric rating scale for knee pain and function, Ranges from 0 to 100; lower scores indicate worse pain. The MCID is 8.9.
[e]A positive within-group change indicates improvement. For difference, in change between groups, a positive difference favors the allogeneic platelet-rich plasma group.
[f]The Assessment of SF-36 is a 36-item questionnaire regarding health-related quality of life. The SF-36 range is 0–100, with higher scores indicating better quality of life. The MCID is unknown.

DISCUSSION

In this randomized, placebo-controlled study, knee injections of allogeneic PRP did not improve the symptoms of KOA in the long term, as shown by a non-clinically relevant difference in the WOMAC total score between patients receiving PRP and patients receiving placebo at 12-month follow-up. Different from the existing studies, all PRPs used for injection in the present study were from the same healthy donor, prepared with the same system, and administered simultaneously. However, knee injections of allogeneic PRP may be beneficial in the short term, as demonstrated by a clinically relevant lower WOMAC total score in the PRP group at 3-month follow-up.

In the primary outcome analysis, the knee injections of allogeneic PRP were not found to be superior to placebo for patients with KOA combined with ITP, based on the WOMAC total score at 12 month. The absolute improvement in both groups from baseline did not exceed the MCID. The outcomes did not differ by BMI, age, or K-L grade. Thus, this trial results do not support an expected benefit in the long term. Similarly, the efficacy of PRP in knee OA has been questioned in recent clinical trials, patients with knee OA who received intra-articular injection of autologous PRP did not result in a significant improvement in symptoms at 12 month compared with those who received the injection of placebo.[1] In a previous clinical study, autologous PRP similarly did not demonstrate an advantage in improving pain and function in knee OA over 24 weeks compared with placebo and plasma.[17] This aligns with the outcomes of our study and all indicate uncertainty about the long-term efficacy of PRP.

In the analysis of the secondary outcomes, knee injections of allogeneic PRP significantly improved the symptoms of KOA at the 3-month follow-up, compared with placebo injections. In addition, the absolute improvement from the baseline obtained by the allogeneic PRP exceeded the MCID. However, there was no evidence of a statistically significant between-group difference in the structural outcomes, as assessed by MRI at the 12-month follow-up. Allogeneic PRP only slightly improved the symptoms of KOA at the 1-month follow-up, compared with placebo injections. This suggests that allogeneic PRP can improve the symptoms of KOA in a short period, but it does not slow disease progression and has a delayed response. Giving serial single injections at 3-month or 6-month intervals can be an option, which may further relieve symptoms for more extended periods and potentially delay KOA progression.

The benefits of knee injections of autologous PRP for KOA are still controversial. Recent studies have reported variable results.[1,8,9,18] This discrepancy could be the result of methodological variations such as PRP preparation procedure and injection regimen, blood samples, and outcome measures, as well as design issues affecting the risk of bias. Our findings are consistent with a short-term clinical improvement of allogeneic PRP for KOA symptoms reported previously in a pilot study.[15] The short-term efficacy and delayed response have also been observed in several autologous PRP studies.[19,20]

A previous RCT with 288 participants demonstrated no improvements in structural outcomes at 12-month follow-up compared with baseline and placebo (n = 144) for knee injections of autologous PRP (n = 144) for KOA.[1] In another trial of 98 participants[21] evaluating structural outcomes at 52-week follow-up, when compared to hyaluronic acid (n = 32) or nonsteroidal anti-inflammatory medications (n = 33), autologous PRP did not show any statistically significant difference in knee cartilage thickness (n = 33). This finding is consistent with this study. In 2 other trials,[22,23] femoral cartilage thickness measured by ultrasound at 6 months did not differ significantly between autologous PRP (n = 30) and saline (n = 30), while autologous PRP (n = 44) significantly improved only ultrasound-assessed synovial hypertrophy/vascularity and effusion at 3 and 6 months compared with control group (n = 45). These last three studies, however, had small sample sizes and might not have enough statistical power.

In the current study, although no differences in overall knee pain score between the two groups were demonstrated at 12 month, in general more PRP-treated participants reduced the use of analgesics. Meanwhile, more participants in the allogeneic PRP group were willing to receive a second injection. This outcome showed that allogeneic PRP is likely to be beneficial in relieving knee symptoms.

Strengths of the study

This study has several strengths, the use of established end measures for symptoms and joint structure is one of the study's many strengths, along with the Randomized controlled trial (RCT) design and relatively long follow-up. Other strengths include masking participants, injectors, assessors, and the statistician to the treatment group.[24,25] In addition, all PRPs used for injection in the present study were derived from the same healthy donor at the same time, prepared with the same system, and assessed to quantify the relevant growth factors and cytokines. This avoided confounding factors and reduced the risk of bias.

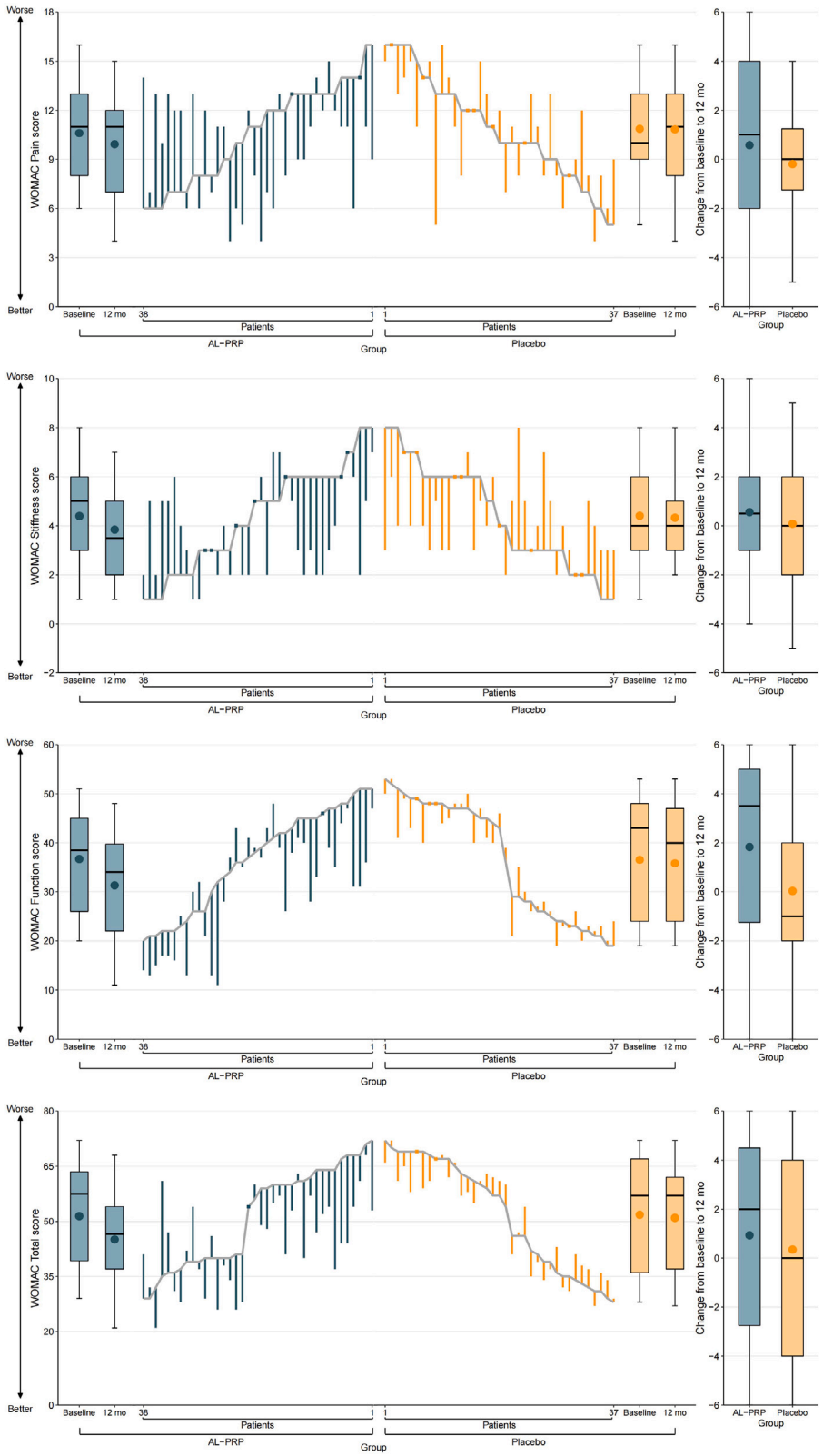

Figure 2. Each vertical line represents an individual participant, with participants ordered by baseline value (gray dots) and vertical lines extending up (worsened) or down (improved) to the 12-month values

The horizontal lines in the boxplots from bottom to top show the 25th, 50th (median), and 75th percentiles. The dot in the boxplot indicates the mean. The whiskers indicate the highest and lowest values no further than 1.5 times the interquartile range.

Table 3. End of follow-up outcomes, including joint structural outcomes

	No./total (%)[a]			
Outcomes	Allogeneic PRP (*n* = 38)	Placebo (*n* = 37)	Risk ratio (95% CI)[b]	*p* value
MRI Osteoarthritis Knee Score subscores at 12 months[c]				
Worse meniscus morphology[d]	9/38 (23.7)	11/37 (29.7)	0.80 (0.37–1.70)	0.68
Worse intercondylar synovosis[e]	4/38 (10.5)	7/37 (18.9)	0.56 (0.18–1.69)	0.31
No. of areas of cartilage thinning[f]				
0	20/38 (52.6)	16/37 (43.2)	1.22 (0.76–1.96)	0.19
1	7/38 (18.4)	8/37 (21.6)	0.85 (0.34–2.11)	0.75
2	7/38 (18.4)	7/37 (18.9)	0.97 (0.38–2.51)	0.89
≥3	4/38 (10.5)	6/37 (16.2)	0.65 (0.20–2.12)	0.57
Change in whole knee effusion[h]				
Improved	10/38 (26.3)	7/37 (18.9)	1.39 (0.59–3.27)	0.09
No change	23/38 (60.5)	22/37 (59.5)	1.02 (0.70–1.47)	0.16
Worsened	5/38 (13.2)	8/37 (21.6)	0.61 (0.22–1.69)	0.36
Other MRI measures at 12 months				
Bone marrow lesion progression[i]	6/38 (15.8)	8/37 (21.6)	0.73 (0.28–1.90)	0.59
Cartilage defects progression[j]	5/38 (13.2)	4/37 (10.8)	1.22 (0.35–4.18)	0.48
Medial tibial cartilage volume[k]				
Reduced	29/38 (76.3)	28/37 (75.7)	1.01 (0.78–1.30)	0.91
No change	5/38 (13.2)	7/37 (18.9)	0.70 (0.24–2.00)	0.52
Increased	4/38 (10.5)	2/37 (5.4)	1.95 (0.38–10.00)	0.16
Change in painkillers use[l]				
Reduced	25/38 (65.8)	9/37 (24.3)	2.71 (1.47–4.99)	0.023
No change	9/38 (23.7)	18/37 (48.6)	0.49 (0.25–0.94)	0.28
Increased	4/38 (10.5)	10/37 (27.0)	0.39 (0.13–1.13)	0.21
Willingness for a second injection[m]				0.037
Yes	27/38 (71.1)	13/37 (35.1)	2.02 (1.25–3.28)	
No	5/38 (13.2)	19/37 (51.4)	0.26 (0.11–0.62)	
No preference	6/38 (15.8)	5/37 (13.5)	1.17 (0.39–3.50)	

MRI, magnetic resonance imaging; CI, confidence intervals.

[a]Counts and proportions are based on complete case data.

[b]Risk ratios greater than 1 indicate that the risk of the outcome is greater in the platelet-rich plasma group.

[c]The MRI Osteoarthritis Knee Score is a semiquantitative MRI scoring tool for knee osteoarthritis. It was assessed by a single rater (blinded to group) grading baseline and 12-month MRI images.

[d]Three regions were scored from 0 to 9 for morphological features for each meniscus, and defined as worse if any region of either the medial or lateral meniscus was scored higher at 12 months than at baseline.

[e]Incorporating synovitis and effusion and scored from 0 to 3, with 0 being normal; 1, mild; 2, moderate; and 3, severe. Defined as worse if the score was higher at 12 months than at baseline.

[f]Fourteen regions each scored from 0 to 3, with 0 indicating no area with cartilage loss; 1, less than 10% of cartilage surface area with loss; 2, 10%–75% of cartilage surface area with loss; and 3, greater than 75% of cartilage surface area with loss. Data are the number of regions for which the score was higher at 12 months than at baseline.

[h]Scored from 0 to 3, with 0 being normal; 1, small; 2, medium; and 3, large. Improved was defined as a lower score at 12 months than at baseline, no change was defined as the same score, and worsened was defined as a higher score.

[i]Assessed by a single rater (blinded to group and time point) grading baseline and 12-month MRI images. Bone marrow lesions were graded in the medial distal femur and medial proximal tibia as 0 to 3 (0, absent; 1, occupies less than one-third of the region; 2, occupies one-third to two-thirds of the region; and 3, occupies greater than two-thirds of the region). Progression was defined as an increase in bone marrow lesion grade of 1 or greater in either the medial distal femur or medial proximal tibia between baseline and 12 months.

[j]Assessed by a single rater (blinded to group and time point) grading baseline and 12-month MRI images. Cartilage defects were graded in the medial tibia and medial femur as 0 to 4 (0, normal cartilage; 1, focal blistering and intracartilaginous low-signal-intensity area with an intact surface and bottom; 2, irregularities on the surface or bottom and loss of thickness of less than 50%; 3, deep ulceration with loss of thickness of more than 50%; and 4, full-thickness chondral wear with exposure of subchondral bone). Progression was defined as a score increase of 1 or greater in either the medial tibia or medial femur between baseline and 12 months.

[k]Medial tibial cartilage volume was measured by manually drawing disarticulation contours around the cartilage edges, section by section (change in medial tibial cartilage volume at 12 months compared to baseline; categorized as reduced, no change, or increased).
[l]The use of pain medication during the 12-month follow-up was registered (change in pain medication use during 12 months compared to baseline; categorized as reduced, no change, or increased).
[m]At the end of the 12-month follow-up, participants were asked if they are willing to receive a second injection.

Limitations of the study

This study has potential limitations. First, the generalizability of results to other PRP products and treatment regimens remains unknown. All PRP products differ in their production method and content, and different treatment regimens regarding dose, timing, and the number of injections are used in clinical practice. However, we prepared PRP using commercial kits and following standardized procedures and analyzed related components (growth factors and cytokines) in the present study. Second, this study was not controlled for variations in physical therapies between the two groups. However, throughout the trial, exercise therapy and lifestyle were registered and they were comparable between the two groups. Third, the population was recruited from a single center. However, as our center is one of the three national clinical research centers for hematological diseases in China, it is likely to attract patients with this condition from different areas, thus improving the generalizability of our results to the population of patients with ITP and KOA.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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- RESOURCE AVAILABILITY
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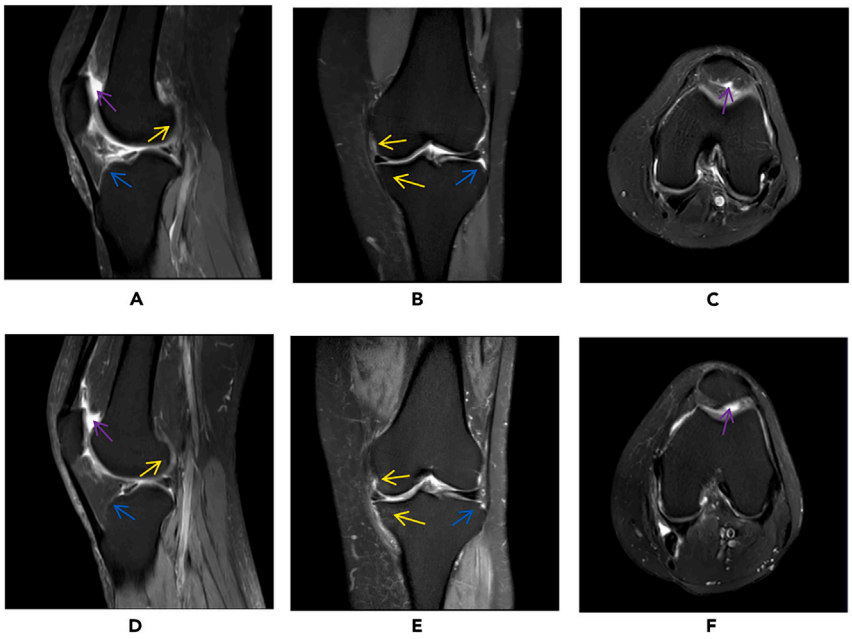

Figure 3. Baseline Knee MRI
(A) Sagittal plane.
(B) Coronal plane.
(C) Transverse section.
12-month follow-up Knee MRI:
(D) Sagittal plane.
(E) Coronal plane.
(F) Transverse section.
In the baseline Knee MRI images, (A), (B) and (C) demonstrated osteoarthritic changes with small effusion (purple arrow), marginal osteophytes (blue arrow), and cartilage degeneration (yellow arrow). In the 12-month follow-up Knee MRI images, (D), (E), and (F) demonstrated no significant improvement in osteoarthritic changes with small effusion (purple arrow), marginal osteophytes (blue arrow), and cartilage degeneration (yellow arrow) compared with baseline Knee MRI.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.109664.

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The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; and decision to submit the article for publication.

AUTHOR CONTRIBUTIONS

Dr Guo and Prof Yu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design*: Guo, Yu, Jiang. *Acquisition, analysis, or interpretation of data*: All authors. *Drafting of the* article: Zhu, Zhao, and Yu, Guo. *Critical revision of the* article *for important intellectual content*: All authors. *Statistical analysis*: Zhu and Zhao. *Obtained funding*: Guo. *Administrative, technical, or material support*: Zhao. *Supervision*: Yu, Jiang, Zhou, and Gatt, Guo. *Other—assessment of the osteopaths' speech content and verbal attitude during the sessions with patients*: Zhu, Guo.

DECLARATION OF INTERESTS

Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, and so forth) that might pose a conflict of interest in connection with the submitted article.

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REFERENCES

1. Bennell, K.L., Paterson, K.L., Metcalf, B.R., Duong, V., Eyles, J., Kasza, J., Wang, Y., Cicuttini, F., Buchbinder, R., Forbes, A., et al. (2021). Effect of Intra-articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients With Knee Osteoarthritis: The RESTORE Randomized Clinical Trial. JAMA *326*, 2021–2030. https://doi.org/10.1001/jama.2021.19415.
2. Paterson, K.L., Hunter, D.J., Metcalf, B.R., Eyles, J., Duong, V., Kazsa, J., Wang, Y., Buchbinder, R., Cicuttini, F., Forbes, A., et al. (2018). Efficacy of intra-articular injections of platelet-rich plasma as a symptom- and disease-modifying treatment for knee osteoarthritis - the RESTORE trial protocol. BMC Muscoskel. Disord. *19*, 272. https://doi.org/10.1186/s12891-018-2205-5.
3. Fice, M.P., Miller, J.C., Christian, R., Hannon, C.P., Smyth, N., Murawski, C.D., Cole, B.J., and Kennedy, J.G. (2019). The Role of Platelet-Rich Plasma in Cartilage Pathology: An Updated Systematic Review of the Basic Science Evidence. Arthroscopy *35*, 961–976.e3. https://doi.org/10.1016/j.arthro.2018.10.125.
4. Xue, Y., Su, X., Jiang, M., Yu, Z., Yang, H., Qin, L., Giannoudis, P.V., and Guo, J.J. (2020). Pure platelet-rich plasma facilitates the repair of damaged cartilage and synovium in a rabbit hemorrhagic arthritis knee model. Arthritis Res. Ther. *22*, 68. https://doi.org/10.1186/s13075-020-02155-6.
5. Duan, W., Su, X., Yu, Z., Jiang, M., Zhao, L., Giannoudis, P.V., and Guo, J.J. (2022). No Benefit to Platelet-rich Plasma Over Placebo Injections in Terms of Pain or Function in Patients with Hemophilic Knee Arthritis: A Randomized Trial. Clin. Orthop. Relat. Res. *480*, 2361–2370. https://doi.org/10.1097/CORR.0000000000002264.
6. Werner, B.C., Cancienne, J.M., Browning, R., Verma, N.N., and Cole, B.J. (2020). An

Analysis of Current Treatment Trends in Platelet-Rich Plasma Therapy in the Medicare Database. Orthop. J. Sports Med. *8*, 2325967119900811. https://doi.org/10.1177/2325967119900811.

7. Zhang, Q., Xu, W., Wu, K., Fu, W., Yang, H., and Guo, J.J. (2022). Intra-articular Pure Platelet-Rich Plasma Combined With Open-Wedge High Tibial Osteotomy Improves Clinical Outcomes and Minimal Joint Space Width Compared With High Tibial Osteotomy Alone in Knee Osteoarthritis: A Prospective Study. Arthroscopy *38*, 476–485. https://doi.org/10.1016/j.arthro.2021.09.013.
8. Filardo, G., Previtali, D., Napoli, F., Candrian, C., Zaffagnini, S., and Grassi, A. (2021). PRP Injections for the Treatment of Knee Osteoarthritis: A Meta-Analysis of Randomized Controlled Trials. Cartilage *13* (suppl), 364S–375S. https://doi.org/10.1177/1947603520931170.
9. Singh, H., Knapik, D.M., Polce, E.M., Eikani, C.K., Bjornstad, A.H., Gursoy, S., Perry, A.K., Westrick, J.C., Yanke, A.B., Verma, N.N., et al. (2022). Relative Efficacy of Intra-articular Injections in the Treatment of Knee Osteoarthritis: A Systematic Review and Network Meta-analysis. Am. J. Sports Med. *50*, 3140–3148. https://doi.org/10.1177/03635465211029659.
10. Chang, M., Nakagawa, P.A., Williams, S.A., Schwartz, M.R., Imfeld, K.L., Buzby, J.S., and Nugent, D.J. (2003). Immune thrombocytopenic purpura (ITP) plasma and purified ITP monoclonal autoantibodies inhibit megakaryocytopoiesis in vitro. Blood *102*, 887–895. https://doi.org/10.1182/blood-2002-05-1475.
11. Houwerzijl, E.J., Blom, N.R., van der Want, J.J.L., Esselink, M.T., Koornstra, J.J., Smit, J.W., Louwes, H., Vellenga, E., and de Wolf, J.T.M. (2004). Ultrastructural study shows morphologic features of apoptosis and para-apoptosis in megakaryocytes from patients with idiopathic thrombocytopenic purpura. Blood *103*, 500–506. https://doi.org/10.1182/blood-2003-01-0275.
12. Rodeo, S.A. (2019). A Call for Standardization in Cell Therapy Studies: Commentary on an article by Iain R. Murray, BMedSci(Hons), MRCS, MFSEM, PhD, et al.: "International Expert Consensus on a Cell Therapy Communication Tool: DOSES". J. Bone Joint Surg. Am. *101*, e47. https://doi.org/10.2106/JBJS.19.00189.
13. Jo, C.H., Lee, S.Y., Yoon, K.S., Oh, S., and Shin, S. (2020). Allogeneic Platelet-Rich Plasma Versus Corticosteroid Injection for the Treatment of Rotator Cuff Disease: A Randomized Controlled Trial. J. Bone Joint Surg. Am. *102*, 2129–2137. https://doi.org/10.2106/JBJS.19.01411.
14. He, M., Guo, X., Li, T., Jiang, X., Chen, Y., Yuan, Y., Chen, B., Yang, G., Fan, Y., Liang, Z., et al. (2020). Comparison of Allogeneic Platelet-rich Plasma With Autologous Platelet-rich Plasma for the Treatment of Diabetic Lower Extremity Ulcers. Cell Transplant. *29*, 963689720931428. https://doi.org/10.1177/0963689720931428.
15. Bottegoni, C., Dei Giudici, L., Salvemini, S., Chiurazzi, E., Bencivenga, R., and Gigante, A. (2016). Homologous platelet-rich plasma for the treatment of knee osteoarthritis in selected elderly patients: an open-label, uncontrolled, pilot study. Ther. Adv. Musculoskelet. Dis. *8*, 35–41. https://doi.org/10.1177/1759720X16631188.
16. Liao, X., Liang, J.X., Li, S.H., Huang, S., Yan, J.X., Xiao, L.L., Song, J.X., and Liu, H.W. (2020). Allogeneic Platelet-Rich Plasma Therapy as an Effective and Safe Adjuvant Method for Chronic Wounds. J. Surg. Res. *246*, 284–291. https://doi.org/10.1016/j.jss.2019.09.019.
17. Dório, M., Pereira, R.M.R., Luz, A.G.B., Deveza, L.A., de Oliveira, R.M., and Fuller, R. (2021). Efficacy of platelet-rich plasma and plasma for symptomatic treatment of knee osteoarthritis: a double-blinded placebo-controlled randomized clinical trial. BMC Muscoskel. Disord. *22*, 822. https://doi.org/10.1186/s12891-021-04706-7.
18. Chu, J., Duan, W., Yu, Z., Tao, T., Xu, J., Ma, Q., Zhao, L., and Guo, J.J. (2022). Intra-articular injections of platelet-rich plasma decrease pain and improve functional outcomes than sham saline in patients with knee osteoarthritis. Knee Surg. Sports Traumatol. Arthrosc. *30*, 4063–4071. https://doi.org/10.1007/s00167-022-06887-7.
19. Patel, S., Dhillon, M.S., Aggarwal, S., Marwaha, N., and Jain, A. (2013). Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am. J. Sports Med. *41*, 356–364. https://doi.org/10.1177/0363546512471299.
20. Kon, E., Buda, R., Filardo, G., Di Martino, A., Timoncini, A., Cenacchi, A., Fornasari, P.M., Giannini, S., and Marcacci, M. (2010). Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. Knee Surg. Sports Traumatol. Arthrosc. *18*, 472–479. https://doi.org/10.1007/s00167-009-0940-8.
21. Buendía-López, D., Medina-Quirós, M., and Fernández-Villacañas Marín, M.Á. (2018). Clinical and radiographic comparison of a single LP-PRP injection, a single hyaluronic acid injection and daily NSAID administration with a 52-week follow-up: a randomized controlled trial. J. Orthop. Traumatol. *19*, 3. https://doi.org/10.1186/s10195-018-0501-3.
22. Elik, H., Doğu, B., Yılmaz, F., Begoğlu, F.A., and Kuran, B. (2020). The efficiency of platelet-rich plasma treatment in patients with knee osteoarthritis. J. Back Musculoskelet. Rehabil. *33*, 127–138. https://doi.org/10.3233/BMR-181374.
23. Ahmad, H.S., Farrag, S.E., Okasha, A.E., Kadry, A.O., Ata, T.B., Monir, A.A., and Shady, I. (2018). Clinical outcomes are associated with changes in ultrasonographic structural appearance after platelet-rich plasma treatment for knee osteoarthritis. Int. J. Rheum. Dis. *21*, 960–966. https://doi.org/10.1111/1756-185X.13315.
24. Hunter, D.J., Altman, R.D., Cicuttini, F., Crema, M.D., Duryea, J., Eckstein, F., Guermazi, A., Kijowski, R., Link, T.M., Martel-Pelletier, J., et al. (2015). OARSI Clinical Trials Recommendations: Knee imaging in clinical trials in osteoarthritis. Osteoarthritis Cartilage *23*, 698–715. https://doi.org/10.1016/j.joca.2015.03.012.
25. Belk, J.W., Kraeutler, M.J., Houck, D.A., Goodrich, J.A., Dragoo, J.L., and McCarty, E.C. (2021). Platelet-Rich Plasma Versus Hyaluronic Acid for Knee Osteoarthritis: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Am. J. Sports Med. *49*, 249–260. https://doi.org/10.1177/0363546520909397.
26. Zhu, X., Zhao, L., Liu, A., Yu, Z., and Guo, J.J. (2022). Efficacy of intra-articular injection of allogeneic platelet-rich plasma for knee osteoarthritis combined with hematologic blood dyscrasias with platelet dysfunction: protocol of a randomized, double-blind, placebo-controlled trial. BMC Muscoskel. Disord. *23*, 1095. https://doi.org/10.1186/s12891-022-06073-3.
27. Schulz, K.F., Altman, D.G., and Moher, D.; CONSORT Group (2010). CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ (Clinical research ed.) *340*, c332. https://doi.org/10.1136/bmj.c332.
28. Neunert, C., Terrell, D.R., Arnold, D.M., Buchanan, G., Cines, D.B., Cooper, N., Cuker, A., Despotovic, J.M., George, J.N., Grace, R.F., et al. (2019). American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. *3*, 3829–3866. https://doi.org/10.1182/bloodadvances.2019000966.
29. Provan, D., Arnold, D.M., Bussel, J.B., Chong, B.H., Cooper, N., Gernsheimer, T., Ghanima, W., Godeau, B., González-López, T.J., Grainger, J., et al. (2019). Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. *3*, 3780–3817. https://doi.org/10.1182/bloodadvances.2019000812.
30. KELLGREN, J.H., and LAWRENCE, J.S. (1957). Radiological assessment of osteo-arthrosis. Ann. Rheum. Dis. *16*, 494–502. https://doi.org/10.1136/ard.16.4.494.
31. Murray, I.R., Geeslin, A.G., Goudie, E.B., Petrigliano, F.A., and LaPrade, R.F. (2017). Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO): Platelet-Rich Plasma and Mesenchymal Stem Cells. J. Bone Joint Surg. Am. *99*, 809–819. https://doi.org/10.2106/JBJS.16.00793.
32. Kon, E., Di Matteo, B., Delgado, D., Cole, B.J., Dorotei, A., Dragoo, J.L., Filardo, G., Fortier, L.A., Giuffrida, A., Jo, C.H., et al. (2020). Platelet-rich plasma for the treatment of knee osteoarthritis: an expert opinion and proposal for a novel classification and coding system. Expet Opin. Biol. Ther. *20*, 1447–1460. https://doi.org/10.1080/14712598.2020.1798925.
33. Harris, J.D., Brand, J.C., Cote, M.P., Faucett, S.C., and Dhawan, A. (2017). Research Pearls: The Significance of Statistics and Perils of Pooling. Part 1: Clinical Versus Statistical Significance. Arthroscopy *33*, 1102–1112. https://doi.org/10.1016/j.arthro.2017.01.053.
34. Bellamy, N., Carette, S., Ford, P.M., Kean, W.F., le Riche, N.G., Lussier, A., Wells, G.A., and Campbell, J. (1992). Osteoarthritis antirheumatic drug trials. II. Tables for calculating sample size for clinical trials. J. Rheumatol. *19*, 444–450.
35. Hunter, D.J., Guermazi, A., Lo, G.H., Grainger, A.J., Conaghan, P.G., Boudreau, R.M., and Roemer, F.W. (2011). Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage *19*, 990–1002. https://doi.org/10.1016/j.joca.2011.05.004.
36. Shen, L., Yuan, T., Chen, S., Xie, X., and Zhang, C. (2017). The temporal effect of

platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. J. Orthop. Surg. Res. *12*, 16. https://doi.org/10.1186/s13018-017-0521-3.

37. Hmamouchi, I., Allali, F., Tahiri, L., Khazzani, H., Mansouri, L.E., Ali Ou Alla, S., Abouqal, R., and Hajjaj-Hassouni, N. (2012). Clinically important improvement in the WOMAC and predictor factors for response to non-specific non-steroidal anti-inflammatory drugs in osteoarthritic patients: a prospective study. BMC Res. Notes *5*, 58. https://doi.org/10.1186/1756-0500-5-58.
38. Lin, K.Y., Yang, C.C., Hsu, C.J., Yeh, M.L., and Renn, J.H. (2019). Intra-articular Injection of Platelet-Rich Plasma Is Superior to Hyaluronic Acid or Saline Solution in the Treatment of Mild to Moderate Knee Osteoarthritis: A Randomized, Double-Blind, Triple-Parallel, Placebo-Controlled Clinical Trial. Arthroscopy *35*, 106–117. https://doi.org/10.1016/j.arthro.2018.06.035.
39. James, K.E., Bloch, D.A., Lee, K.K., Kraemer, H.C., and Fuller, R.K. (1996). An index for assessing blindness in a multi-centre clinical trial: disulfiram for alcohol cessation–a VA cooperative study. Stat. Med. *15*, 1421–1434. https://doi.org/10.1002/(SICI)1097-0258(19960715)15:13<1421::AID-SIM266>3.0.CO;2-H.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
SPSS	IBM	https://www.ibm.com/analytics/spss-statistics-software
Other		
Regen PRP ACR®	Regen Lab SA	SFDA Certified NO.20173667130

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, JiongJiong Guo (drjjguo@163.com; guojiongjiong@suda.edu.cn).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- Data reported in this paper will be shared by the lead contact upon request.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

This was a prospective, randomized, double-blind, placebo-controlled study. All participants provided written informed consent. Ethical approval was obtained from the the clinical research ethics committee at National Clinical Research Center for Hematologic Disease, the First Affiliated Hospital of Soochow University(study approval number was 2021-356). The trial protocol (1.0) has been published previously and the revised protocol (2.0) can be found in ref.[26] The Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed and the CONSORT checklist is available in Supplement Information.[27]

Participants were recruited from the orthopedic outpatient clinics or from the hematological patients' databases at the First Affiliated Hospital of Soochow University. Eligible participants were aged between 18 and 80 years and of either gender; had chronic primary ITP (more than 12 months's duration, diagnosed by American Society of Hematology 2019 guidelines[28] and updated international consensus[29]); had symptomatic KOA with a history of chronic pain (for at least 4 months) or swelling; had a knee pain score of at least 4 on an 11-point visual analogue scale (VAS) score in the past week; and had mild to moderate radiographic imaging findings of KOA (Kellgren and Lawrence grade 1-3).[30]

Exclusion criteria were (1) systemic or inflammatory disease, (2) cutaneous infections in the area to be injected, (3) injection of a glucocorticoid in the past 3 months or hyaluronic acid in the past 6 months, (4) previous treatment with stem cell preparation, (5) previous knee surgery. In cases of bilateral KOA, the most symptomatic knee joint was considered for this study.

METHOD DETAILS

Randomization and treatment

Randomization was centralized, and participants were allocated in a 1:1 ratio. An independent statistician provided a computer-generated randomization list using a permuted block design with block sizes of 4 and 6. The sequence was concealed by means of a computer interface implemented in the electronic case report form. Each registered participant corresponds to a different serial number. Participants, injecting physicians, assessors, and the statistician were blinded to group allocation. An unblinded study nurse had access to the randomization result and the allocated intervention.

All participants completed an initial evaluation to determine eligibility. Patients deemed potentially eligible underwent a radiographic screening (conventional X-ray: weight-bearing long-leg, anteroposterior and lateral views) and a serological screening (laboratory test for ITP) before visiting the study site for routine clinical screening (collection of medical history and knee examination). At the time of enrolment, participants had a baseline assessment, which consisted of several questionnaires and knee magnetic resonance imaging (MRI) scans, and were randomized. Age, sex, body mass index, duration of symptoms, and symptoms in other joints were also recorded as baseline information. Follow-up questionnaires were filled out at 1, 3, 6, and 12 months. An additional MRI was done after a 12-month follow-up.

Participants were instructed to refrain from using of non-steroidal anti-inflammatory drugs and other analgesics for knee pain from 3 weeks before the baseline assessment until the 12-month follow-up. Throughout the study period, all concomitant treatments (including conventional treatment, such as exercise therapy and healthy lifestyle guidance; KOA medications, such as painkillers; physical therapies; intra-articular injections; knee surgery) were registered.

All participants received one intra-articular knee injection by two experienced orthopedic surgeons. The injection consisted of allogeneic PRP in the PRP group or saline in the placebo group. The unblinded study nurse prepared the injection in a separate room and placed an opaque patient label over the syringe and needle base to mask the contents. Both the participants and the physicians were blinded to the contents of the injection. After the injection, passive knee flexion and extension were performed three times and the participant rested for 10 minutes thereafter.

For the PRP group, one healthy volunteer donor, a 30-year-old male, donated about 350 ml of peripheral venous blood. To assess the safety of the allogeneic PRP, tests for hepatitis B, hepatitis C, human immunodeficiency virus, and syphilis were performed and confirmed as negative before injection. Allogeneic PRP was obtained using a commercial product (Regenlab PRP Kit-RegenACR®, Le Mont-sur-Lausanne, Switzerland) with a single centrifugation at 1500g for 5 minutes. This method is leukocyte-poor, produces platelet concentration factors that are 1.6 to 5 times higher than whole blood values and recovers around 80% of the initial platelets.[1] In accordance with accepted standards,[31,32] details about PRP characteristics, such as growth factor and cytokine concentrations in PRP preparations, are provided in Table S4 in Supplement Information. Overall, 43 tubes of PRP were obtained from this blood donation: 40 PRP tubes were used for injection and 3 tubes were sent to the laboratory for analysis. All tubes contained the same volume of PRP (4 ml). All participants received injections on the same day (October 25, 2021).

Outcomes

The primary outcome was the 12-month change, compared to baseline, in knee pain and function, measured using the Western Ontario and McMaster Universities (WOMAC) total score. This is a validated 96-point numerical rating scale (5-point Likert for each question) with total scores of 0-32 points representing mild OA, 33-48 points for moderate OA, and 49-96 points for severe OA. Based on previous studies, the minimum clinically important difference (MCID) for the WOMAC total score was reported to be 11.5 points.[33]

The secondary self-reported symptom-related outcomes were as follows: (1) 1-, 3- and 6-month changes in the WOMAC total score; (2) 1-, 3-, 6- and 12-month changes in WOMAC subscales (pain, range 0-20 points; stiffness, range 0-8 points; function, range 0-68 points); (3) 1-, 3-, 6- and 12-month changes in overall knee pain score during activities of daily living (using an 11-point VAS, range 0-10 points, with higher scores indicating worse pain; reported MCID 1.8 points)[34]; (4) 1-, 3-, 6- and 12-month changes in Lysholm knee scoring scale (range 0-100 points, with lower scores indicating worse outcomes; reported MCID 8.9 points[33]); (5) 1-, 3-, 6- and 12-month changes in the Physical Component Summary (PCS) and Mental Component Summary (MCS) of the 36-Item Short-Form General Health Survey (SF-36) (range 0-100, with higher scores indicating a better quality of life; no reported MCID).

Knee MRI, performed at baseline and 12 months, used a 3T whole body system with a dedicated extremity coil and a T1-weighted fat-suppressed 3D gradient recall acquisition sequence. Secondary MRI outcomes at 12 months were the results of the MRI Osteoarthritis Knee Score (MOAKS)[35] for (1) meniscal morphology (any region worsening at 12 months; scored as yes or no); (2) intercondylar synovosis incorporating synovitis and effusion (worsening at 12 months; scored as yes or no); (3) cartilage morphology (number of areas worsening in thickness; categorized as 0, 1, 2, or $\geq$3); (4) whole knee effusion (categorized as worsened, no change, or improved); (5) progression of medial distal femur and proximal tibia bone marrow lesion size (scored as 0-3 per region, with higher scores indicating greater size); (6) progression of cartilage defects (scored as 0-4 per region, with higher scores indicating greater cartilage defects). Progression (yes or no) was defined as a score increase of 1 or greater from baseline in either compartment, and (7) medial tibial cartilage volume was measured by manually drawing disarticulation contours around the cartilage edges, section by section (categorized as reduced, no change, or increased). All participants' paired image sets were evaluated by two radiologists (blinded to treatment allocation) with excellent reliability (intraclass correlation coefficient, 0.92 [95% CI, 0.82-0.97]). The MCID for the MRI outcomes is unknown.

Adverse events were self-reported following injection and follow-up. At the end of the 12-month follow-up, participants were asked if they were willing to receive a second injection.

QUANTIFICATION AND STATISTICAL ANALYSIS

Sample size calculation

Regarding the primary outcome (12-month change in knee pain and function measured using the WOMAC total score), based on previous studies,[8,9,33,36–38] an 11.5 points reduction in WOMAC total score was considered as the MCID to be detected between the groups with a standard deviation (SD) of 16. Accepting a false-positive rate of 5% (α= 0.05) and a power of 80% (β= 0.20), we have calculated that a minimum sample size of 64 participants is required. To allow an approximate dropout rate of 20%, a total of 40 participants in each group were deemed necessary. After the necessary minimum number of patients was reached, patient recruiting was stopped.

Statistical analysis

All patients were included in the analyses and an intention-to-treat analysis was conducted. There was no crossover between groups. All statistical analyses were performed as 2-sided tests with a significance level of $P < .05$. The statistical software SPSS v. 26.0 (SPSS Inc., Chicago, Illinois, USA) was used to perform the analysis.

Multivariable imputation by chained equations with predictive mean matching and 5 nearest neighbors was used to impute missing outcomes for the sensitivity analysis of the primary and secondary outcomes.

The means and SDs of continuous variables were calculated and compared using the Student's t test (for normally distributed variables) and the Mann-Whitney U test (for not-normally distributed variables). Categorical data were reported as frequencies and were compared using either the chi-square or Fisher's exact test. The Kolmogorov-Smirnov test was used to evaluate normality. For the primary and secondary continuous outcomes, the difference between the two groups was compared using the repeated-measures mixed linear model (MLM) with Sidak's test for multiple comparisons, including an interaction between month (time point) and treatment group. Structural outcomes (MRI results) were analyzed via binomial regression models with a log-link fit using generalized estimating equations to account for multiple measurements per participant, including terms for month and treatment group and an interaction between them, using the same analysis plan to analyze pain medication consumption, with results reported as risk ratios (RR) with 95% confidence intervals (CI). The outcome regression models were used to assess whether PRP effects on the primary outcome at 12 months were moderated by age, body mass index, and Kellgren and Lawrence grade. The within-group differences at different times of continuous, normally distributed and homoscedastic data were compared for their means using the analysis of variance (ANOVA). Secondary outcomes were interpreted as exploratory because of the potential for type I error due to multiple comparisons. The success of blinding was assessed using the James Blinding Index,[39] calculated by asking participants and researchers whether they believed that each patient was assigned to the treatment group, or to the control group, or they were uncertain. Incorrect guesses, uncertain responses, and disagreements are indications that blinding was successful.

Additional resources

TRIAL REGISTRATION Chinese Clinical Trial number: ChiCTR2100048624.