Original Article

Comparative evaluation of platelet-rich plasma and prolotherapy Injections in knee osteoarthritis: A randomized controlled trial

Satyendra Singh Yadav[1], Manish Kumar Singh[2], Pallavee Priyadarshini[3], Sarita Singh[4]

[1,3]Department of Anaesthesiology, GSVM Medical College, Kanpur, Uttar Pradesh, India. [2,4]Department of Anaesthesiology, King George's Medical University, Lucknow, Uttar Pradesh, India

Abstract

Background: Knee osteoarthritis (OA) is a common degenerative joint disorder that impairs mobility and quality of life and has a rising prevalence in India. Platelet-rich plasma (PRP) and prolotherapy (PRL) are minimally invasive regenerative interventions. This study compared the effects of platelet-rich plasma (PRP) and prolotherapy (PRL) on pain relief and functional improvement in patients with grade I-II knee osteoarthritis (OA). **Material and Methods:** This single-blind randomized controlled trial enrolled Sixty-four patients aged 40-70 years with radiographically confirmed Kellgren-Lawrence grade I-II OA, who were randomized equally into groups A (PRP) and B (PRL). The interventions were administered intra-articularly under aseptic conditions. Pain and functional outcomes were evaluated using the Visual Analog Scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at baseline, weekly from weeks 1-6 months. Data were analyzed using SPSS v21.0. **Results:** Both groups showed significant reductions in the VAS and WOMAC scores over time ($p<0.001$). However, Group A (PRP) demonstrated significantly greater improvement than Group B (PRL) at each follow-up point after the baseline. At 6 months, PRP reduced VAS by a mean of -3.41 (95% CI -3.9 to -2.9) compared with -2.88 in PRL ($p=0.0012$). Mean WOMAC at 6 months was 30.28±4.78 (PRP) vs 38.31±4.88 (PRL), $p<0.0001$. Fewer patients in the PRP group required repeated doses (28% vs. 75%, $p=0.0002$) rescue analgesia (21.88% vs. 46.88%, $P=0.0353$). The side effect profiles were comparable. **Conclusion:** PRP demonstrated superior efficacy over prolotherapy and may be the preferred injectable option for early-stage OA; however, larger multicenter studies are needed.

Keywords: Knee osteoarthritis, platelet-rich plasma, prolotherapy, VAS, WOMAC, regenerative therapy.

Received: 30 September 2026 **Revised: 19 October 2026** **Accepted: 04 November 2026** **Published: 12 November 2026**

Introduction

Osteoarthritis (OA) is the most prevalent chronic degenerative joint disorder and is characterized by progressive loss of articular cartilage, subchondral bone remodeling, synovial inflammation, and osteophyte formation. OA primarily affects weight-bearing joints such as the knee and hip and is the 11th leading cause of disability-adjusted life years (DALYs) worldwide.[1,2] In India, the burden of OA is rising abruptly, with a reported prevalence ranging from 22% to 39%, particularly among postmenopausal women and individuals aged > 65 years.[3,4]

The pathophysiology of OA is complex and multifactorial, and involves mechanical, inflammatory, metabolic, and genetic factors. Histopathological changes in advanced OA include cartilage softening, fibrillation, ulceration, and focal loss, often accompanied by subchondral sclerosis and alterations in the synovial membrane.[5,6] Despite this complexity, therapeutic strategies remain palliative, rather than curative. Conventional treatment options, including NSAIDs, intra-articular corticosteroids, and hyaluronic acid (HA) injections, provide only temporary relief and do not modify the course of OA. Surgical interventions, such as arthroplasty or osteotomy, are often delayed because of their associated risks, especially in elderly or comorbid patients.[7-9]

In response to the limitations of current therapies, regenerative medicine has gained traction, particularly the use of Platelet-Rich Plasma (PRP) and prolotherapy (PRL). PRP is an autologous biological product derived from centrifuged whole blood, rich in platelets and growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF), all of which promote cellular repair, angiogenesis, and matrix regeneration.[10-12] PRP has been shown to reduce inflammation and improve cartilage anabolism, making it a promising minimally invasive intervention for knee OA.[13-15]

Conversely, prolotherapy (PRL), also referred to as proliferation therapy, involves the injection of hyperosmolar dextrose or other non-biological irritant solutions into periarticular soft tissues or intra-articularly. This mechanism is thought to involve the stimulation of local inflammatory cascades and tissue proliferation, leading to increased tensile strength of the

Address for correspondence: Dr. Satyendra Singh Yadav, Department of Anaesthesiology, GSVM Medical College, Kanpur, Uttar Pradesh, India.
E-mail: satyendrab786@gmail.com

DOI:
10.21276/amit.2026.v13.i3.1182

How to cite this article: Yadav SS, Singh MK. Priyadarshini P, Singh S. Comparative evaluation of platelet-rich plasma and prolotherapy Injections in knee osteoarthritis: A randomized controlled trial. Acta Med Int. 2026;13(3):980-986.

ligaments and potential stabilization of the joint.[16-19] While both modalities aim to stimulate the body's natural healing mechanisms, they differ significantly in their composition, biological action, and cost-effectiveness.

Despite growing clinical use, high-quality head-to-head trials directly comparing PRP and prolotherapy remain scarce, particularly in Indian populations and most existing evidence is restricted by small sample sizes, heterogeneous protocols, and short follow-up durations.[20-22] Furthermore, little is known about the differential efficacy of PRP in patients who have undergone prior surgical intervention for cartilage repair (e.g., microfracture or shaving), which may influence the therapeutic response due to pre-existing alterations in the joint microenvironment and tissue remodeling.

Given the increasing use of biological and regenerative approaches for knee OA and the absence of definitive comparative evidence, this single-blind, randomized controlled trial was designed to evaluate the comparative efficacy and safety of PRP versus prolotherapy in patients with knee osteoarthritis. The primary objective of this study was to assess pain relief using the visual analog scale (VAS) and WOMAC scores at week, 1-6 months respectively. The secondary objective was to evaluate improvement in joint stiffness and document any adverse events or complications associated with either therapy.

Additionally, this study aimed to explore whether prior operative interventions for cartilage lesions influence the effectiveness of PRP, thereby providing a novel layer of personalized clinical insight. By addressing these gaps, this study seeks to identify optimal therapeutic strategies and contribute to evidence-based practice in the management of knee osteoarthritis.

Materials and Methods

Study Population and selection: This single-center, single-blind, randomized controlled trial (CTRI-2021/11/038195) was conducted at the Pain Clinic of the Anesthesia Department, King George's Medical University (KGMU), Lucknow, India. Based on an estimated effect size of 0.7, a power of 80%, and a significance level of 0.05, the minimum required sample size was 32 patients per group. A total of 64 patients clinically and radiologically diagnosed knee osteoarthritis (OA) Grade I or II (based on the Kellgren-Lawrence classification) were recruited based on criteria-

Inclusion Criteria

Eligible participants were adults aged between 40 -70 years with a radiographically confirmed diagnosis of primary knee osteoarthritis classified as Grade I or II according to the Kellgren and Lawrence (K-L) grading system. Only patients who provided written informed consent prior to enrollment were included. Participants were required to have experienced chronic knee pain for a minimum of three months, accompanied by functional limitations, and to have demonstrated a suboptimal response to standard conservative management, including analgesics, physiotherapy, or lifestyle modification. Additional prerequisites included the ability to comply with the study protocol, scheduled follow-up visits, and completion of clinical outcome assessments.

Exclusion Criteria

Patients were excluded if they had advanced radiographic osteoarthritis (K-L Grade III/IV) or a history of intra-articular injections, arthroscopic procedures, or major trauma to the index knee. Individuals with secondary causes of arthritis, including rheumatoid arthritis, gout, pseudogout, psoriatic arthritis, and septic arthritis, were not eligible. The exclusion criteria were uncontrolled diabetes mellitus, bleeding diathesis, anticoagulant therapy, immunosuppressive treatment, and chronic systemic corticosteroid use. Patients with local or systemic infections, known hypersensitivity to components of the investigational agents, or significant comorbidities that could confound the outcome assessment or increase procedural risk were also excluded. Furthermore, individuals with structural knee deformities, severe obesity (BMI > 35 kg/m²), pregnancy, or lactation were not recruited for the study (Fig.1 CONSORT flow diagram).

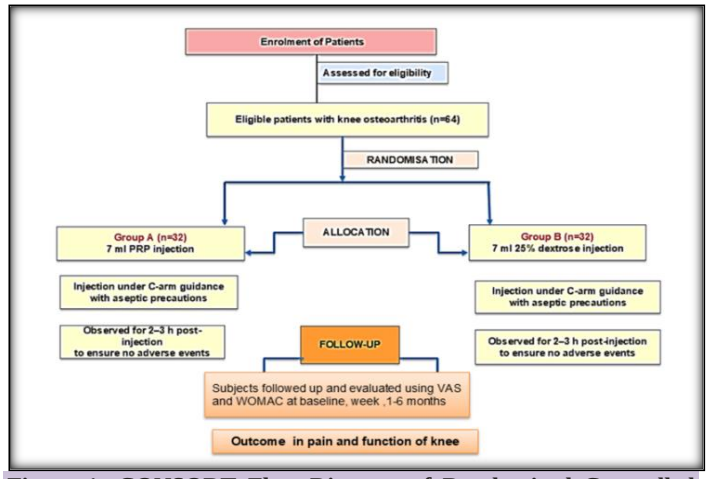


Figure 1: CONSORT Flow Diagram of Randomized Controlled Trial Comparing Platelet-Rich Plasma and Prolotherapy in Knee Osteoarthritis

Flowchart outlines the study design and participant flow for a single-blind randomized controlled trial conducted on 64 patients diagnosed with knee osteoarthritis who fulfilled predefined inclusion criteria.

Ethical approval was obtained from the Institutional Ethics Committee of KGMU (Ref No. 1306), and written informed consent was obtained from all participants.

Randomization and blinding

Patients who fulfilled the eligibility criteria were randomized into two groups using a computer-generated randomization sequence. The allocation was concealed using sealed opaque envelopes, and the study was single-blind. Patients were blinded to the treatment group, but the physicians who administered the injections were not.

Interventions

Preparation of Autologous Platelet-Rich Plasma (PRP)

In Group A, autologous PRP was prepared in the Department of Transfusion Medicine, KGMU, according to institutional standard operating procedures. A 50 mL of venous blood was collected under aseptic conditions in a quadruple bag system. Differential centrifugation was performed in a closed system, yielding approximately 7 mL of PRP, which was immediately

transported in a sterile closed bag to the Department of Anesthesiology for intra-articular use.

Procedure monitoring

All injections were administered under strict aseptic precautions in the Pain Outpatient Department of Anesthesiology using C-arm fluoroscopic guidance. The patients were positioned supine with the affected knee in mid-flexion. After skin preparation with Savlon, spirit, and povidone-iodine, and administration of local anesthesia, a sterile needle was introduced via the lateral approach and directed superomedially into the joint cavity.

Group A (PRP group): A total of 7 mL of autologous PRP was injected intra-articulately.

Group B (prolotherapy group): A total of 7 mL of 25% hypertonic dextrose was injected intra-articularly. Post-procedure, patients received acetaminophen for up to one week as required, were advised to rest the knee for 2-4 days and gradually resumed normal activity within one month. The use of NSAIDs and initiation of other osteoarthritis therapies were prohibited during the study. Prolotherapy injections were repeated at 1, 2, and 3 months, with optional booster doses at 4-5 months depending on patient-reported pain and functional outcomes.

All injections were administered under C-arm fluoroscopy guidance, with full aseptic precautions. Patients in both groups received up to three injections over a 3-month period, spaced four weeks apart. Additional doses were permitted based on clinical needs, with a maximum of five injections during follow-up. Following each injection, the patients were monitored for 2-3 h in the recovery area to observe for immediate adverse events.

Follow-Up and outcome assessment: Patients were followed-up at a baseline, week and 1-6-months respectively. The outcomes were assessed as follows:

The primary endpoints were pain intensity and functional status. Pain was quantified using the Visual Analog Scale (VAS), Pain, joint stiffness, and physical function were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), as previously described by Bellamy et al. [23] and documentation of rescue analgesic use, with paracetamol permitted up to 2 g/day. Radiographic evaluation of the knees was performed using standard views. Two independent blinded readers graded the images using the Kellgren-Lawrence (KL) classification, which stratifies osteoarthritis severity based on osteophyte formation and joint space narrowing.[24]

Statistical Analysis: Data were analyzed using SPSS v21.0. Continuous variables (age, BMI, VAS, and WOMAC scores) are expressed as mean ± SD and were compared using independent t-tests. Categorical variables (e.g., sex, affected side, and responder rate) were compared using the chi-square test or Fisher's exact test. Subgroup analyses were performed according to age, body mass index (BMI), and KL grade using t-tests. Multivariate linear regression was conducted to identify independent predictors of 6-month WOMAC scores, with results reported as β-coefficients and 95% confidence intervals. Statistical significance was set at $p < 0.05$.

Results

Baseline Characteristics: At baseline, there were no statistically significant differences between the PRP (n = 32) and PRL (n = 32) groups in terms of age, sex distribution, BMI, side of knee affected, radiographic severity (Kellgren-Lawrence grade), or platelet count (all $p > 0.05$). Similarly, the initial pain (VAS) and functional (WOMAC) scores were comparable, confirming that both groups were well matched before the intervention [Table 1].

Table 1: Demographic and clinical baseline characteristics of the participants in the PRP and prolotherapy groups.

Characteristic	PRP Group (n=32)	PRL Group (n=32)	t= value ,p-value
Age (years, mean ± SD)	54.59 ± 9.05	52.06 ± 8.26	t=1.168, p=0.247
Gender, n (%)			
Male	18 (56.25%)	20 (62.5%)	$\chi2$=0.259, p=0.611
Female	14 (43.75%)	12 (37.5%)	
BMI (kg/m², mean ± SD)	28.16 ± 1.53	27.95 ± 1.72	t=0.879, p=0.386
Laterality (Right side affected)	17 (53.1%)	20 (62.5%)	$\chi2$=0.576, p=0.448
KL Grade (mean ± SD)	1.91 ± 0.29	1.84 ± 0.36	t=0.856, p=0.395
Platelet count (×10⁶/μL)	2.00 ± 0.61	2.03 ± 0.55	t=0.206, p=0.837

BMI; Body mass index, KL; Kellgren-Lawrence grade, $\chi2$; chi square, t; t test. $p < 0.05$ considered as significant

Pain Reduction Over Time (VAS Scores)

Significant differences in pain reduction were observed between the groups as early as one week post-intervention. Patients receiving PRP reported a greater reduction in pain (mean VAS: 4.16 ± 1.09) than those receiving PRL (5.31 ± 1.38; $p = 0.0005$). This trend continued over the subsequent months, with PRP maintaining a consistent advantage. At 6 months, the PRP group reported a mean VAS score of 3.03 ± 0.98, which was significantly lower than that of the PRL group (4.06 ± 1.41; $P = 0.0012$), indicating sustained pain relief [Figure 2].

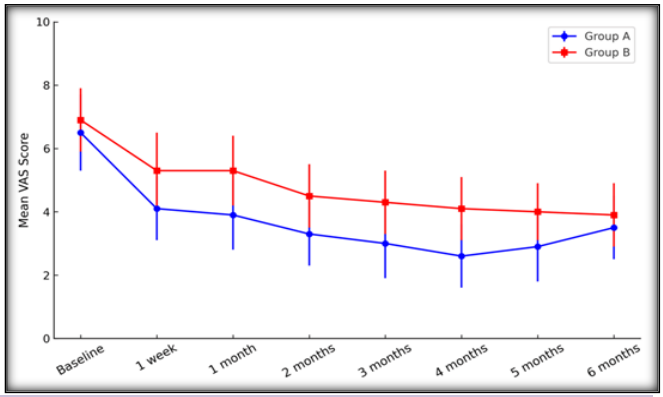


Figure 2: Change in Visual Analog Scale (VAS) Pain Scores over 6 Months

Line plot showing the mean Visual Analog Scale (VAS) scores for patients treated with platelet-rich plasma (PRP) and prolotherapy (PRL) from baseline through 6 months.

Improvement in Functional Outcomes (WOMAC Scores)

Functional improvement, as measured by WOMAC scores, was significantly greater in the PRP group at every time point after the intervention. By 1 month, PRP-treated participants showed a mean WOMAC score of 39.81 ± 4.52, compared to 48.56 ± 4.73 in the PRL group ($p < 0.0001$). This difference persisted through the 6-month follow-up, with PRP showing a final mean score of 30.28 ± 4.78 versus 38.31 ± 4.88 in the PRL group ($p < 0.0001$), suggesting better functional recovery and mobility [Figure 3].

Line graph illustrating changes in mean WOMAC scores in the PRP and PRL groups over 6 months. Patients receiving PRP demonstrated a significantly larger improvement in joint function and symptom reduction across all follow-ups.

Treatment Burden: Injections and Analgesic Use

Fewer patients in the PRP group required repeated injections (≥2 doses, 28.1%) than those in the PRL group (75.0%; p = 0.0002). Additionally, the need for rescue analgesics was significantly lower in the PRP group (21.9%) than that in the PRL group (46.9%; p = 0.035). Side effects were rare and similar between the groups (PRP: 6.3%, PRL: 9.4%; p = 0.641), confirming that both interventions were generally well tolerated [Table 2].

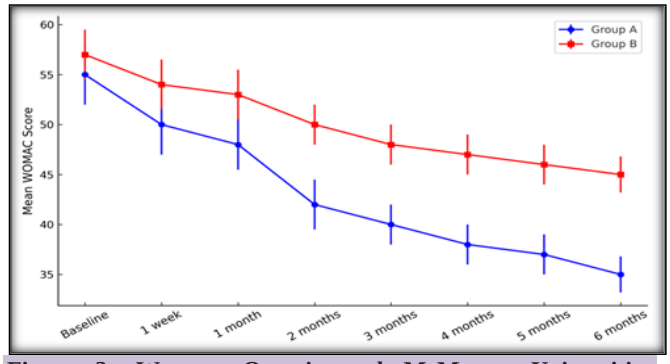


Figure 3: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Scores following Treatment

Table 2: Clinical Outcomes: Injection Needs, Analgesia Use, and Side Effects

Parameter	PRP Group (n=32)	PRL Group (n=32)	χ2, p-value
Patients requiring ≥2 doses, n (%)	9 (28.1%)	24 (75.0%)	$\chi2=14.08$,p=0.0002
Use of rescue analgesia, n (%)	7 (21.9%)	15 (46.9%)	$\chi2=4.433$, p=0.035
Reported side effects, n (%)	2 (6.3%)	3 (9.4%)	$\chi2=0.216$, p=0.641

Evaluation of baseline laboratory and radiographic parameters in the two intervention groups.χ2; chi square. $p < 0.05$ considered as significant

Subgroup Analysis: Age, BMI, and KL Grade

Stratified analysis demonstrated that the superiority of PRP persisted across all the clinical subgroups. Among patients aged <55 years, mean WOMAC improvement (Δ from baseline to 6 months) was 40.2 ± 4.5 in the PRP group compared to 28.6 ± 5.1 in PRL ($p < 0.001$). Similar results were observed in patients aged ≥55 years, with PRP showing greater functional gain ($p < 0.001$). This benefit extended across BMI categories and KL grades, reinforcing PRP's consistent efficacy of PRP, regardless of patient demographics or radiological severity [Table 3, Figure 4].

Baseline (A) and 6-month follow-up (B) AP X-rays of bilateral knee osteoarthritis. Image A shows the right knee with KL Grade II changes (joint space narrowing, early osteophytes) and the left knee with KL Grade I changes. Image B shows no radiographic progression in either knee, indicating structural stability post-treatment.



Figure 4: Bilateral Knee AP Radiographs Pre- and Post-Treatment

Table 3: Subgroup Analysis of WOMAC Improvement at 6 Months

Variable	Subcategory	PRP (Δ WOMAC Mean ± SD)	PRL (Δ WOMAC Mean ± SD)	t-value, p-value
Age	<55 years	40.2 ± 4.5	28.6 ± 5.1	t=6.82, p<0.001
	≥55 years	36.8 ± 5.2	27.9 ± 5.0	t=4.93, p<0.001
BMI	<28 kg/m²	39.6 ± 4.8	29.1 ± 4.6	t=6.32, p<0.001
	≥28 kg/m²	36.2 ± 4.9	27.4 ± 5.2	t=4.93, p<0.001
KL Grade	Grade I	42.1 ± 3.9	30.2 ± 4.7	t=7.79, p<0.001
	Grade II	35.3 ± 5.1	26.5 ± 5.0	4.91,p <0.001

Changes in VAS pain scores in the PRP and prolotherapy groups during the follow-up periods, baseline week, and 1–6 months. PRP showed greater 6-month WOMAC improvement across all age, BMI, and KL grade. $p < 0.05$ considered as significant

Responder Rate (WOMAC Improvement): By 6 months, 81.2% of the patients in the PRP group achieved a clinically meaningful improvement (≥30% reduction in WOMAC score) compared to only 46.9% in the PRL group (p = 0.004). When stratified by age and disease severity, PRP maintained a significantly higher response rate across all subgroups (p = 0.019-0.045), confirming its broader therapeutic potential [Table 4].

Table 4: Responder Analysis Based on ≥30% Improvement in WOMAC Score at 6 Months

Subgroup	PRP Responders (n, %)	PRL Responders (n, %)	χ^2 value, p-value
All Participants	26 (81.2%)	15 (46.9%)	χ^2 =8.21, p=0.004
Age <55	13/16 (81.2%)	8/16 (50.0%)	χ^2 =3.46, p=0.045
Age ≥55	13/16 (81.2%)	7/16 (43.8%)	χ^2 =4.80, p=0.028
KL Grade I	15/18 (83.3%)	9/17 (52.9%)	χ^2 =3.74, p=0.032
KL Grade II	11/14 (78.6%)	6/15 (40.0%)	χ^2 =4.44, p=0.019

Alterations in WOMAC scores in the PRP and prolotherapy cohorts during the follow-up periods, baseline week, and 1–6 months. Higher ≥30% responders in PRP group across all subgroups. $\chi 2$; chi square. $p < 0.05$ considered as significant.

Predictors of Outcome: Multivariate Regression

Multivariate linear regression identified PRP as an independent predictor of greater functional improvement at 6 months (β = -6.2; 95% CI: -8.9 -3.5; $p < 0.001$), even after adjusting for age, BMI, KL grade, and baseline WOMAC score. Age and KL Grade II were both associated with poorer outcomes ($p = 0.043$ and $p < 0.001$, respectively), while baseline WOMAC score also had a modest predictive effect ($p = 0.007$). The model explained 62% of the variance in the final WOMAC scores (adjusted $R^2 = 0.58$), supporting the robustness of the findings [Table 5, Figure 5].

Multivariate regression model predicting WOMAC improvement at 6 months.

Forest plot showing regression coefficients (β) with 95% confidence intervals for treatment group, age, BMI, KL grade, and baseline WOMAC score. PRP treatment was an independent predictor of greater functional recovery, while higher age and KL grade were associated with poorer outcomes.

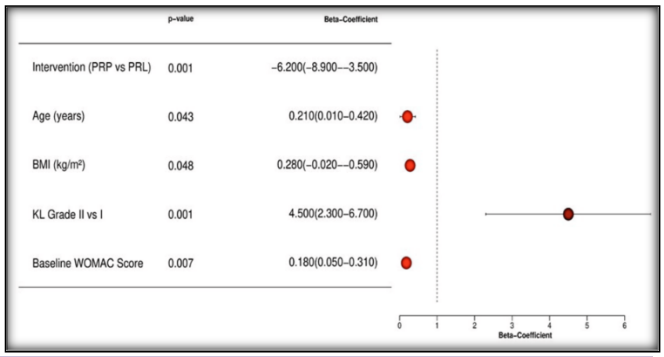


Figure 5: Forest plot Multivariate linear regression identified PRP as an independent predictor of greater functional improvement at 6 months.

Table 5: Multivariate Linear Regression for Predictors of 6-Month WOMAC Score

Predictor Variable	β Coefficient	95% CI	p-value
Intervention (PRP vs PRL)	-6.2	-8.9 to -3.5	<0.001
Age (years)	0.21	0.01 -0.42	0.043
BMI (kg/m²)	0.28	-0.02 -0.59	0.048
KL Grade II vs I	4.5	2.3 -6.7	<0.001
Baseline WOMAC Score	0.18	0.05 -0.31	0.007

Regression coefficients (β), 95% confidence intervals (CI), and p-values are presented. Adjusted $R^2 = 0.58$. $p < 0.05$ considered significant.

Discussion

The present randomized, single-blinded controlled trial demonstrated that intra-articular injection of platelet-rich plasma (PRP) provides superior pain relief and functional improvement compared with prolotherapy (PRL) in patients with early to moderate knee osteoarthritis (OA). Improvements in VAS and WOMAC scores in the PRP group were not only statistically significant at each post-treatment interval, but also clinically meaningful, with a higher proportion of patients achieving ≥30% improvement. These benefits were consistent across patient subgroups stratified by age, BMI, and Kellgren-Lawrence (KL) radiological grade,[10] suggesting the broad therapeutic applicability of PRP.

In the current study, PRP achieved faster and more sustained pain relief, with mean VAS decreasing from 6.44 ± 1.03 at baseline to 2.56 ± 0.70 at 4 months and stabilizing at 3.03 ± 0.98 by 6 months. In contrast, the PRL group exhibited more modest pain reduction, with VAS falling from 6.94 ± 1.00 at baseline to 4.06 ± 1.41 at 6 months. These findings are consistent with those of the trial by Rahimzadeh et al,[14] who compared 7 mL of PRP with 25% dextrose prolotherapy in 42 patients with knee OA. They reported a significantly greater reduction in both pain and stiffness scores in the PRP group for up to 24 weeks, confirming the results observed in our trial. Similarly, Gobbi et al,[25] found PRP to be more effective than PRL for symptomatic relief and functional improvement in both operated and non-operated OA patients.

The functional outcomes in our study, measured using the WOMAC, reflected similar trends. PRP-treated patients showed a reduction from 69.81 ± 4.52 at baseline to 30.28 ± 4.78 at 6 months, while PRL-treated patients declined from 70.19 ± 6.13 to 38.31 ± 4.88 over the same period. Our results strongly support the observations of Kon et al,[26] who noted that PRP contributes to the modulation of joint homeostasis and symptomatic relief through its concentrated pool of platelet-derived growth factors (PDGF, TGF-β1, VEGF, and IGF-1). The regenerative potential of PRP is due to its ability to recruit mesenchymal stem cells, stimulate chondrocyte proliferation, and suppress NF-κB-driven inflammation, all of which contribute to improved joint function and reduced stiffness,[27] as observed through substantial WOMAC gains in the PRP group.

In terms of treatment burden, PRP required significantly fewer repeated injections, with only 28.1% of patients needing two or

more doses compared with 75.0% in the PRL group (p = 0.0002). Additionally, fewer PRP recipients required rescue analgesics than non-PRP recipients (21.9% vs. 46.9%, p = 0.035). These findings align with those of Dhillon et al,[28] who reported that even a single dose of PRP was effective in early stage OA and provided sustained benefits. Their three-arm study compared single and double PRP injections with saline, and concluded that two doses provided only marginal gains over one. This supports the interpretation in our cohort that a single PRP injection can result in clinically relevant outcomes for at least 6 months, with a lower intervention intensity than PRL.

The consistency of PRP benefits across patient subgroups is another notable finding of our trial. In younger (<55 years) and older (≥55 years) participants, PRP consistently yielded greater WOMAC improvements (40.2 ± 4.5 vs 28.6 ± 5.1 and 36.8 ± 5.2 vs 27.9 ± 5.0, respectively; both p < 0.001). Comparable trends were observed in the BMI subgroups and in both KL Grade I and II disease. Similar results were documented by Akpancar et al,[29] who noted that both PRP and prolotherapy were effective for osteochondral lesions of the talus (OLT), but PRP showed slightly better clinical ratings and patient satisfaction, especially among younger individuals with better cartilage integrity. Although the anatomical sites differ, their data reinforce the advantage of PRP in early-stage disease.

Although prolotherapy remains a valid minimally invasive approach for chronic musculoskeletal pain, its mechanism relies primarily on hyperosmolar dextrose-induced local inflammation to stimulate tissue repair. This process is inherently slower and is more dependent on repeated stimulation cycles. In contrast, PRP offers a more direct biological effect through anti-inflammatory cytokines (e.g., IL-4 and HGF) and chondrogenic growth factors that contribute not only to symptom relief but also to the possible modulation of early degenerative processes. Lai et al,[30] demonstrated that activated PRP enhances chondrocyte differentiation and matrix production and suppresses inflammatory signaling via the inhibition of NF-κB, which supports the mechanisms likely responsible for the superior response observed in our PRP cohort.

Eroglu et al,[31] compared PRP and PRL with saline in a knee OA population and found improvements in the WOMAC scores in both active treatment arms, although the difference was not statistically significant. The discrepancy with our results may be due to differences in sample size, platelet concentration, or number and timing of injections. In our study, PRP achieved statistical and clinical superiority across all time points from one week to six months, and in all domains (pain, stiffness, and function), highlighting the importance of optimized PRP preparation protocols and patient selection.

A significant proportion of PRP-treated patients in our study were classified as responders (81.2% achieved ≥30% improvement in WOMAC score) versus only 46.9% in PRL (p = 0.004). These findings are clinically relevant and indicate a higher likelihood of meaningful functional recovery with PRP. They also support the hypothesis that PRP is not merely a symptomatic treatment but may also act on the underlying pathological mechanisms in early OA.

Despite these encouraging results, our study has some limitations. The relatively small sample size and single-center design may limit the external generalizability. Additionally, the absence of a placebo or sham injection restricts our ability to fully account for placebo effects. Moreover, we did not assess structural changes via imaging modalities such as MRI or synovial biomarkers that could have provided mechanistic insight. However, the strengths of this study, including randomized allocation, standardized outcome assessment, and subgroup analyses, enhance its internal validity.

Conclusion

This trial provides strong evidence that PRP is more effective than prolotherapy in managing the symptoms of knee OA over a 6-month period. PRP resulted in greater and earlier pain reduction, superior functional recovery, fewer injections, and higher proportion of clinical responders. These benefits were consistent across patient profiles and were achieved without a significant increase in adverse events. Our findings support that PRP is the preferred regenerative injectable therapy for symptomatic knee OA. Future multicenter studies with larger samples, extended follow-up, and imaging-based endpoints are warranted to confirm these benefits and to assess long-term structural outcomes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Kumar H, Pal CP, Sharma YK, Kumar S, Uppal A.: Epidemiology of knee osteoarthritis in India and related factors. Indian J Orthop. 2016, 50:518-522. 10.1016/j.jcot.2019.05.019
2. Mathers CD, Bernard C, Iburg KM, et al.: Global burden of disease in 2002: data sources, methods and results. 2003.
3. Davis MA, Ettinger WH, Neuhaus JM, et al.: Sex differences in osteoarthritis of the knee. The role of obesity. Am J Epidemiol. 1988, 127:1019. 10.1093/oxfordjournals.aje.a114878
4. Hunter W: Of the structure and diseases of articulating cartilages. Philos Trans R Soc Lond. 1742. 42:514-521. 10.1098/rstl.1742.0079
5. Solomon L, Beighton P, Lawrence JS: Rheumatic disorders in the South African Negro. Part II. Osteo arthrosis. S Afr Med J. 1975, 49:1737-1740. 10520/AJA20785135_24226
6. Dwivedi G, Flaman L, Alaybeyoglu B, et al.: Inflammatory cytokines and mechanical injury induce post traumatic osteoarthritis like changes in a human cartilage bone synovium microphysiological system. Arthritis Res Ther. 2022, 24:198. 10.1186/s13075-022-02881-z
7. Cucchiarini M, de Girolamo L, Filardo G, et al.: Basic science of osteoarthritis. J Exp Orthop. 2016, 3:22. 10.1186/s40634-016-0060-6
8. Anitua E, Sánchez M, Nurden AT, et al.: New insights into and novel applications for platelet rich and fibrin therapies. Trends Biotechnol. 2006, 24:227-234. 10.1016/j.tibtech.2006.02.010
9. Piccolo CL, Mallio CA, Vaccarino F, et al.: Imaging of knee osteoarthritis: a review of multimodal diagnostic approach. Quant Imaging Med Surg. 2023, 13:7582-7595. 10.21037/qims-22-1392

10. Kohn MD, Sassoon AA, Fernando ND: Classifications in brief: Kellgren Lawrence classification of osteoarthritis. Clin Orthop Relat Res. 2016, 474:1886-1893. 10.1007/s11999-016-4732-4
11. Anitua E, Sánchez M, Nurden AT, et al.: Platelet released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts. Rheumatology (Oxford. 2007, 46:1769-1772. 10.1093/rheumatology/kem234
12. Bendinelli P, Matteucci E, Dogliotti G, et al.: Molecular basis of the anti inflammatory action of platelet rich plasma on human chondrocytes: mechanisms of NF κB inhibition via HGF. J Cell Physiol. 2010, 225:757-766. 10.1002/jcp.22274
13. Rahimzadeh P, Imani F, Faiz SHR, et al.: The effects of injecting intra articular platelet rich plasma or prolotherapy on pain score and function in knee osteoarthritis. Clin Interv Aging. 2018, 13:73-79. 10.2147/CIA.S147757
14. Riboh JC, Saltzman BM, Yanke AB, et al.: Effect of leukocyte concentration on the efficacy of platelet rich plasma in the treatment of knee osteoarthritis. Am J Sports Med. 2016, 44:792-800. 10.1177/0363546515580787
15. Bian G, Zhao W, Zhang L: Comparative efficacy of platelet rich plasma injection vs ultrasound guided hyaluronic acid injection in the rehabilitation of hip osteoarthritis: an observational study. Ann Med. 2025, 57:2524091. 10.1080/07853890.2025.2524091
16. Filardo G, Kon E, Di Martino A, et al.: Platelet rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. BMC Musculoskelet Disord. 2012, 13:229. 10.1186/1471-2474-13-229
17. Gormeli G, Gormeli CA, Ataoglu B, et al.: Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double blind, placebo controlled trial. Knee Surg Sports Traumatol Arthrosc. 2017, 25:958-965. 10.1007/s00167-015-3705-6
18. Raeissadat SA, Rayegani SM, Hassanabadi H, Fathi M, Ghorbani E, Babaee M, Azma K : Knee Osteoarthritis Injection Choices: Platelet- Rich Plasma (PRP) versus Hyaluronic Acid (A one-year randomized clinical trial).. Clin Med Insights Arthritis Musculoskelet Disord. 2015, 8:1-8. 10.4137/CMAMD.S17894
19. Patel S, Dhillon MS, Aggarwal S, et al.: Treatment with platelet rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double blind, randomized trial. Am J Sports Med. 2013, 41:356-364. 10.1177/03635465124712
20. Rabago D, Zgierska A, Fortney L, et al.: Hypertonic dextrose injections (prolotherapy) for knee osteoarthritis: results of a single arm uncontrolled study with 1 year follow up. J Altern Complement Med. 2012, 18:408-414. 10.1089/acm.2011.0030
21. Krsticevic M, Jeric M, Dosenovic S, et al.: Proliferative injection therapy for osteoarthritis: a systematic review. Int Orthop. 2017, 41:837-847. 10.1007/s00264-017-3422-5
22. Vora A, Borg Stein J, Nguyen RT: Regenerative injection therapy for osteoarthritis: fundamental concepts and evidence based review. PM R. 2012, 4:109. 10.1016/j.pmrj.2012.02.005
23. Bellamy N: The clinical evaluation of osteoarthritis in the elderly. Clinics in rheumatic diseases. 19861, 12:131-53. 10.1016/S0307-742X(21)00624-X
24. Kellgren JH, Lawrence JS: Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957, 16:494-502. 10.4324/9780203214237
25. Gobbi A, Karnatzikos G, Mahajan V, et al.: Platelet rich plasma treatment in symptomatic patients with knee osteoarthritis: preliminary results in a group of active patients. Sports Health. 2012, 4:162-172. 10.1177/1941738111431801
26. Kon E, Filardo G, Di Martino A, et al.: Platelet rich plasma (PRP) to treat sports injuries: evidence to support its use. Knee Surg Sports Traumatol Arthrosc. 2011, 19:516-527. 10.1007/s00167-010-1306-y
27. Jaffery H: The role of NF κB regulator Bcl 3 in the skeleton. University of Glasgow (United Kingdom). ProQuest Dissertations & Theses, 2018. 31501466.. 2018.
28. Dhillon MS, Patel S, John R: PRP in OA knee - update, current confusions and future options. Sicot J. 2017, 3:27. 10.1051/sicotj/2017004
29. Akpancar S, Gül D: Comparison of platelet rich plasma and prolotherapy in the management of osteochondral lesions of the talus: a retrospective cohort study. Med Sci Monit. 2019, 25:5640-5648. 10.12659/MSM.914111
30. Lai LP, Stitik TP, Foye PM, et al.: Use of platelet rich plasma in intra articular knee injections for osteoarthritis: a systematic review. Am J Phys Med Rehabil. 2015, 94:478-484. 10.1016/j.pmrj.2015.02.003
31. Eroğlu A, Sarı A, Durmuş B: Platelet rich plasma vs prolotherapy in the management of knee osteoarthritis: randomized placebo controlled trial. Turk J Sports Med. 2016, 51:34-43. 10.5152/tjsm.2016.005.