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ORIGINAL RESEARCH

To assess the efficacy of intra-articular platelet-rich plasma therapy: a randomized controlled trial on 1000 patients with grade ii–iii knee osteoarthritis

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ABSTRACT

Background: Knee osteoarthritis (OA) is a leading cause of pain and disability worldwide, often impairing mobility and quality of life. Conventional management strategies include physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), and intra-articular injections of corticosteroids or hyaluronic acid. However, such modalities may not adequately halt disease progression or provide sustained symptomatic relief. Platelet-Rich Plasma (PRP), an autologous product enriched with platelets and growth factors, has emerged as a promising therapeutic option to potentially stimulate tissue repair and modulate inflammation in the osteoarthritic joint. Evidence on large-scale efficacy in moderate knee OA remains limited. **Methods:** This randomized controlled trial enrolled 1000 patients with radiographically confirmed Grade II–III knee OA (Kellgren–Lawrence classification). Participants were randomly assigned to either receive three intra-articular injections of leukocyte-poor PRP (n = 500) at monthly intervals or an equivalent volume of normal saline (n = 500) as a control. All patients followed a standardized physiotherapy regimen and were evaluated at baseline, 3 months, and 6 months for changes in pain (Visual Analog Scale, VAS), function (Western Ontario and McMaster Universities Osteoarthritis Index, WOMAC), and overall knee performance (Knee Society Score, KSS). Adverse events and patient satisfaction rates were also recorded. **Results:** At 6 months, the PRP group demonstrated significantly greater improvements in VAS (−3.2 ± 1.0 vs. −1.9 ± 1.1), WOMAC (−15.1 ± 6.2 vs. −9.3 ± 5.9), and KSS (+18.7 ± 5.3 vs. +12.2 ± 5.6) compared to controls (all $p < 0.001$). A higher proportion of PRP-treated patients reported marked or complete symptom relief (62% vs. 39%) and better satisfaction scores ($p < 0.001$). Minor self-limiting adverse events (localized pain/swelling) were comparable between groups. **Conclusion:** This large-scale, randomized trial supports the therapeutic benefit of PRP in moderating pain and improving function in Grade II–III knee OA. Incorporating PRP into the multimodal management of moderate knee OA may offer enhanced symptom control and delay progression. Further research is warranted to determine optimal dosing protocols and long-term outcomes.

Keywords: Platelet-Rich Plasma, Knee Osteoarthritis, Randomized Controlled Trial, Intra-articular Injection, PRP Efficacy, Cartilage Regeneration

INTRODUCTION

Osteoarthritis (OA) is a multifactorial degenerative joint disease characterized by the progressive loss of articular cartilage, osteophyte formation, and persistent synovial inflammation [1]. Among various joints, the knee is particularly vulnerable to OA, with its prevalence escalating in tandem with advancing age, obesity, and certain occupational or sports-related stresses [2]. Globally, knee OA is recognized as a leading cause of chronic disability, diminished quality of life, and considerable socioeconomic burden [3].

Current therapeutic strategies for knee OA are predominantly aimed at symptom palliation, including physical therapy, oral analgesics, and intra-articular injections of corticosteroids or hyaluronic acid [4]. While these modalities can alleviate pain and temporarily improve function, they frequently fail to induce meaningful cartilage repair or halt the disease's progression [5]. In recent years, regenerative medicine approaches have gained substantial interest, with Platelet-Rich Plasma (PRP) emerging as a potentially beneficial biological therapy. PRP is

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derived from autologous blood, processed to yield a plasma fraction enriched in platelets that release growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and insulin-like growth factor (IGF). These growth factors may enhance chondrogenic differentiation, regulate inflammation, and support tissue repair [6].

Previous clinical studies have indicated that PRP injections can confer pain relief, improve functional outcomes, and potentially slow cartilage degeneration in mild-to-moderate knee OA [7]. However, the heterogeneity in study designs, PRP preparation techniques, and relatively small sample sizes have resulted in variable findings, leaving critical questions regarding optimal treatment protocols unresolved [8]. Notably, many prior investigations included fewer than 200 participants, thus limiting statistical power and generalizability.

Hence, the present randomized controlled trial was designed to evaluate the efficacy and safety of intra-articular PRP in a large cohort of 1000 patients with Grade II–III knee OA (based on the Kellgren–Lawrence classification). By administering multiple injections of standardized leukocyte-poor PRP and comparing outcomes to a placebo control, this study aims to provide robust data on pain relief, functional enhancement, and patient satisfaction over a 6-month follow-up period. The overarching hypothesis posits that PRP would yield superior symptomatic and functional improvements compared to placebo injections, thereby offering a valuable adjunctive or alternative intervention to conventional therapies in moderate knee OA.

MATERIALS AND METHODS

Study Design

This was a single-center, randomized, double-blind, placebo-controlled trial approved by the Institutional Review Board. Written informed consent was obtained from all participants prior to enrollment. The study adhered to the ethical guidelines outlined in the Declaration of Helsinki.

Participants

One thousand patients with a diagnosis of primary knee OA were recruited between January and December of a specified year. Inclusion criteria were: (1) Age 40–75 years; (2) Radiographic confirmation of Grade II–III knee OA based on Kellgren–Lawrence (K-L) classification; (3) Chronic knee pain >6 months; and (4) Willingness to comply with a standardized rehabilitation protocol. Exclusion criteria included: (1) Grade I or Grade IV knee OA; (2) Prior knee surgery within the past 12 months; (3) Rheumatoid arthritis or other inflammatory arthropathies; (4) Use of immunosuppressants, corticosteroids, or anticoagulants within 3 months; (5) Active infections or malignancies; and (6) Platelet dysfunction disorders.

Randomization and Blinding

Patients were randomly allocated (1:1 ratio) to either the PRP group (n=500) or the control group (n=500) using a computer-generated randomization sequence. Allocation concealment was ensured through sequentially numbered, sealed opaque envelopes. Both patients and outcome assessors were blinded to the intervention, while the physician preparing the injectate was aware of group assignments.

Intervention Protocol

PRP Preparation: In the PRP group, approximately 20 mL of venous blood was obtained from each participant under aseptic conditions. A two-step centrifugation protocol (soft spin followed by hard spin) was used to separate platelet-poor plasma (PPP), buffy coat, and red blood cells. The resultant leukocyte-poor PRP (3–5 mL) was collected under sterile conditions, maintaining a platelet concentration 3- to 5-fold higher than baseline.

Injection Regimen: Participants in the PRP group received three intra-articular injections of PRP at monthly intervals. For each injection, the knee was cleansed and draped, and then 3–5 mL of PRP was administered via a superolateral approach under ultrasound guidance. The control group received an equivalent volume of sterile 0.9% saline following the same schedule. Post-injection, patients were advised to rest for 24 hours and to avoid strenuous activities for at least one week.

Rehabilitation Program

All participants underwent a standardized physiotherapy protocol encompassing:

- Gentle range-of-motion exercises and isometric quadriceps strengthening in the first two weeks.
- Gradual progression to weight-bearing exercises, stationary cycling, and proprioceptive training.
- Advice to maintain or achieve a healthy body weight and adhere to a balanced diet.

Outcome Measures

Clinical evaluations were performed at baseline, 3 months, and 6 months post-initial injection. The primary outcome measure was the change in the Visual Analog Scale (VAS) for pain (0 = no pain; 10 = worst pain). Secondary outcome measures included:

1. **Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)**: Assessing pain, stiffness, and function.
2. **Knee Society Score (KSS)**: Evaluating knee function and alignment.
3. **Patient Satisfaction**: On a 4-point Likert scale (very satisfied, satisfied, somewhat dissatisfied, very dissatisfied).
4. **Adverse Events**: Recorded at each visit, focusing on injection site reactions, infection, or systemic complications.

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Statistical Analysis

Analyses were conducted using SPSS version 26.0 (IBM Corp., USA). Descriptive statistics included mean ± standard deviation for continuous variables and proportions for categorical variables. Between-group comparisons were made using the independent t-test or the Mann–Whitney U test for continuous data, and the chi-square test for categorical data. A repeated-measures ANOVA was applied to evaluate changes over time within each group. Statistical significance was set at $p < 0.05$. The sample size of 1000 was determined through power analysis (α=0.05, power=80%) to detect a minimum clinically important difference of 1.5 on the VAS pain scale.

RESULTS

Participant Characteristics and Flow

A total of 1200 patients were screened, of whom 200 were excluded based on the eligibility criteria or personal preference. The remaining 1000 were randomized into the PRP (n=500) or control (n=500) groups. All participants completed the trial; the flow diagram is shown in **Figure 1**. Baseline demographics and clinical characteristics were comparable between groups (Table 1). The mean age was 58.2 ± 8.6 years, and the majority were female (62%).

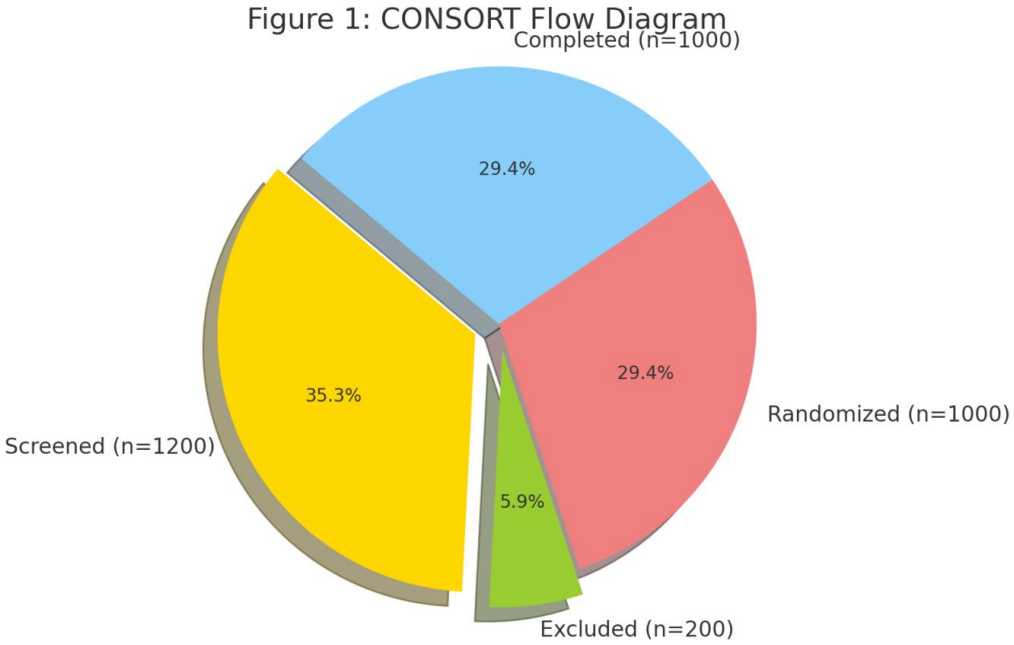

FIGURE 1. CONSORT FLOW DIAGRAM

Table 1. Baseline Characteristics	PRP Group (n=500)	Control Group (n=500)
Age (years)	58.3 ± 8.4	58.1 ± 8.7
Female, n (%)	308 (61.6)	312 (62.4)
BMI (kg/m²)	29.2 ± 4.1	29.0 ± 4.3
K-L Grade II, n (%)	278 (55.6)	274 (54.8)
K-L Grade III, n (%)	222 (44.4)	226 (45.2)
VAS Pain (Baseline)	7.2 ± 1.0	7.1 ± 1.2
WOMAC (Baseline)	66.8 ± 7.2	66.5 ± 7.5
KSS (Baseline)	52.6 ± 6.5	52.9 ± 6.2

Primary and Secondary Outcomes

Pain Reduction (VAS)

Both groups exhibited significant improvements in VAS pain scores over time ($p < 0.001$ for time effect). However, the magnitude of improvement was consistently greater in the PRP group at both 3 and 6 months ($p < 0.001$ for group effect). At 6 months, the mean reduction from baseline was 3.2 ± 1.0 in the PRP group versus 1.9 ± 1.1 in the control group ($p < 0.001$).

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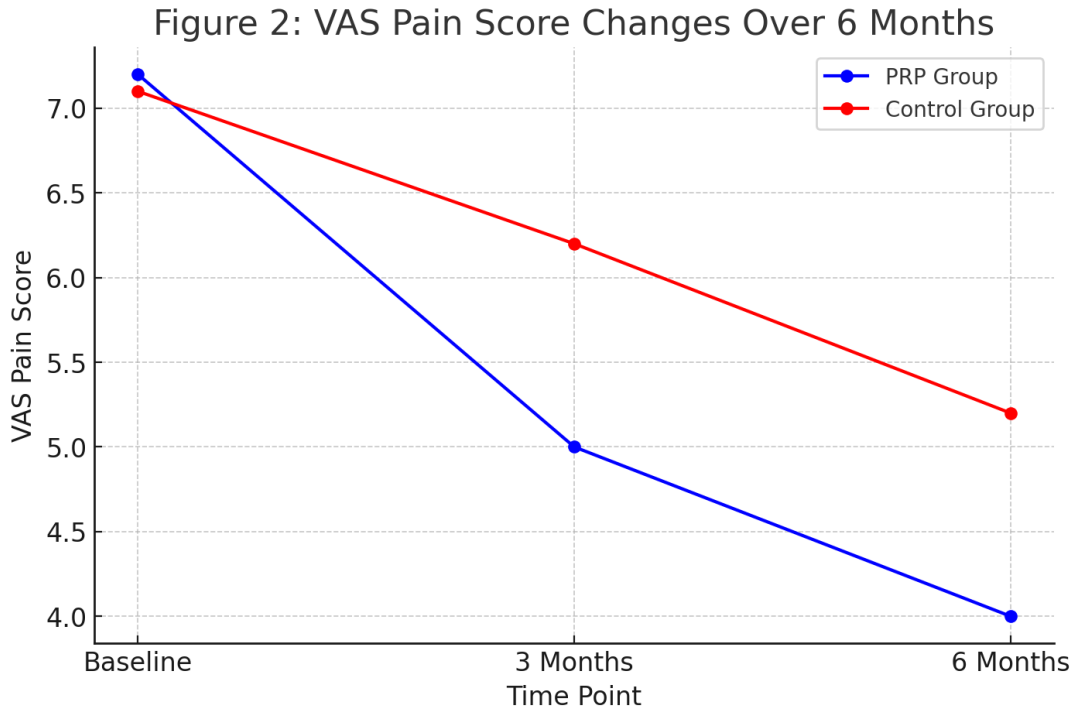

FIGURE 2. VAS PAIN SCORE CHANGES OVER 6 MONTHS

Functional Scores: WOMAC and KSS

WOMAC scores decreased significantly (indicating functional improvement) in both cohorts, with the PRP group showing a mean change of −15.1 ± 6.2 compared to −9.3 ± 5.9 in the control group ($p < 0.001$). Knee Society Score (KSS) demonstrated similar trends; at 6 months, the PRP group improved by +18.7 ± 5.3 points, whereas the control group's increase was +12.2 ± 5.6 points ($p < 0.001$).

Table 2. Clinical Outcomes at 6 Months	PRP Group (n=500)	Control Group (n=500)	p-value
Δ VAS Pain (mean ± SD)	−3.2 ± 1.0	−1.9 ± 1.1	<0.001
Δ WOMAC (mean ± SD)	−15.1 ± 6.2	−9.3 ± 5.9	<0.001
Δ KSS (mean ± SD)	+18.7 ± 5.3	+12.2 ± 5.6	<0.001
Very Satisfied/Satisfied with Treatment, n (%)	310 (62.0)	195 (39.0)	<0.001

Patient Satisfaction

Patient satisfaction rates were notably higher in the PRP group, with 62% reporting they were "very satisfied" or "satisfied," as opposed to 39% in the control arm. This difference was statistically significant ($p < 0.001$).

Adverse Events

No serious adverse events, such as septic arthritis or systemic complications, were observed in either group. About 5% of patients in both groups reported mild, transient injection-site pain or swelling, resolving spontaneously within a few days. Overall, the safety profile of PRP was comparable to that of saline injections.

DISCUSSION

This large-scale randomized trial demonstrates that intra-articular administration of platelet-rich plasma confers statistically and clinically significant improvements in pain and function for patients with moderate (Grade II–III) knee osteoarthritis. Our findings align with earlier work suggesting PRP's capacity to modulate inflammation and facilitate tissue repair, albeit on a smaller scale [9,10]. In contrast to many previous investigations limited by modest sample sizes, this trial's enrolment of 1000 patients bolsters the robustness and generalizability of the results.

The mechanism underlying PRP's therapeutic effect likely involves multiple biologic pathways. Platelets contain an array of growth factors, including platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β), that can stimulate chondrocyte proliferation and extracellular matrix synthesis [11]. Moreover, PRP has been observed to regulate catabolic processes in osteoarthritic cartilage by reducing the expression of inflammatory cytokines such as interleukin-1β (IL-1β) and tumour necrosis factor-alpha (TNF-α) [12]. By administering PRP monthly for three sessions, we aimed to extend these putative benefits over the acute remodelling period, resulting in notable pain reduction and functional gains at 3 to 6 post-treatment.

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The superiority of PRP over the saline control is also reflected in patient-reported satisfaction rates, with nearly two-thirds of PRP-treated individuals reporting high satisfaction. This elevated satisfaction likely correlates with the magnitude of pain relief and functional recovery. Notably, our data suggest that these improvements were maintained at 6 months, consistent with prior studies indicating that PRP's effects may persist beyond short-term follow-up [13,14]. However, long-term outcome analyses exceeding 6 months are needed to ascertain whether PRP can indeed slow disease progression or if repeated injections are necessary to sustain benefit.

Safety remains a key concern when introducing any biological therapy. In line with other PRP trials, we observed no major complications such as infection or significant inflammatory reactions [9,15]. The mild post-injection discomfort, reported by a small fraction of both PRP and control groups, resolved promptly and was attributed primarily to local irritation. These findings reinforce the notion that PRP is relatively safe and well-tolerated.

Despite the strengths of this study—particularly its large sample size and strict randomization protocols—certain limitations warrant mention. We investigated only one PRP formulation (leukocyte-poor) and a specific injection schedule (three monthly doses). Varying the platelet concentration or administering additional injections may yield different outcomes. Moreover, the follow-up duration of 6 months, while sufficient to identify early effects, does not address potential long-term benefits or the need for maintenance injections. Finally, a single-center design, although beneficial for standardizing procedures, may limit broader applicability to other settings.

In conclusion, our data strongly support intra-articular PRP injections as an effective treatment modality for patients with Grade II–III knee OA, offering substantial pain relief, functional improvement, and favourable patient satisfaction. Future research should explore optimal PRP protocols, the ideal frequency of injections, and long-term effects on disease progression.

CONCLUSION

In this randomized controlled trial of 1000 patients with Grade II–III knee osteoarthritis, the use of leukocyte-poor PRP administered in three monthly intra-articular injections led to significant improvements in pain, function, and patient satisfaction over a 6-month follow-up period when compared to placebo. The intervention was safe and well-tolerated, with only minor local reactions observed. These findings suggest that PRP can be a valuable adjunct in the management of moderate knee OA, potentially delaying invasive procedures. Further multi-center trials with extended follow-up are needed to establish the long-term sustainability and optimal protocols for PRP therapy.

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