

Evaluation of the Efficacy of Platelet-Rich Plasma (PRP) Combined with Hyaluronic Acid for the Treatment of Chondral Lesions in the Knee

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Received: 11 Junn 2025; Accepted: 07 July 2025; Published: 18 July 2025

Citation: Leandro Gregorut Lima, Francis Ribeiro de Souza, Marco Aurélio Silvério Neves, et al. Evaluation of the Efficacy of Platelet-Rich Plasma (PRP) Combined with Hyaluronic Acid for the Treatment of Chondral Lesions in the Knee. *Stem Cells Regen Med.* 2025; 9(3): 1-5.

ABSTRACT

Platelet-rich plasma (PRP) has been widely used as an adjunctive tool in surgical tissue repair and, more recently, as a percutaneous approach to stimulate tissue regeneration. Among its applications, PRP stands out in the treatment of musculoskeletal disorders, including knee chondral lesions, osteoarthritis, tendinopathies, and soft tissue injuries. However, robust evidence is still required to establish standardized clinical use of PRP, especially when combined with other therapies. This study aimed to evaluate the efficacy of intra-articular infiltration of PRP combined with hyaluronic acid (HA) in the treatment of knee chondral lesions. A total of 313 patients were included and evaluated using the Knee Injury and Osteoarthritis Outcome Score (KOOS) and Short Form Health Survey (SF-12 scores), with a 12-month follow-up. The results showed statistically significant improvement ($p < 0.0001$) at all evaluated time points, with an average gain of up to 90 points in joint function and quality of life scores by the end of follow-up. The combined PRP and HA treatment provided progressive and sustainable clinical benefits, proving to be an effective and safe alternative for chondral regeneration and symptom relief in the knee.

Keywords

Platelet-Rich Plasma, PRP, Hyaluronic Acid, Chondral Lesions, Knee, Regenerative Medicine, Orthobiologics.

Introduction

An increasing number of physicians believe that localized injection of platelet-rich plasma (PRP) is an effective treatment for various musculoskeletal disorders. For some practitioners, PRP serves as a bridge between conservative therapies and invasive surgical interventions. PRP has been used for decades to facilitate surgical tissue repair, and its percutaneous injectable use to theoretically enhance tissue regeneration and repair is a logical progression [1]. PRP is applicable in the treatment of osteoarthritis, tendinopathy, chondropathy, acute and chronic soft tissue injuries, and muscle

or ligament ruptures. It is also employed to enhance healing following bone or tissue reconstruction. However, the current evidence supporting its use in these conditions remains limited [2].

Initially used in veterinary medicine and oromaxillofacial and dermatological treatments, the application of PRP has grown exponentially in orthopedic settings, particularly in bone formation, soft tissue injury, and as an adjuvant in surgical reconstruction [3].

PRP refers to an autologous blood sample with platelet concentrations above baseline levels, it is an autologous concentrate of human platelets and plasma produced by centrifuging the patient's own blood. Platelets in PRP contain growth factors such as transforming growth factor beta 1 (TGF- β 1), platelet-

derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF), which, once concentrated, are applied to injury sites to stimulate the body's natural regenerative process. PRP is typically defined as any plasma fraction that contains platelet concentrations above baseline (150,000 to 350,000/mL). PRP preparations are commonly categorized as leukocyte-rich PRP (LR-PRP) or leukocyte-poor PRP (LP-PRP), depending on the neutrophil concentration [3,4].

Platelets typically remain in the upper plasma layer, while red blood cells settle at the bottom and white blood cells form an intermediate layer. The first centrifugation is a soft spin that separates plasma and platelets from erythrocytes and leukocytes. The second, or hard spin, concentrates the platelet-rich and platelet-poor plasma fractions. This step is somewhat controversial, as some commercial kits omit it, and the potential healing benefits of platelet-poor plasma remain unclear. Although PRP is considered a promising and attractive treatment modality, more high-quality studies are needed to establish its safety and efficacy. When considering PRP for cartilage pathologies, it is essential to understand that osteoarthritis (OA) presents unique challenges regarding joint biology, homeostasis, and inflammatory cytokine activity. *In vitro*, studies have suggested that PRP-derived growth factors can enhance chondrocyte activity by upregulating gene expression, proteoglycan synthesis, and type II collagen deposition [3-5].

A meta-analysis showed that PRP intra-articular injections significantly improved osteoarthritis indices at 3, 6, and 12 months compared to controls. These studies concluded that PRP is more effective than conventional intra-articular treatments in relieving pain and improving joint function. Multiple randomized controlled trials (RCTs) have confirmed the clinical safety and efficacy of PRP in reducing knee osteoarthritis symptoms and enhancing local tissue regeneration [6,7].

Although fewer studies have evaluated PRP in hip osteoarthritis, the available evidence suggests that intra-articular PRP is safe and improves pain and functional outcomes, with some studies reporting greater initial pain relief compared to hyaluronic acid injections [8].

Articular cartilage lesions of the knee remain a significant clinical challenge, often associated with chronic pain, joint dysfunction, and decreased quality of life. Conservative treatments, such as physical therapy and nonsteroidal anti-inflammatory drugs (NSAIDs), frequently fail to promote adequate cartilage regeneration or halt disease progression [9].

PRP, rich in growth factors like TGF- β , PDGF, and VEGF, is known for its anti-inflammatory, angiogenic, and regenerative properties in connective tissues, including articular cartilage. Meta-analyses have demonstrated that PRP provides superior improvements in pain and function compared to hyaluronic acid alone, as reflected in WOMAC (descrever a sigla) (44%) and IKDC (descrever a sigla) scores [10].

Hyaluronic acid (HA), on the other hand, contributes to joint lubrication, shock absorption, and homeostatic maintenance due to its viscoelastic properties and anti-inflammatory effects.

Recent studies have investigated the combined use of PRP and HA, aiming to enhance both the mechanical benefits of HA and the biological effects of PRP. A systematic meta-analysis published in 2024 confirmed that the combined therapy provides superior improvements in pain (VAS), function (WOMAC), and physical performance compared to HA alone, with statistically significant benefits at 6 and 12 months. Randomized clinical trials have also shown that PRP + HA reduces synovial inflammation and improves joint function, with outcomes comparable or superior to PRP alone in some clinical endpoints [11].

However, the heterogeneity in PRP preparation protocols, platelet concentrations, infiltration frequency, and HA formulations limit the generalizability of these findings. Furthermore, few studies have specifically evaluated focal chondral lesions of the knee, as most available data focus on generalized osteoarthritis.

Based on this context, the present study aimed to: Evaluate the clinical efficacy and functional progression of knee chondral lesions treated with intra-articular PRP combined with HA using the KOOS and SF-12 scores; Quantify functional improvement over a 12-month period; Contribute to the development of a standardized, evidence-based therapeutic protocol [12].

The relevance of this study lies in its longitudinal analysis of three consecutive years (2022 to 2024), with follow-up extending to 12 months post-treatment, using validated clinical instruments to assess function and quality of life, providing scientific support for the application of PRP and HA in knee chondral lesion management.

Materials and Methods

Ethical Considerations

Prior to the procedure, patients were thoroughly informed about the study protocol, including its potential benefits and risks. All participants signed an informed consent form, in accordance with the guidelines established by Resolution No. 196/96, which regulates human subject research in Brazil.

Inclusion and Exclusion Criteria

Inclusion criteria encompassed patients over 18 years of age who underwent PRP infiltration and provided informed consent. Exclusion criteria included patients with prior PRP injections at the same anatomical site, individuals with rheumatoid arthritis, patients undergoing chronic corticosteroid therapy, and those who declined to participate or sign the consent form.

Sample Design

This prospective interventional study included 313 patients diagnosed with knee chondropathies. Patients were consecutively selected based on clinical and imaging confirmation magnetic resonance image (MRI) of patellar chondromalacia (grades 2 to

4) and/or femorotibial chondral lesions (grades 2 to 3 according to Outerbridge classification).

Lesion assessment was conducted via MRI following standardized chondral classification criteria. Patients with prior knee surgeries, inflammatory joint diseases, or unstable ligament injuries were excluded from the study.

Treatment Protocol

Patients underwent three intra-articular infiltrations of PRP combined with medium molecular weight hyaluronic acid, SupraHyal® Duo 25mg/2,5ml from Adium, with one infiltration per month and a maximum interval of 28 days between each session. All patients were referred for physiotherapy and were clinically assessed over a one-year follow-up period at pre-treatment, 1, 3, 6, and 12 months.

PRP Preparation and Administration

Venous blood samples were collected using a 21G butterfly needle and vacuum tubes containing acid-citrate-dextrose (ACD) anticoagulant. Six tubes of 9 mL each were collected per patient.

PRP processing was performed in a Class II-A biological safety cabinet, following ANVISA biosafety guidelines. Blood samples underwent an initial centrifugation at 500 G for 10 minutes to separate plasma and the buffy coat layer. The plasma was then transferred to 15 mL Falcon tubes and centrifuged again at 700 G for 17 minutes.

The resulting pellet was resuspended by recovering 20% of the lower plasma volume. The final PRP product was transferred to sterile syringes for intra-articular infiltration.

This procedure ensured both the efficacy of PRP and compliance with biosafety regulations, guaranteeing treatment quality and safety and is intended to concentrate the plasma at least 5 fold from the baseline reaching 1.000.000/ml to 1.500.000/ml platelet concentration.

Results

Sample Characterization

A total of 313 patients with knee chondral lesions were included. Clinical evolution was monitored using the Knee Injury and Osteoarthritis Outcome Score (KOOS) and Short Form Health Survey (SF-12) scores, with assessments conducted at baseline, and at 1, 2, 3, 6, and 12 months post-treatment.

Statistical Analysis

Data analysis was performed using GraphPad Prism software (version X.X). Statistical significance was set at $\alpha = 0.05$, with p-values < 0.05 considered significant.

A one-sample t-test was employed to compare each time point with the baseline (pre-infiltration) scores. This statistical method was selected because all patients received the same intervention and served as their own control, making intra-group comparisons appropriate. This approach effectively assessed whether post-treatment means differed significantly from baseline scores.

Additional analyses included the calculation of 95% confidence intervals, standard error of the mean (SEM), and partial eta squared (R^2) to quantify the effect size and consistency of the treatment response.

The one-sample t-test was chosen for its sensitivity in detecting progressive clinical improvements over the 12-month follow-up period.

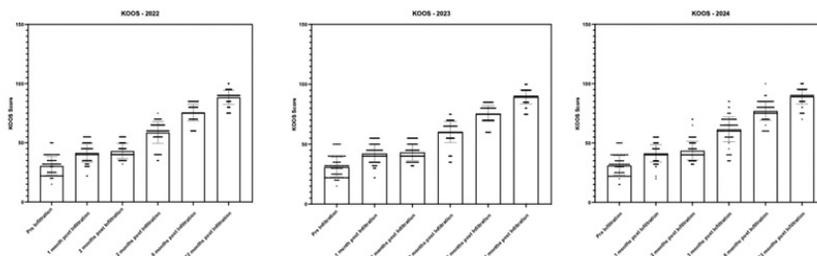


Figure 1: KOOS scores with assessments conducted at baseline, and at 1, 2, 3, 6, and 12 months post-treatment.

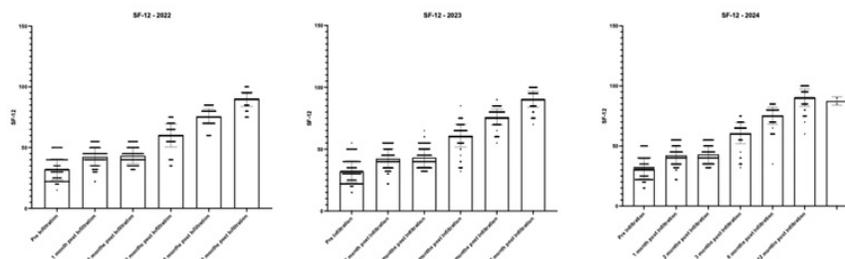


Figure 2: SF-12 scores with assessments conducted at baseline, and at 1, 2, 3, 6, and 12 months post-treatment.

Clinical Outcomes

In 2022, statistically significant improvements ($p < 0.0001$) in KOOS scores were observed at all time points. The mean difference increased progressively from 30.42 at baseline to 88.40 at 12 months. The R^2 values ranged from 0.9364 to 0.9955, indicating a robust treatment effect.

In 2023, similar trends were confirmed, with mean differences increasing from 30.97 at baseline to 89.42 at 12 months (R^2 : 0.9329 to 0.9957).

In 2024, continued clinical improvement was observed, with KOOS mean differences rising from 31.04 to 89.18 over 12 months (R^2 : 0.9343 to 0.9949).

SF-12 scores also showed significant improvements across all periods. In 2022, the mean difference increased from 31.93 at baseline to 89.80 at 12 months (R^2 : 0.9305 to 0.9955). This trend persisted in 2023 and 2024, with mean differences reaching up to 90.38 and 90.18, respectively, by the end of the follow-up.

These consistent improvements over three consecutive years highlight the clinical efficacy and sustainability of the PRP + HA treatment protocol for knee chondral lesions.

Discussion

This study demonstrated significant and sustained clinical improvements in KOOS and SF-12 scores in patients treated with PRP combined with hyaluronic acid for knee chondral lesions. The magnitude of these improvements exceeded those typically reported in the literature for monotherapies with PRP or HA.

Previous meta-analyses have shown that both PRP and HA, when used alone, yield meaningful but limited improvements in knee osteoarthritis symptoms. Zhao et al. found that PRP was superior to HA in pain control and functional outcomes over 12 months. Belk et al. also reported superior improvements in WOMAC and VAS scores with PRP compared to HA, although their reported gains ranged from 20 to 50 points, notably lower than those observed in our study [13,14].

Studies evaluating the combination of PRP and HA, such as those by Shu et al. and Moghaddam et al., reported additional clinical benefits, including improved joint viscosity and prolonged anti-inflammatory effects. However, the magnitude of the improvements (~30-50 points) in these studies was still lower than the ~90-point gains observed in our cohort, suggesting that our treatment protocol or patient selection may have contributed to superior clinical outcomes [15,16].

Hyaluronic acid is known for its viscoelastic properties and chondroprotective effects, while PRP delivers growth factors like TGF- β , VEGF, and PDGF, which are crucial for tissue repair and inflammation modulation. The combination of these therapies may create an optimized joint environment for cartilage regeneration by integrating mechanical protection with biological stimulation [17].

Furthermore, our protocol of three-monthly infiltrations with intervals of less than 28 days may have enhanced treatment efficacy by maintaining a favorable intra-articular regenerative environment, as supported by Andia et al. [18].

This study supports the safety and clinical efficacy of PRP combined with hyaluronic acid as a superior strategy compared to monotherapies for the treatment of knee chondral lesions, offering sustained pain relief and functional improvement over a 12-month period.

We recognize certain limitations in our study. The absence of a control group is a limitation that precludes direct comparison with PRP or HA alone. Further randomized controlled trials are necessary to confirm the superiority of this combination over standard treatments.

Conclusion

The combination of PRP and hyaluronic acid for the treatment of knee chondral lesions proved to be an effective, safe, and clinically impactful strategy, providing progressive improvements in joint function and quality of life over a 12-month follow-up. In addition, the results suggest that this combination may be superior to monotherapy, though comparative clinical trials are warranted to validate this hypothesis.

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