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Original Research Article

Evaluation of efficacy and safety of intraarticular injections of leucocyte poor platelet rich plasma in osteoarthritis knee patients

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ABSTRACT

Background: The present study evaluates the safety and efficacy of intraarticular injections of leucocyte poor platelet rich plasma (LP-PRP) in osteoarthritis (OA) knee patients. Patients with early osteoarthritis (K-L grading 1 and 2)-clinically and radiologically and those who gave consent to participate in the study were injected with 2.4 ml per knee of LP-PRP over unilateral or bilateral knees at 0, 1, 2 and 6 months of LP-PRP injections.
Methods: 100 patients with osteoarthritis knee pain were injected with LP-PRP at 0.1.2 months on OPD basis. LP-PRP was prepared in a centrifugation machine at 2000 RPM for 4 minutes and 2000 RPM for 10 minutes for two consecutive times and then injected into knee with a medial suprapatellar approach using 20/21 G needle. This was repeated at 1 and 2 months of follow-up. Assessment of efficacy in terms of pain relief was done on the basis of visual analog score (VAS) and clinical outcomes on the basis of knee injury and osteoarthritis outcome scores (KOOS) at 0, 1, 2, 6 months following injection of LP-PRP.
Results: The mean VAS at pre-injection was 7.22±0.965 which reduced to 3.06±1.223 at post-injection follow-up at 6 months. The mean KOOS at pre injection was 33.4±7.51 which increased to 78.86±8.80 at post-injection follow-up at 6 months.
Conclusions: LP-PRP has emerged as an intriguing therapy option for knee OA, and our study has shown that it is effective after 6 months.

Keywords: K-L classification, KOOS score, Osteoarthritis, PRP injections, VAS score

INTRODUCTION

Osteoarthritis (OA), a multifactorial chronic disease, is defined by the reduction of joint space due to the degradation of articular cartilage. Various studies have been conducted to repair the damaged cartilage in knee osteoarthritis (KOA). For cartilage repair and KOA pain management, there are a number of surgical procedures such as microfracture, osteochondral and tissue engineered grafts, as well as various non-surgical therapeutic options such as single molecule drugs, hyaluronic acid and corticosteroid injections.[1,2]

Currently, there is a great need for biological immunomodulatory techniques to treat cartilage abnormalities and prevent the progression of OA. According to reports, platelet-rich plasma (PRP) can accelerate the healing process and relieve the symptoms of osteoarthritis (OA) in the longer term. There are also reports of cartilage regeneration using synovial stem cells. After PRP injections, the synovium experiences a long-lasting anti-inflammatory response that also protects cartilage.[3,4]

According to the Kellgren-Lawrence classification (K-L classification), treatment with PRP is useful for OA

patients with low-grade inflammation; however, a large proportion of individuals with clinical OA who experience acute pain have advanced inflammation. Reportedly, repeated injections may be effective for treating high-grade inflammation.[5]

According to Kurtz et al, both the average age of the population and the increasing prevalence of obesity will contribute to an increase in the proportion of knee OA over the next decade. In addition, a recent study found that in people over 50 years of age with a body mass index (BMI) of 25 or more, cartilage thickness and volume are significantly reduced.[6]

Several meta-analytic studies evaluated the efficacy of platelet-rich plasma (PRP)compared to other surgical and nonsurgical techniques using PRP. The results showed that PRP produced greater pain relief and functional improvement at various time points after injection. PRP, an autologous blood product, contains a high concentration of several growth factors (GF), including fibroblast growth factor, epidermal growth factor, vascular endothelial growth factor, transforming growth factor, and platelet-derived growth factor.[7]

According to a recent study, various growth factors and cytokines produced by platelets after damage from an accident or disease may play an important role in controlling the inflammatory processes that support the maintenance or regeneration of tissue structures.

In an animal model, growth factors were found to promote tendon healing when added to the damaged tendon. In humans, injection of whole blood into tendon has been shown to relieve pain. PRP is described as a prime example of an autologous, biologic blood-derived product that can be administered exogenously to a variety of tissues and releases high levels of platelet-derived growth factors to enhance tendon, bone and wound healing. In addition, PRP has antibacterial properties that can help prevent infections. Growth factors are released from activated platelets and trigger the body's own healing response.[8-10]

PRP therapy provides an effective combination of growth factors to promote the healing process. PRP these include both anabolic (b-FGF, TGF-R1, TNF-RII, IL-1, TNF-RII, IL-4, IL-10, IL-13 and IFN) and anti-inflammatory (IL-1, TNF-R1, TNF-RII, EGF, IGF-1, PDGF-AB, PDGF-BB and VEGF) cytokines, and the combination of these cytokines is a viable way for PRP to exert its effects by preventing the production of inflammatory cytokines such as IL-1 and NF-kB. When secreted, these substances control important tissue repair processes such as cell division, migration, chemotaxis, proliferation, and extracellular matrix production. Growth factor activity: platelet-derived growth factor (PDGF) promotes angiogenesis, epithelialization, and granulation tissue development. Transforming growth factor (TGF) regulates bone cell metabolism and promotes extracellular matrix formation. Angiogenesis is promoted by vascular endothelial growth factor (VEGF). VEGF promotes cell differentiation and induces angiogenesis, re-epithelialization and collagenase activity. Fibroblast growth factor (FGF) stimulates fibroblast and endothelial cell growth and also promotes angiogenesis.[11,12]

The goal of using platelet-enriched preparations is to promote tissue regeneration by releasing platelet-derived substances in a "supra-physiological" manner at the treatment site. When PRP begins to act, the local tissue in contact with it benefits from the specific actions of the growth factors, which can interact both collectively and individually with various extracellular matrix proteins and cell surface receptors. PRP is derived from the centrifugation of autologous whole blood and contains a platelet concentration 3 to 5 times higher than that of normal whole blood.[13,14]

PRP is synthesized from autologous whole blood, which contains a higher concentration of autologous platelets than normal. Numerous tissue problems, including osteoarthritis, muscle strains, bone healing, and tendon injuries, have been successfully treated in clinics with PRP. In sports medicine, PRP has been successfully used as a therapeutic method to restore damaged muscles.[15-17]

The objective of this study was to evaluate the decrease in pain using visual analogue score (VAS score) at 1, 2, 3 and 6 months following first injection of leucocyte poor platelet rich plasma in patients of osteoarthritis knee in age group more than 40 years of age. Patients were evaluated based on clinical outcomes, using the knee injury and osteoarthritis outcome scores (KOOS) at 1, 2, 3 and 6 months after first injection of leucocyte poor platelet rich plasma. Also, to assess the complications of intraarticular injections of leucocyte poor platelet rich plasma in osteoarthritis knee patients.

METHODS

This prospective study was conducted at Geetanjali medical college and Hospital between July 2021 and August 2022 after being approved by the institutional ethics and research committee.

Patients were followed up until 6 months after the first PRP injection. Written informed consent was obtained from all participants.

Sampling procedure

Consecutive random sampling was employed.

Inclusion criteria

All patients presenting to the orthopedic outpatient department with knee pain in the age group 40-80 years with knee arthralgia (>3 months) and radiological evidence of articular damage with Kellgren-Lawrence grade 1 and 2. Also, the patients with desired activity level

and pain not achieved despite three months of treatment with NSAIDS.

Exclusion criteria

Systemic disease such as rheumatoid arthritis, malignant cancer, hematologic disease, infection, or immunodeficiency history. Recent intra-articular injection of corticosteroids and HA in the past 2 weeks. Recent administration of anticancer drugs or immunosuppressive drugs.

Technique of PRP injection

The indications for intraarticular PRP injection in our study were knee OA of radiological KL grade I- II in knees with <5 grade genu varum or valgum deformity with knee arthralgia for more than 3 months. The contraindications for intra-articular PRP knee injections in our study were critical thrombocytopenia, overlying skin infection, adjacent osteomyelitis, nonsteroidal anti-inflammatory drug (NSAID) use within 2 weeks before the procedure, corticosteroid injection into the knee within 3 months, or systemic corticosteroid use within 2 weeks.

Venipuncture was performed in all participating patients; 40 ml of venous blood was collected from the antecubital vein and collected in sterile tubes containing acid citrate dextrose (ACD). In our study, we prepared PRP according to the method PRP.[18]

In this method, the collected blood was first spun at 2000 rpm for 4 minutes. Then, the supernatant platelet-containing plasma was transferred to another sterile 10 ml tube (without anticoagulant). This tube was then centrifuged at a second rapid spin at 2000 rpm for 10 minutes to obtain a platelet concentrate. The lower third of the tube contained the PRP and the upper 2/3 contained platelet-poor plasma (PPP), which was aspirated with a pipette and discarded. The platelet pellets formed at the bottom of the tube.

These freshly prepared 3 ml PRP were injected into the affected knee via a classic lateral approach under full aseptic precautions. After injection, the knee was passively flexed 20 times to ensure even distribution of PRP in the joint. The patient was then discharged home after 15-20 minutes of rest. One tablet of paracetamol 325mg was prescribed based on SOS. All patients were instructed to use cold packs for 10 minutes 3-4 times daily for up to 72 hours. A total of 3 PRP injections were given 1 month apart. Injections were administered by an independent physician who was not involved in patient assessment or data collection and analysis.

All blood samples, samples from PPP, and PRP were analysed for complete blood count using an automated cell counter (Sysmex).

The methodology has been illustrated in Figures 1-4 below.

Figure 1: PRP being prepared from autologous blood in a centrifugation machine in ACDA vial.

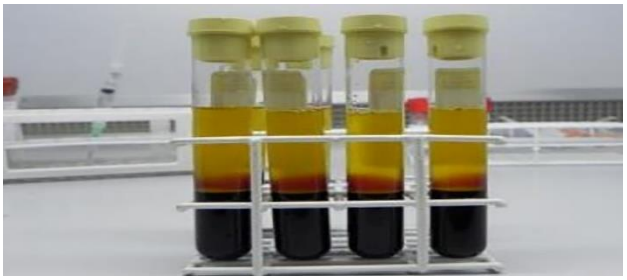

Figure 2: PRP- post centrifugation.

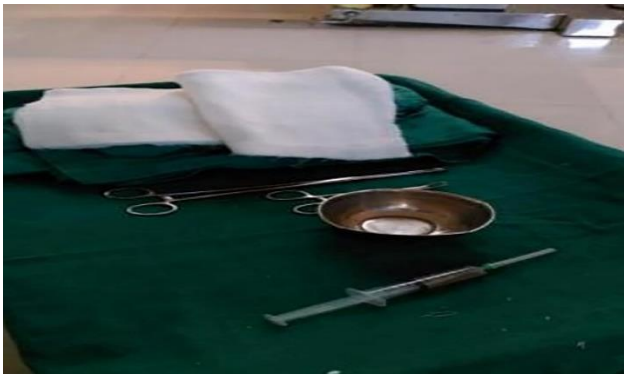

Figure 3: Sterile Instruments, drapes and PRP injection ready to inject.

Figure 4: PRP injection being injected in Medial Suprapatellar fossa of the knee under total Aseptic conditions.

A schedule for evaluation

Patients were evaluated using the knee injury and osteoarthritis outcome scores (KOOS) and the visual analogue scale (VAS): pre-injection- first visit. First follow-up 1 month after the first injection. Second follow-up 2 months after the first injection. Third follow-up 3 months after the first injection. Follow-up 6 months after the injection.

Outcome assessment tools

The KOOS score and the VAS score were assessed in person before the first injection, during the subsequent months, and at the follow-up examination 6 months after the injection. The assessment was performed by an orthopedic specialist who was not involved in the study.

The knee injury and osteoarthritis outcome score (KOOS) is a questionnaire used to assess short- and long-term patient-relevant outcomes after knee injury. The KOOS is self-completed by patients and measures five aspects: pain, symptoms, activities of daily living, sports and recreational function, and knee-related quality of life. The KOOS meets the basic criteria for outcome measures and can be used to evaluate the progression of a knee injury and treatment outcome. The KOOS is self-completed by the patient, the format is user-friendly, and it takes approximately 10 minutes to complete.

Instructions for evaluation

The five patient-relevant dimensions of the KOOS are evaluated separately: pain (nine items); symptoms (seven items); ADL function (17 items); sports and recreational function (five items); quality of life (four items). A Likert scale is used, and all items have five possible response options ranging from 0 (no problems) to 4 (extreme problems), with each of the five scores calculated as the sum of the included items.

Interpretation of results scores are converted to a scale ranging from 0 to 100, with 0 representing extreme knee problems and 100 representing no knee problems, as is common in orthopedic scales and general measurements. Scores between 0 and 100 indicate the percentage of the total score obtained.[19]

The visual analogue scale is a psychometric subjective response scale labelled on a 100 mm line with numbers from “0” to “10”, where “0” indicates no pain, “1-2” indicates mild pain that can be ignored, “3-4” indicates moderate pain that interferes with tasks, “5-6” indicates moderate pain that interferes with concentration, “7-9” indicates severe pain that interferes with basic needs, and “10” indicates the worst possible pain that warrants bed rest. Patient-reported adverse events, if any, were recorded at each visit.

Demographic variables such as age, sex, BMI, and KL classification were recorded for each patient.

Statistical analysis

The sample size was calculated to be 50 with a 95% confidence interval, assuming a prevalence of OA knees of 39% with an absolute precision of 2%. Based on these results, a sample was designed with an α value of 0.05 and a power (1 - β) of 0.80.

RESULTS

Age group 40-50 contributed to the majority of the patients (39%) followed by age group 50-60 was the next largest group.

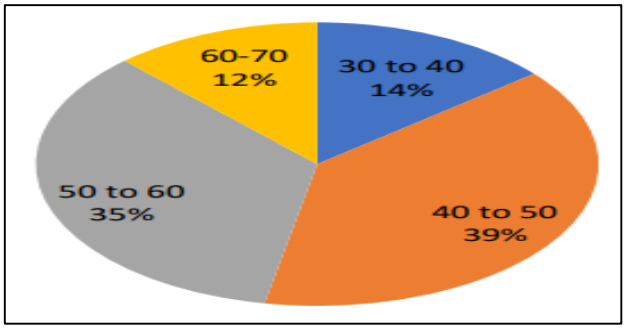

Figure 5: Age group distribution.

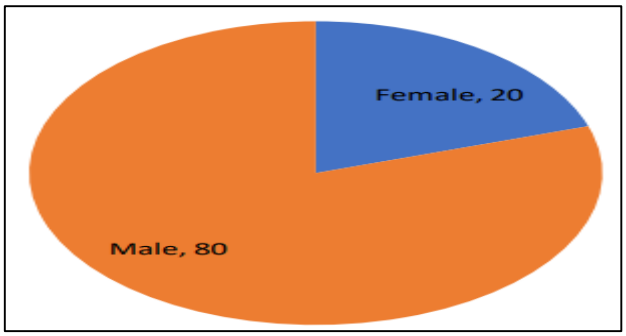

Figure 6: Sex distribution.

Majority of the patients in the study group consisted of male patients. i.e. 80%.

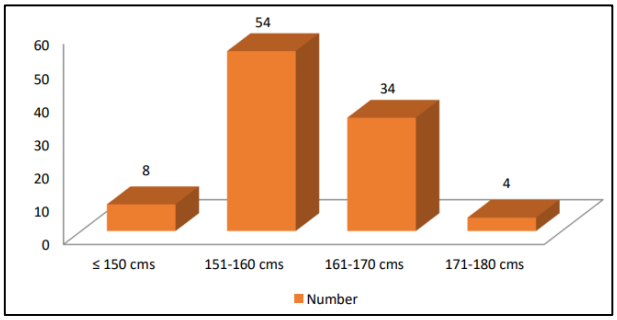

Figure 7: Height distribution.

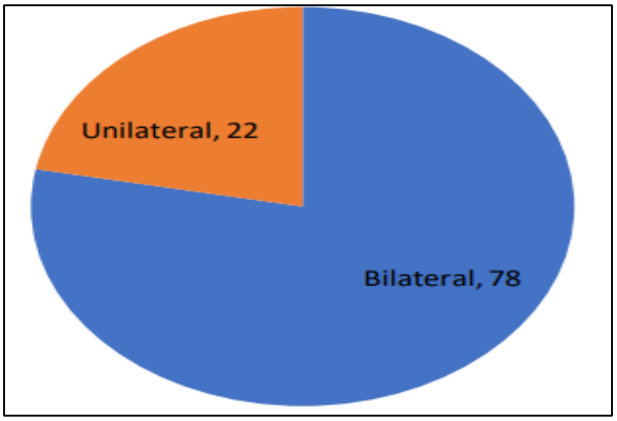

Figure 8: Side of the knee affected.

The majority of the patients consisted of height group 151-160 cm in our study group. A total of 78 patients underwent bilateral knee injections and 22 underwent unilateral knee injections. Out 22 unilateral knees there were 15 left sided knees and 7 were right sided knees.

Table 1: Number of cases according to BMI.

BMI Distribution	Number	Percentage
Underweight (≤18.49)	0	0
Normal (18.50-24.99)	22	22
Overweight (25-29.99)	66	66
Obese	12	12
Total	100	100

The majority of patients were overweight (BMI 25 to 29.99), or 66% (Table 1).

Overall comparison of the mean VAS score before injection, at 1st, 2nd, and 3rd follow-up was made. A significant decrease in scores was observed at successive follow-up visits after 6 months (Table 2).

Table 2: Comparison of VAS score at pre-injection, 1st, 2nd, 3rd follow-up and post-injection score.

VAS score	Pre-injection	At 1st follow-up	At 2nd follow-up	At 3rd follow-up	Post- injection (6 months)
N	100	100	100	100	100
Mean	7.22	6.25	5.37	4.31	3.06
SD	0.965	0.942	0.901	0.891	1.223
P value	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001

Table 3: Comparison of KOOS score at pre-injection, 1st, 2 nd, 3rd follow-up and post-injection score.

KOOS score	Pre-injection	At 1st follow-up	At 2nd follow-up	At 3rd follow-up	Post-injection (6 months)
N	100	100	100	100	100
Mean	33.4	47.68	62.46	74.20	78.46
SD	7.51	8.07	6.53	4.82	8.80
P value	P≤0.0001	P≤0.0001	P≤0.0001	P≤0.0001	P≤0.0001

Overall comparison of mean KOOS score before injection, at first, second, and third follow-up at 6 months. A significant decrease in score was noted at successive 6-month follow-ups. In addition, no complications were noted with intra-articular injection of PRP for early-stage osteoarthritis (K-L grades 1 and 2) (Table 3).

DISCUSSION

The present study evaluated the outcome of intra-articular PRP injections in 100 patients (178 knees) with mild to moderate knee OA. After the intervention, VAS and KOOS scores were shown to significantly decrease 6 months after the injection ($p<0.05$). The final follow-up scores for the different grades of KL were not significantly different from each other, but this was a significant difference before the intervention, with worse outcomes for the higher grades of KL. Variables such as age, sex, BMI, KL grade, baseline VAS, and baseline KOOS did not predict final outcomes. Preinjection and 6-month postinjection outcomes VAS and KOOS scores were positively correlated.

The role of PRP in the treatment of osteoarthritis to improve clinical outcomes has been well documented in many studies.[20-22]

Our study is consistent with the study by Gobbi et al.[23] PRP In their study of 93 patients (113 knees), they found that there was a significant reduction in pain and improvement in function after 12 months, which can be further improved after 18 months by repeating the treatment annually. They also concluded that the beneficial effects were not sustained after 2 years, but that the results were encouraging compared with function before treatment. In the present study, no repeat intra-articular injection PRP was administered during the 6-month follow-up period. KOOS and VAS scores decreased significantly from baseline even at 6 months, indicating improvement in symptoms up to 6 months.

Mendia et al concluded in their study that triple infiltration of PRP was more clinically effective than single use at 48 weeks follow-up in patients with mild knee osteoarthritis. Huda et al. conducted a study of 50 patients (92 knees) and concluded after 12 months of follow-up that three injections of PRP one month apart were both safe and effective as a treatment modality for KL grade I, II, and III OA knees.[24,25]

The available literature on the injection protocols of PRP is so heterogeneous that there is no general consensus on the number and frequency of injections, and many results on single vs. double or single vs. triple injections are conflicting, with many favoring single and others triple injections.[26]

Gobbi et al administered 3 intra-articular injections of PRP at monthly intervals.[23] In our study, we also administered injections at monthly intervals.

Filardo et al repeated three injections at 3-week intervals.[27]

Patel et al conducted a study in which they divided patients into three groups and followed them for up to 6 months. Group A received one injection of PRP, group B received 2 injections of PRP at 3-week intervals, and group C received one injection of saline (placebo). They concluded that a single dose of WBC-filtered PRP at a concentration equivalent to 10 times the normal amount was as effective as two injections in relieving symptoms in early knee OA and that PRP was better than placebo.[15]

In their study, Filardo et al administered three weekly intra-articular injections of leukocyte-depleted PRP to 45 patients (51 knees) and followed the patients to a median duration of 14.5 months (6-24). They had divided patients into two groups: one with early/moderate OA (KL grade 0-III) and one with severe OA (KL grade IV). The clinical outcomes were positive in both groups, with the patients with early/moderate OA showing a better clinical outcome than the patients with severe OA. They concluded that low-leukocyte, low-concentration PRP injections in patients with early/intermediate OA are a safe conservative procedure that can reduce pain and improve the functional status of the knee.[28]

Chang et al showed in a meta-analysis that participants with lower degrees of degeneration benefited more from PRP injections, while in our study there was a significant improvement in final scores, i.e., at 2-year follow-up, across all KL grades.[29]

In the present study, we had mild to moderate grade of OA (KL grade I-II), and we did not find significant differences in outcome between the two groups at 6-month follow-up, although there were significant differences at baseline and 6-month follow-up. This suggests that the improvement in the long term (6 months) is similar for KL grade I, II, and II OA.

No serious adverse events occurred after intra-articular injection PRP. Also, no other complications such as infections, local edema, and joint stiffness at the injection site were noted.

In contrast to our study, Filardo et al, Aquerizo et al, and Sampson et al reported a transient increase in pain after injection and showed a better outcome after three PRP injections one month apart.[27,28,30]

All KOOS parameters (pain, stiffness, and physical function) had significantly improved at the 6-month follow-up. KOOS and VAS scores decreased significantly at 6 months compared with baseline.

Study limitations include the lack of a placebo group. A double-blinded study would have been better. Although PRP showed significant functional improvement, the association with actual changes in articular cartilage could have been investigated by imaging studies such as MRI.

CONCLUSION

Our study focused on injecting a highly concentrated platelet mixture into the joint cavity and observing patients for improvement in physical function and a decrease in pain and knee stiffness. After our study, patients' lifestyle habits improved significantly, and their pain and stiffness consistently decreased. The mean VAS before injection was 7.22±0.965 and decreased to 3.06±1.223 at 6-month follow-up, indicating that pain decreased significantly after three injections (PRP) one month apart. The mean KOOS score before injection was 33.4±7.51, which increased to 78.76±8.80 at 6-month follow-up, indicating a positive functional and clinical outcome from three PRP injections at 1-month intervals.

Platelet-rich plasma has emerged as an interesting therapeutic option for knee osteoarthritis, and our study demonstrated that it is effective during a 6-month follow-up period. In our study of 100 patients with early stage osteoarthritis (K-L grades 1 and 2) treated with three injections of PRP one month apart, no major complications or infections occurred.

Recommendations

Although the use of PRP for treating knee OA appears to be beneficial, methodological issues and significant heterogeneity between studies are obvious. To further evaluate the effectiveness and longevity of PRP treatment for patients with knee OA, large RCTs are required. The lack of standardization is the biggest barrier to PRP application, and more study is needed to understand how leukocyte inclusion, activation, and platelet concentration affect therapeutic efficacy. Further study is required on the cost-effectiveness of PRP, the population most likely to benefit, and the ideal PRP regimen. This means that before this effective treatment can be widely used, optimization

is still needed with regard to timing, dosage, volume, frequency, formulation, and post-injection rehabilitation.

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