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ORIGINAL ARTICLE

Serial Platelet-Rich Plasma Intra-articular Injections in Kellgren and Lawrence Grade IV Knee Joint Osteoarthritis: A Prospective Blinded Placebo-Controlled Interventional Study

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Abstract

Purpose The purpose of this study was to evaluate whether serial intra-articular (IA) Platelet-Rich Plasma (PRP) injections improve pain and function in patients of Kellgren–Lawrence (K–L) Grade IV primary knee osteoarthritis (KOA), not willing for arthroplasty or having relative contraindications to surgery.

Methods 90 patients (84 available at final follow-up) of Grade IV KOA were given 3 PRP or Normal Saline injections at 1-month interval. Pain and functional assessment was done with Visual analog scale (VAS) and Western Ontario and McMaster universities osteoarthritis index (WOMAC) respectively, at baseline and then at three and six months of follow-up. Both groups were homogenous with similar baseline characteristics.

Results Both groups showed statistically significant improvements in the outcome scores but only PRP showed minimal clinically important difference (25% in WOMAC and > 2 cm difference of mean in VAS at follow-up). For inter-group comparison, PRP showed better results as there was statistically significant difference in WOMAC at 3 months (Difference = −9.220, 95% CI = −13.1945 to −5.2455, $P < 0.0001$) and at 6 months (Difference = −10.360, 95% CI = −14.5358 to −6.1842, $P < 0.0001$). Similar results were seen for VAS also (Difference = −0.580, 95% CI = −1.1412 to −0.0188, $P = 0.04$ at 3 months, Difference = −0.870, 95% CI −1.3993 to −0.3407, $P = 0.001$ at 6 months). Outcome scores significantly correlated with age and sex but not with body mass index (BMI).

Conclusion Serial Intra-articular Injections of autologous PRP mildly improve short-term subjective pain and knee function scores in patients of Grade IV KOA without any major complications.

Keywords Knee osteoarthritis · Kellgren–Lawrence (K–L) grading · VAS · WOMAC · Platelet-rich plasma (PRP)

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Introduction

The most common joints affected by osteoarthritis is knees, followed by hips, joints of hand and spine. Knee osteoarthritis (KOA) constitutes 85% of the global disease burden of osteoarthritis and tenth leading cause of non-fatal burden [1, 2]. The main risk factors for primary osteoarthritis (OA) include old age, female gender, African American race, obesity, and genetic predisposition [3]. KOA presents clinically as pain, crepitus, deformity, limitation of movement and occasionally effusion, and adversely affects quality of life of a patient. Radiographically, the grading of the severity (grade I–IV) is done with Kellgren–Lawrence (K–L) system based on joint space reduction and osteophyte formation [4]. In K–L Grade IV KOA, large osteophytes are seen with sclerosis and bony deformity and the articular cartilage is

markedly destroyed, which is seen on radiographs as severe narrowing of joint space.

Unlike the early grades of KOA where the main goal of treatment is to prevent or to slow the further degradation of joint, the aim of management in Grade IV KOA is to improve quality of life by combating pain, stiffness and improving mobility. The treatment of choice for Grade IV KOA is total knee arthroplasty (TKA); however, a large proportion of people in the middle and lower-income countries are not willing to undergo TKA due to lack of financial support and fear of invasive surgery. The non-operative management options for these patients include both pharmacological (oral, topical and intra-articular) and non-pharmacological methods (bracing and other mobility aids, exercises, lifestyle modification). The commonest drugs prescribed for this group of patients are NSAIDs (non-steroidal anti-inflammatory drugs). They act by inhibiting prostaglandin synthesis (cyclooxygenase inhibitors) which is the first step in inflammatory processes. The long-term use of these drugs may cause gastrointestinal ulcers, serious cardiovascular events, hypertension, renal failure, and worsening of pre-existing heart failure. Since these patients are elderly and might have multiple co-morbidities, the potential for adverse effects with long-term NSAIDS use is high [5]. The other oral medications used in these patients are opioids and non-opioids (acetaminophen, collagen, chondroitin, Diacerin).

Intra-articular (IA) injections have the ability to provide symptom relief with minimal complications. Steroids, hyaluronic acid (HA) and Platelet-Rich Plasma (PRP) are most commonly used for this purpose. The use of autologous PRP in KOA has risen drastically in recent years. The concentration of platelets is very high in PRP and the growth factors released by platelet alpha granules not only have favorable effects on chondrocytes and mesenchymal stem cell (MSC) proliferation but also have anti-nociceptive and anti-inflammatory properties via inhibition of nuclear factor kB [6–8]. Studies have reported favorable pain and function outcomes with intra-articular PRP injections in KOA, compared to placebo and other IA therapies, particularly in early grades [9–18].

There are only a few studies that have evaluated autologous PRP as a therapeutic measure for patients with advanced OA knee [19]. In this prospective hospital-based Placebo-Controlled, Blinded Interventional Study, we set out to evaluate whether the serial injections of PRP can improve the subjective function and pain scores in patients suffering from K–L Grade IV OA knee who are not willing to undergo arthroplasty and/or patients having relative contraindications.

Materials and Methods

This study was conducted from May 2019 to November 2021 in a tertiary care center after due approval from institutional review board (IRB).

Inclusion Criteria

Patients of radiographically confirmed K–L Grade IV KOA who were not willing for total knee replacement and those in whom total knee replacement is relatively contraindicated.

Exclusion Criteria

Patients with a history of knee surgery within 3 months**,** active knee infection and malignancy**,** Anemia, Bleeding Disorders**,** uncontrolled Diabetes Mellitus**,** secondary osteoarthritis, knee instability (Tested clinically)**,** and the patients on NSAIDS during the preceding 3 weeks.

Study Design

A sample size calculation was done and the minimum required number was found to be 79 patients.

Patients complaining of knee pain attending the outpatient department of orthopedics were screened. Standing anteroposterior and lateral radiographs of knees were obtained and they were graded according to K–L system. A total of 90 patients of K–L Grade IV OA knee fulfilling the inclusion criteria were initially enrolled after obtaining permission from Institutional Ethics Committee (IEC). These patients were assigned randomly (computer-generated sequences) to one of the two groups: the study group (PRP group) and the control group (NS: Normal Saline group). Written informed consent was taken from all patients as per IEC guidelines. Three injections of autologous PRP or NS were administered into the knee joint at an interval of one month by a single surgeon in a properly curtained cubicle not allowing him to know the identity of patient. Patients were also blinded to the treatment received. Similar syringes and an equal amount of PRP/saline was used.

Assessment of pain was done with VAS (VISUAL ANALOG SCALE [20], which was measured on a 10 cm line with extremes of 10 and 0 being the worst possible pain and no pain respectively while 5 was moderate pain.

Function was assessed using WESTERN ONTARIO AND MCMASTER UNIVERSITIES OSTEOARTHRITIS INDEX (WOMAC) [21] having a total score of 96. Higher the score, the worst is the function or symptoms.

Baseline (Pre-intervention) assessment of these scores was done, and then in 3rd and 6th month of follow-up by an

independent accessor not involved in the procedure. Body mass index (BMI) was also calculated. 84 patients in total (41 in NS group and 43 in PRP group) were available for assessment at final follow-up as 6 patients were excluded because they took pain medications for a time period during follow-up.

Method of PRP Preparation

Platelet-Rich Plasma was made by PRP Method [22] with the help of Centrifuge Machine Yorko, available in our Department of Pathology Blood Bank. 34–42.5 ml blood in 8.5 ml acid citrate dextrose (ACD) tubes was collected from antecubital vein from each patient following all aseptic precautions. Then the blood was centrifuged @3000 rpm using a soft spin for 3 minutes. To obtain a concentrate rich in platelets, the supernatant plasma which contains platelets was then transferred to another sterile tube of 10 ml (with no anticoagulant), and was again centrifuged @ 4000 rpm using hard spin for a duration of 15 minutes. The lower one-third in this concentrate is PRP while the upper two-thirds is PPP (platelet-poor plasma). Pellets of platelets are formed at the bottom of this tube. The upper two-thirds containing PPP were discarded and the remaining PRP was suspended in 3 ml of plasma by gently shaking the tube.

Intervention and Statistical Analysis

Under all sterile conditions, the freshly prepared PRP (3 ml) or same amount of NS was administered to the affected knee, using anterolateral approach. Patients were encouraged to move the knee several times through flexion and extension to allow for the distribution of PRP. Local anesthesia was not given. Patients were observed for 1 hour and then allowed to go home after prescribing 50 mg of oral tramadol, twice in a day for five days. A total of three PRP or NS injections were administered at monthly intervals. Patients were taught quadriceps and hamstring strengthening exercises. All the patients were advised not to take NSAIDS, chondroprotective supplements or use of braces and other mobility aids and were told to continue with their routine activities.

Statistical analysis was done using statistical package for social sciences (SPSS 22.00 for windows). Significance level was set at $P < 0.05$. Tukey HSD post hoc test was used for comparison among groups and the effect of independent variables on outcome measures was studied with regression analysis.

Results

There was no significant difference of baseline WOMAC and VAS scores and demographic variables (age, sex, BMI) among the two groups ($P > 0.05$) (Table 1). We did not observe any complications during the course of treatment except for pain at the injection site which resolved within a few hours.

Table 1 Baseline parameters

	Intervention groups		*P* value
	NS	PRP	
Age (years)	63.24 ± 5.98	57.74 ± 7.41	0.51
Sex, female/male, *n* (%)	22/19,53.7/46.3	24/19,55.8/44.2	0.83
BMI (kg/m^2)	26.21 ± 4.68	26.05 ± 3.03	0.85
K–L Grade: IV, *n* (%)	41 (100%)	43 (100%)	1
WOMAC baseline	78.49 ± 6.69	81.54 ± 7.43	0.055
VAS baseline	7.90 ± 1.04	8.02 ± 1.12	0.61

NS normal saline; *PRP* platelet-rich plasma

$P > 0.05$ not significant

Outcomes Scores

WOMAC

The difference between baseline WOMAC and subsequent follow-up in 3 and 6 months reached statistical significance for both the groups ($P < 0.01$) (Table 2).

On inter-group comparison, WOMAC scores improved significantly more in the PRP group at 3 months (Difference = −9.220, 95% CI = −13.1945 to −5.2455, $P < 0.0001$) and at 6 months (Difference = −10.360, 95% CI = −14.5358 to −6.1842, $P < 0.0001$) (Table 3).

On analysis of the effect of confounding factors on WOMAC, age (RC = −0.51, 95% CI = −0.62–0.12, $P = 0.046$) and female gender (RC = −5.47, 95% CI = −11.06 to −1.94, $P < 0.01$) had statistically significant influence while as BMI had no statistically significant effect on WOMAC (RC = −0.70, 95% CI = −1.38–0.46, $P = 0.06$) (Table 6).

VAS

The improvements in VAS also reached statistical significance in both the groups compared to baseline at 3 and 6 months ($P < 0.05$) (Table 4).

Although the VAS improved slightly in PRP group and worsened in NS group from 3 to 6 months, these changes were statistically not significant ($P > 0.05$).

For the inter-group comparison, PRP showed better VAS outcome scores with statistical significance at 3 months (difference = −0.580, 95% CI −1.1412 to −0.0188, $P = 0.04$) and 6 months (difference = −0.870, 95% CI −1.3993 to −0.3407, $P = 0.001$) (Table 5).

In the analysis of possible correlations of independent variables with VAS, age (RC = −0.48,

Table 2 Intra-group WOMAC score comparison at different time points

Tukey HSD post hoc test (NS group)
Baseline vs 3 months: Diff = −8.2700, 95% CI = −13.1558 to −3.3842, *P* = 0.0003*
Baseline vs 6 months: Diff = −7.7600, 95% CI = −12.6458 to −2.8742, *P* = 0.0007*
3 months vs 6 months: Diff = 0.5100, 95% CI = −4.3758 to 5.3958, *P* = 0.9667
Tukey HSD post hoc test (PRP group)
Baseline vs 3 months: Diff = −20.5400, 95% CI = −24.6496 to −16.4304, *P* = < 0.01*
Baseline vs 6 months: Diff = −21.1700, 95% CI = −25.2796 to −17.0604, *P* = < 0.01*
3 months vs 6 months: Diff = −0.6300, 95% CI = −4.7396 to 3.4796, *P* = 0.9298

Diff difference; *CI* confidence interval

*Statistically significant

Table 3 Comparison of WOMAC score at different intervals among the groups

WOMAC score	NS group		PRP group		*t* test	*P* value
	Mean	SD	Mean	SD		
Baseline	78.49	6.69	81.54	7.43	4.89	0.052
3 months	70.22	10.51	61	7.64	21.28	< 0.01*
6 months	70.73	10.27	60.37	8.95	24.35	< 0.01*

*Statistically significant

Table 4 Intra-group comparison of VAS at different time points

Tukey HSD post-hoc test (NS group)
Baseline vs 3 months: Diff = −1.5300, 95%CI = −2.2403 to −0.8197, *P* = < 0.01*
Baseline vs 6 months: Diff = −1.2900, 95%CI = −2.0003 to −0.5797, *P* = 0.0001*
3 Months vs 6 months: Diff = 0.2400, 95%CI = −0.4703 to 0.9503, *P* = 0.7026
Tukey HSD post-hoc test (PRP group)
Baseline vs 3 months: Diff = −2.2300, 95%CI = −2.7582 to −1.7018, *P* = < 0.01*
Baseline vs 6 months: Diff = −2.2800, 95%CI = −2.8082 to −1.7518, *P* = < 0.01*
3 Months vs 6 months: Diff = −0.0500, 95%CI = −0.5782 to 0.4782, *P* = 0.9725

*Statistically significant

Table 5 Comparison of VAS at different intervals among the groups

VAS	NS group		PRP group		*t* test	*P* value
	Mean	SD	Mean	SD		
Baseline	7.90	1.04	8.02	1.12	0.26	0.61
3 Months	6.37	1.58	5.79	0.94	4.17	0.044*
6 Months	6.61	1.39	5.74	1.03	10.57	0.002*

*Statistically significant

Table 6 Effect of independent variables functional outcome

Variables	WOMAC score			VAS score		
	RC	95% CI	*P* value	RC	95% CI	*P* value
Age	−0.51	−0.62–0.12	0.046*	−0.48	−0.52–0.09	0.002*
Gender						
Male	Ref			Ref		
Female	−5.47	−11.06 to −1.94	< 0.01*	−4.99	−10.36 to −1.68	0.006*
BMI	−0.70	−1.38–0.46	0.06	−0.77	−1.23–0.38	0.13

RC regression coefficient; *CI* confidence interval

*Statistically significant

95%CI = −0.52–0.09, $P = 0.002$) and female gender (RC = −0.499, 95%CI = −10.36–1.68, $P = 0.006$) showed significant correlation while as BMI did not (RC = −0.77, 95%CI = −1.23–0.38, $P = 0.13$) (Table 6).

Discussion

The important findings of this study are that the clinical outcome scores of VAS and WOMAC were significantly better with serial intra-articular PRP injection therapy than with placebo at 3 and 6 months of follow-up in Grade IV KOA. VAS and WOMAC continued to slightly improve in the PRP group and worsened in the Saline group from 3 to 6 months, but the change was statistically not significant.

It was interesting to see that the VAS and WOMAC scores improved in NS group also, which suggests that there was a placebo effect, affirming the role of placebo from previous studies [23, 24]. This also shows that there was a lack of investigator bias. The mechanism of how a placebo effect works has been a matter of debate for years and is poorly understood. The possible explanations include a neurobiological (activation of endogenous opioids and non-opioids) and psychological (expectancy and conditioning) mechanisms [24]. The simple awareness of being treated considerably enhances the overall analgesic effect of placebo. The Placebo-Controlled trials are considered to be the gold standard for evaluating the efficacy of a drug/treatment as it proves that the efficacy of the treatment is beyond and above the neuropsychological result of belief in the ability of drug to cure.

The patients and clinicians consider improvement in WOMAC as clinically significant (minimal clinically important difference; MCID) if the change is 12% of baseline or 6% of the maximum value [25]. Our results showed that such clinically significant improvement was seen in PRP group (25.2% of baseline in PRP group vs 10% in NS group). In the case of VAS, although the MCID varied greatly between studies, it is understood to be a difference of 2 cm (20 mm) (difference of mean) between two time points for patients with VAS of more than 7 [26, 27]. In our study, although the absolute mean VAS scores were above 5.5 in both groups, the difference in mean as compared to baseline, was more than 2 cm only in PRP group at 3 and 6 months, showing PRP may provide some clinically significant symptomatic benefit in these patients.

The exact cause of OA remains unknown, but the major mechanism of articular cartilage damage is thought to be an imbalance in anabolic and catabolic processes, resulting in the breakdown of primary cartilage components including type II collagen and accompanied by inflammation of synovium, synovial fluid, and bony changes as well [28]. This leads to the release of cytokines like IL (interleukin), matrix metalloproteinases, tumor necrosis factor (TNF) alpha, nitric oxide, and prostaglandins which are pro-inflammatory [28]. These chemical mediators not only trigger joint degradation but also lead to inadequate synthesis of proteoglycans, collagen, anti-inflammatory cytokines (IL-10, IL-4), and growth factors [28]. The hallmark of KOA is pain and the subchondral bone, synovium, joint capsule, periarticular ligaments, and periarticular muscle are all richly innervated and are the likely source of pain in OA [29]. Our study has shown that PRP can provide short-term symptom relief even in Grade IV KOA, possibly because of its anti-inflammatory and anti-nociceptive properties.

The patients in our study were predominantly female (55%). In our analysis of possible confounding factors, we observed that age and female gender significantly affected both the outcome variables (outcome scores were better in younger and female patients). This is in contrast to findings by Patel [11] and Reissadeit et al. [12] who reported age not to be a significant factor in the outcome scores but Kon et al. [17] found PRP to be more effective in younger patients. Other studies have found no differences between sexes and these studies had a greater proportion of female participants [9–13, 19]. There is also a lack of consensus on influence of BMI on outcomes after intra-articular PRP injection therapy with some authors [17] reporting better results with low BMI and others [11] have reported no effect of BMI. The mean BMI in our study was 26.1 kg/m^2 and BMI had no effect on the outcome in our study.

There are only a few studies in the literature evaluating the role of PRP in advanced grades of KOA. McLarnon et al. [16] in their meta-analysis of studies comparing PRP with steroids found that only 9% of the studies had Grade IV OA knee. Jupert et al. [19] compared the results of IA steroid injections with PRP in K–L grade III, IV KOA. Only single injections were given in this study and the target enrollment was not achieved in control group. They found that VAS did not differ significantly among groups but the function scores were significantly better in PRP group. They reasoned that it was because the majority of patients in that study were female (72%), older (mean age 67 years), mean BMI was higher (31 kg/m^2) and 58% of patients had K–L Grade IV KOA and the authors suggested that reduction in pain in cases of late-stages of OA knee could be achieved with serial injections having high concentrations of PRP. Raeissadat et al. [12] concluded that pain and function scores (WOMAC) improved significantly in PRP group than hyaluronic acid group, which was independent of grade but only 14% of patients with Grade IV KOA were included. In another study [13] with 24% of Grade IV KOA patients, the authors reported that there was a meaningful improvement in pain over 3-month period after three weekly PRP injections, but this study lacked a control group. They observed

that reduction in pain response was better in individuals with early grades.

There is also conflicting evidence with regard to frequency of injections. Some studies [15] and meta-analysis [16] have found that triple weekly injections of PRP produced superior symptomatic relief than one PRP or steroid injection and benefit was most pronounced at 6 months. Others have injected PRP at monthly intervals with benefits lasting up to 2 years in patients with grades I, II, III KOA [30].

In our study, we have recruited patients with Grade IV OA knee only and they were administered with monthly PRP/NS injections for three months. At follow-up of 3 and 6 months, although significant improvements were observed in outcome measures (WOMAC and VAS) in both the groups, PRP group showed better results than NS.

The complications reported are pain, erythema, and synovitis [11, 16, 19]. We did not observe any major complications apart from injection-related pain in some patients which resolved spontaneously within a few hours.

The limitations of our study were that, the sample size was small and we did not measure the concentration of platelets in PRP. The outcome scores were patient-reported rather than being objective. Large multi-center randomized clinical trials using a therapeutic regime with objective outcome measures and the use of modern and highly sensitive imaging techniques and or inflammatory biomarkers to assess outcomes, are needed to further evaluate the efficacy of PRP injections in treatment of patients with advanced grades of degeneration.

Conclusion

In conclusion, our findings have shown that serial PRP injections are safe, minimally invasive treatment modality for advanced OA knee, providing clinically significant symptom improvements in the short term for patients not willing to undergo TKA.

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Declarations

Conflict of Interest We do not have any conflict of interest to declare.

Ethical Approval The study was conducted only after obtaining permission from the institutional review board (IRB) and the authors have maintained conformity to the ethical guidelines of the Helsinki declaration (as revised in Tokyo 2004).

Consents Consent was taken from all the patients included in the study for the intervention as well as for publication of data. We have not made any studying advertisement and neither any remuneration was offered.

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