

ORIGINAL RESEARCH

A Prospective Study of Intra- Articular Injection of Platelet Rich Plasma (PRP) in Knee Osteoarthritis

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ABSTRACT

Background: Osteoarthritis (OA) is a degenerative disease characterized by joint damage, inadequate healing response, and progressive deterioration of joint structure, often affecting the knee and / or hip joint. PRP is an autologous preparation containing concentrated bioactive factors⁴. It is easily derived from the blood by the simple technique of centrifugation.

Materials and Methods: 100 patients presenting to the Orthopedics outpatient department with symptomatic knee osteoarthritis of grade 1-3 of Kellgren-Lawrence classification⁶ were selected for the study according to inclusion and exclusion criteria, out of which 20 patients lost to follow up, so 80 patients included in this study. All 80 patients were subjected to Western Ontario and McMaster Universities Osteoarthritis Index Score (WOMAC) for pain evaluation and functional outcome.

Results: At pre-treatment, the mean WOMAC score was lowest in grade 1 patients while it was highest in grade 3 patients. In post-treatment evaluation, the mean WOMAC scores obtained in grade 1 and grade 2 patients showed a reducing trend at each follow-up visit. Kellgren-Lawrence grade 1 values reduced from 76.269 at pre-treatment evaluation to 38.423 after 12 months of treatment. Similarly, in grade 2 patients, the mean WOMAC reduced from 77.830 at pre-treatment to 47.617 after 12 months. This signified an improvement observed in the patients' symptomatology. However, no such decline was seen in the mean WOMAC scores of grade 3 patients. The pre-treatment 78.143 and post-treatment 78.000 values remained almost the same. The results obtained concluded that injection of autologous PRP is indeed an effective treatment modality for Kellgren-Lawrence grade 1 and grade 2 osteoarthritis at least for the 12 months, and had satisfactory effects in reducing pain and stiffness, as well as in restoring joint function. In advanced stages (Kellgren-Lawrence grade 3) of the disease, not much improvement was seen even after PRP therapy.

Conclusion: Injection of autologous PRP is indeed an effective treatment modality for Kellgren-Lawrence grade 1 and grade 2 osteoarthritis. It had satisfactory effects in reducing pain and stiffness, as well as in restoring joint function. PRP is a safe, simple,

economic, and efficacious modality in the treatment of Kellgren-Lawrence grade 1 and grade 2 osteoarthritis.

Keywords: PRP (Platelet Rich Plasma), PPP (Platelet Poor Plasma), WOMAC SCORE (Western Ontario and McMaster Universities Osteoarthritis Index Score) OA (Osteoarthritis).

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INTRODUCTION

Around the world, osteoarthritis is the foremost cause of physical morbidity. It also causes a marked decrease in quality of life.^[1] Patients present with symptoms of pain, swelling and stiffness. Osteoarthritis is defined pathologically, being distinguished by focal areas of loss of articular cartilage within a synovial joint, accompanied by sclerosis of the underlying bone and varying degree of change in other joint tissues. It has a multifactorial etiology which includes the following: age, genetic predisposition, female gender, preceding trauma, obesity and idiopathic.^[2]

The role of articular cartilage is to permit efficient load bearing and distribution in synovial joints, as well as to limit friction. Chondrocytes, present in the cartilage, are solitary cell-type responsible for producing the extra cellular matrix (ECM). Cartilage is made up of 5% of chondrocytes, 25% of ECM and 70% of water. The cartilage is avascular, aneural and alymphatic.^[3] It is due to these properties that cartilage has a very low intrinsic regenerative capacity. Its natural repair mechanisms are insufficient and ineffective. This explains why cartilage is susceptible to developing osteoarthritis and why damage advances with time.

PRP is an autologous preparation containing concentrated bioactive factors.^[4] It is easily derived from the blood by the simple technique of centrifugation. Platelets have an important role in tissue homeostasis as well as tissue healing and restoration. This is due to the fact that platelets contain a large number of growth factors, cytokines, and bioactive proteins. Studies have shown that PRP techniques have helped increase cell proliferation, migration, differentiation, inflammation mediation and matrix synthesis.^[5]

The aim of this study was to evaluate the clinical effects and safety of intra-articular injection of platelet rich plasma in osteoarthritis of the knee joint.

MATERIALS & METHODS

This study was conducted in between February 2019 to August 2021. It is a prospective observational study. 100 patients presenting to the Orthopaedics outpatient department with symptomatic knee osteoarthritis of grade 1-3 of Kellgren-Lawrence classification were selected for the study according to inclusion and exclusion criteria, out of which 20 patients lost to follow up. So, 80 patients included in this study, out of which 44 were male and 36 were female, were treated with three intra-articular injections of autologous platelet-rich plasma (PRP) at 0,1,2 months. These patients were followed up for a minimum period of 12 months.

Inclusion criteria:

- Age of patients between 40 to 80 years.
- Grade 1 -3 of knee joint osteoarthritis as per the Kellgren- Lawrence classification.^[6]
- Symptoms persisting for more than 3 months treated conservatively.
- Ability of patients to understand and give informed consent.

Exclusion criteria:

- Patient previously operated in the same knee.
- Patients formerly treated with injections of PRP and hyaluronic acid.
- Patients who have received steroid injections within past 6 months.
- Patients with ongoing infections and on antibiotics.
- Immunocompromised patients.
- Patients with secondary osteoarthritis.
- Patients with connective tissue disorders.
- Patients with inflammatory disorders of joints.
- Patients with tumors or metabolic disease of bone.
- Patients with grade 4 OA Kellgren-Lawrence classification.
- Patients with low platelet count.
- Patients on Antiplatelet therapy.

All the patients included in the study were sent for further radiographic evaluation. The standard radiographic evaluation included standing AP view, lateral 30-degree flexion view and skyline patellofemoral view of the affected knee. The patients were classified according to the Kellgren-Lawrence classification.⁶ Following this, standard blood investigations were done which included complete blood count (CBC) including platelet count, coagulation profile, random blood sugar, RA factor, and tests for transmittable diseases before initiation of treatment.

Then, all 80 patients were subjected to Western Ontario and McMaster Universities Osteoarthritis Index Score (WOMAC) for pain evaluation. This score was taken prior to treatment, as well as subsequently at 1-, 2-, 6-, and 12-months follow-up. Procedure and preparation of platelet-rich plasma was done using the double-spin method as follows.

20 ml of venous autologous whole blood was collected, maintaining all aseptic precautions, into tubes containing tri-sodium citrate as anticoagulant. The collected blood was then spun down using Autologous Platelet Separator System at 1000 rpm (soft spin) for a duration of 10 minutes. This first spin yielded three layers to separate red blood cells at the bottom of the tube, buffy coat containing white blood cells in the middle and plasma layer above. The portion of plasma was transferred into another plain tube, not containing anticoagulant, and centrifuged a second time at 2000 rpm (hard spin) for 10 minutes. This yielded a platelet-rich plasma (PRP) layer at the bottom of the tube and a platelet-poor plasma layer (PPP) in the upper part of the tube. This PPP layer was removed and calcium gluconate was added to act as an activator of PRP. The quality of PRP was maintained by ensuring that the platelet count was 10 lakh per ml in 5 ml of PRP.

Under aseptic conditions, the injection procedure was carried out in the operation theatre. The patient was placed in supine position on the operation table with the knee flexed to 90 degrees. The procedure site was painted with povidone-iodine solution and draped. A 24-gauge needle was attached to a 10 ml syringe filled with the PRP preparation composed of 8 ml of platelet-rich plasma mixed with 1 ml of calcium gluconate. Careful palpation of the anatomical landmarks of the knee joint was done and the injection site was chosen inferior to the patella. This injection site lies one centimeter proximal to the tibial plateau and lateral to the patellar tendon. It was felt as a soft spot. Keeping all aseptic precautions, the injection was given.

The skin was cleaned, and a band aid was applied over the needle-puncture site. The patient was further monitored for 15 minutes in order to watch for any adverse reactions. The patient

was then advised to do ice fomentation and avoid strenuous work, squatting or sitting crossed legged. Two further PRP injections were given to the patient following the same protocol after an interval of 1 month each.

RESULTS

Table 1: Distribution Based on Kellgren-Lawrence Classification Grade

KL Grade	Frequency	Percent
1	26	32.5
2	47	58.75
3	7	8.75
Total	80	100

Table 2: Pre And Post-Treatment Mean Womac Scores Of All three Kellgren Lawrence Grades

Time Interval	K Grade	N	Mean WOMAC	Std. Deviation
PRE	1	26	76.269	3.131
	2	47	77.830	4.365
	3	7	78.143	2.035
1 Month	1	26	63.269	5.518
	2	47	70.170	5.530
	3	7	78.000	1.915
2 Month	1	26	54.538	5.077
	2	47	63.106	4.678
	3	7	77.857	1.952
6 Month	1	26	47.615	3.395
	2	47	56.043	3.945
	3	7	78.000	2.082
12 Month	1	26	38.423	3.668
	2	47	47.617	4.932
	3	7	78.000	2.000

Table 3: Pre-Post Treatment Comparison of Mean WOMAC Scores of Kellgren-Lawrence Grade 1 Patients

Paired Samples	Time Interval	N	Mean WOMAC	Std. Deviation	T Test	P Value	Result
Pair1	Pre	26	76.269	3.131	19.807	0.000	Significant
	1 Month	26	63.269	5.518			
Pair2	Pre	26	76.269	3.131	29.823	0.000	Significant
	2 Month	26	54.538	5.077			
Pair3	Pre	26	76.269	3.131	42.185	0.000	Significant
	6 Month	26	47.615	3.395			
Pair4	Pre	26	76.269	3.131	45.823	0.000	Significant
	12 Month	26	38.423	3.668			
Pair5	1 Month	26	63.269	5.518	15.854	0.000	Significant
	2 Month	26	54.538	5.077			
Pair6	2 Month	26	54.538	5.077	10.227	0.000	Significant
	6 Month	26	47.615	3.395			
Pair7	6 Month	26	47.615	3.395			

	12 Month	26	38.423	3.668	10.398	0.000	Significant
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Table 4: Pre-Post Treatment Comparison of Mean WOMAC Scores of Kellgren-Lawrence Grade 2 Patients

Paired Samples	Time Interval	N	Mean WOMAC	Std. Deviation	T Test	P Value	Result
Pair1	Pre	47	77.830	4.365	14.072	0.000	Significant
	1Month	47	70.170	5.530			
Pair2	Pre	47	77.830	4.365	22.955	0.000	Significant
	2Month	47	63.106	4.678			
Pair3	Pre	47	77.830	4.365	35.124	0.000	Significant
	6Month	47	56.043	3.945			
Pair4	Pre	47	77.830	4.365	35.299	0.000	Significant
	12Month	47	47.617	4.932			
Pair5	1Month	47	70.170	5.530	15.401	0.000	Significant
	2Month	47	63.106	4.678			
Pair6	2Month	47	63.106	4.678	22.004	0.000	Significant
	6Month	47	56.043	3.945			
Pair7	6Month	47	56.043	3.945	12.687	0.000	Significant
	12Month	47	47.617	4.932			

Table 5: Pre-Post Treatment Comparison of Mean WOMAC Scores of Kellgren-Lawrence Grade 3 Patients

Paired Samples	Time Interval	N	Mean WOMAC	Std. Deviation	T Test	P Value	Result
Pair1	Pre	7	78.143	2.035	1.000	0.356	Non-Sig
	1Month	7	78.000	1.915			
Pair2	Pre	7	78.143	2.035	1.549	0.172	Non-Sig
	2Month	7	77.857	1.952			
Pair3	Pre	7	78.143	2.035	1.000	0.356	Non-Sig
	6Month	7	78.000	2.082			
Pair4	Pre	7	78.143	2.035	0.548	0.604	Non-Sig
	12Month	7	78.000	2.000			
Pair5	1Month	7	78.000	1.915	1.000	0.356	Non-Sig
	2Month	7	77.857	1.952			
Pair6	2Month	7	77.857	1.952	1.000	0.356	Non-Sig
	6Month	7	78.000	2.082			
Pair7	6Month	7	78.000	2.082	0.000	1.000	Non-Sig
	12Month	7	78.000	2.000			

[Table 1] shows the distribution of patients according to their Kellgren-Lawrence (KL) classification grade. The majority of patients, 58.75%, belonged to KL grade 2 group, while 32.5% belonged to KL Grade 1 and only 8.75% belonged to KL Grade 3.

[Table 2] shows the mean WOMAC scores of all three Kellgren-Lawrence grade patients at different periods of evaluation, namely pre-treatment and post-treatment follow-up at 1, 2, 6, and 12 months. At pre-treatment, the mean WOMAC score was lowest in grade 1 patients while it was highest in grade 3 patients. The mean value of grade 1 WOMAC score

was 76.269, while it was 77.830 for grade 2 and 78.143 for grade 3. This signified that the more advanced was the disease, the more pain, stiffness, and alteration of physical function was perceived by the patient.

Furthermore, in post-treatment evaluation, the mean WOMAC scores obtained in grade 1 and grade 2 patients showed a reducing trend at each follow-up visit. Kellgren-Lawrence grade 1 values reduced from 76.269 at pre-treatment evaluation to 38.423 after 12 months of follow-up. Similarly, in grade 2 patients, the mean WOMAC reduced from 77.830 at pre-treatment to 47.617 after 12 months. This signified an improvement observed in the patients' symptomatology. However, no such decline was seen in the mean WOMAC scores of grade 3 patients. The pre-treatment 78.143 and post-treatment 78.000 values remained almost the same. This implied that in advanced stages of the disease, not much improvement was seen even after PRP therapy.

[Table 3] shows the pre-treatment and post-treatment comparison of mean WOMAC scores of Kellgren-Lawrence grade 1 patients. Each follow-up visit scores obtained was compared with the pre-treatment scores and statistical test was applied. For all the pairs of time intervals, the difference in mean WOMAC values found to be statistically significant ($P < 0.05$). This implied that each difference in WOMAC scores obtained between the pre-treatment results and the post-treatment results was significant. Moreover, a significant decline between the mean WOMAC scores was seen at each subsequent follow-up visit which implicated an improvement in the patient's symptoms after treatment.

[Table 4] shows the pre-treatment and post-treatment comparison of mean WOMAC scores of Kellgren-Lawrence grade 2 patients. Each follow-up visit scores obtained was compared with the pre-treatment scores and statistical testing was applied. For all the pairs of time intervals, the difference in mean WOMAC values found to be statistically significant ($P < 0.05$). This implies that each difference in WOMAC scores obtained between the pre-treatment results and the post-treatment results was significant. Moreover, a significant decline between the mean WOMAC scores was seen at each subsequent follow-up visit which implicates an improvement in the patient's symptoms after treatment.

[Table 5] shows the pre-treatment and post-treatment comparison of mean WOMAC scores of Kellgren-Lawrence grade 3 patients. Each follow-up visits scores obtained was compared with the pre-treatment scores and statistical testing was applied. For the majority pairs of time intervals, the difference in mean WOMAC values was found to be statistically non-significant ($P > 0.05$). This implied that each difference in WOMAC scores obtained between the pre-treatment results and the post-treatment results was not significant. Indeed, no decline between the mean WOMAC scores was seen at each subsequent follow-up visit which implicated that there was no significant improvement in the patient's symptoms after treatment. Moreover, even for the pair of time interval between the follow up at 6 months and 12 months, the difference in mean WOMAC scores obtained was found to be statistically non-significant ($P > 0.05$).

Statistical analysis:

The collected data was summarized by using frequency, percentage, mean & S.D. To compare the qualitative outcome measures Chi-square test or Fisher's exact test was used. To compare the quantitative outcome measures Independent t test was used. If data was not following normal distribution, Mann Whitney U test was used. SPSS version 22 software was used to analyse the collected data. p value of < 0.05 was considered to be statistically significant.

DISCUSSION

The purpose of this study was to observe the effectiveness of PRP in symptomatic osteoarthritis patients belonging to grade 1 to 3 of the Kellgren-Lawrence classification. The

effectiveness of treatment was analyzed by subjecting the patients to WOMAC scoring system pre-treatment and post-treatment at 1-, 2-, 6-, and 12-months follow-up.

The total number of patients that were included in this study was 80. All the patients were between 40 to 80 years of age, with the mean age being 60 years. Most patients, 38.8%, belonged to the age group between 60-69 years (31 patients), while 31.3% belonged between 40-49 years (25 patients), 18 patients or 22.5% belonged between 50-59 years and 6 patients or 7.5% were between 70-79 years of age. Similarly, in a study conducted by Filardo et al,^[7] the mean age of their patients was found to be 58.5 years. In another study by Patel et al,^[8] the mean age was 56.1 years. In few studies the mean age varied such as in one by Gobbi et al,^[9] where it was found to be 37.7 years and in one by Kon et al,^[10] it was found to be 60 years. Therefore, it can be concluded that osteoarthritis is a disease that typically affects the elderly population.

In this study, age demographics were such that 54% of the participants were male while 46% were female. Similar distribution was seen in a study conducted by Bansal et al,^[11] in which 60% of the study participants were male and 40% were female. However, in a systematic review conducted by Meheux et al,^[12] that analyzed six articles in which 39% were male, while 61% were female.

WOMAC scoring system evaluated the patients' symptoms in three parts, namely pain, stiffness, and function of the joint. The results obtained showed that the mean WOMAC scores of Grade 1 and Grade 2 Kellgren-Lawrence patients at different periods of evaluation, namely pre-treatment and post-treatment follow-up at 1, 2, 6, and 12 months, showed a decreasing trend. At the pre-treatment evaluation, the mean WOMAC score was lowest in grade 1 patients (76.269) while it was highest in grade 3 patients (78.143). This signified that the more advanced the disease process was, the more pain, stiffness, and alteration of physical function was perceived by the patient. Similarly, in post-treatment evaluation, the mean WOMAC scores obtained were lowest in Grade 1 patients and highest amongst Grade 3 patients. However, an obvious decline in these scores was seen at each follow-up visit for Grade 1 and Grade 2 patients. This signified that an improvement in the patients' symptomatology. Similar results were seen in a study conducted by Bansal et al in which significant changes in the WOMAC baseline and post treatment scores were seen.^[11]

A systematic review conducted by Shen et al,^[13] also shows that patients having undergone PRP treatment when subjected to WOMAC in relation to knee pain scores showed a statistically significant difference as compared to controls at each follow up at 3 months, 6 months and 12 months. Moreover, when analyzing the WOMAC scores obtained in relation to physical function, there was a significant difference found in favour of PRP treatment when compared with controls. Indeed, PRP therapy plays a significant role in improving the physical function of these patients. A study conducted by Huang et al,^[14] showed that there was a significant improvement in WOMAC scores at each subsequent follow-up visit as compared to the pre-treatment values ($p < 0.05$).

Furthermore, a comparison of the pre-treatment and post-treatment mean WOMAC scores was done in each individual group. Each follow-up visit scores obtained was compared with the pre-treatment scores and statistical test was applied. Amongst the Kellgren-Lawrence grade 1 patients, for all the pairs of time intervals, the difference in mean WOMAC values was found to be statistically significant ($P < 0.05$). This implied that each difference in WOMAC scores obtained between the pre-treatment results and the post-treatment results was significant. Moreover, a significant decline between the mean WOMAC scores was seen at each subsequent follow-up visit which implicated an improvement in the patients' symptoms after treatment.

Similarly, in the Kellgren-Lawrence Grade 2 patients, for all the pairs of time intervals, the difference in mean WOMAC values was also found to be statistically significant ($P < 0.05$).

This implied that each difference in WOMAC scores obtained between the pre-treatment results and the post-treatment results was significant. Moreover, a significant decline between the mean WOMAC scores was seen at each subsequent follow-up visit which implicated an improvement in the patients' symptoms after treatment.

However, no such decline was seen in the mean WOMAC scores of grade 3 patients. For all the pairs of time intervals, the difference in mean WOMAC values was found to be statistically non significant ($P > 0.05$). The pre-treatment 78.143 and post-treatment 78.00 values remained almost the same. This implied that, in more advanced stages of the disease, not much improvement was seen even after therapy.

This study found this treatment modality to be safe, since no study participants experienced any adverse effects such as pain, stiffness, post-injection swelling, and infection. In a study conducted by Paterson et al,^[15] no treatment-related major adverse events were experienced by the participants. Two participants experienced minor pain and swelling during the injection period but that it most likely related to the injection technique rather than the PRP therapy itself. Another study by Huang et al,^[14] showed that from pre-treatment to the final follow-up, none of their study participants experience any major adverse effects such as low-grade fever, deep venous thrombosis, or infection. Mild complications of short duration were however seen in 5 patients (4.2%) that included pain, nausea and dizziness.

CONCLUSION

The results obtained concluded that injection of autologous PRP is indeed an effective and safe treatment modality for Kellgren-Lawrence grade 1 and grade 2 osteoarthritis. It had satisfactory effects in reducing pain and stiffness, as well as in restoring joint function. This led to an improvement in the lifestyle of the patients, by enabling them to resume their activities as before. It is therefore safe to conclude that PRP is a safe, simple, economic and efficacious modality in the treatment of osteoarthritis. The study also concludes that no beneficial effect of Intraarticular PRP injection was found in Kellgren-Lawrence grade 3 patients.

Declarations:

Funding: None Conflicts of interest/Competing interests: None Availability of data and material: Department of Orthopaedics L N Medical College Bhopal Madhya Pradesh Code availability: Not applicable Consent to participate: Consent taken Ethical Consideration: There are no ethical conflicts related to this study. Consent for publication: Consent taken

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