

# Quasi - Experimental Study using Platelet Rich Plasma in the Treatment of Osteoarthritis of Knee

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## Abstract

### Background:

Osteoarthritis (OA) is a chronic degenerative condition causing articular cartilage damage. Platelet-rich plasma (PRP) is a limited volume of plasma containing concentrated platelets (minimum 200,000 platelets/microl), growth factors of which enhance cartilage healing and regeneration. Aim of the study was to measure effect of PRP in the treatment of osteoarthritis using WOMAC Questionnaire obtained at baseline and then at 3 months, 6 months and 9 months after administration of PRP.

### Methods:

A quasi-experimental with a pre and post intervention design was conducted on 50 patients (64 knee joints) (Kellgren and Lawrence Degree 1,2) seeking care in out patient department of a tertiary care hospital. Patients with hemophilia, history of previous knee surgery, use of anticoagulants and NSAIDs in last 7 days were excluded from the study. Assuming WOMAC score change (from baseline 65 to post PRP with difference SD), sample size has been worked out as 54. 5ml of PRP freshly prepared by centrifugation at 3200 rpm for 2 minutes was administered intra-articular twice in the interval of 1 month. The data was analyzed by RStudio version 1.1.456 © 2009-2018 RStudio, Inc. Paired T-test was used to compare WOMAC scores at baseline and 3 months after PRP administration, baseline and 6 months after administration; & baseline and 9 months after administration.

### Results:

The mean age of participants was 46 years with SD 6.2 years and 68.9% were female patients. Mean WOMAC score at baseline was 50.6%. At 3 months after PRP administration the mean WOMAC score was 35.9%, which was significantly lower than the baseline (p-value <0.001). At 6 months the mean WOMAC score was 35.4%, which was significantly lower as compared to the baseline (p-value <0.001). At 9 months the mean WOMAC score was 40.5%, which was significantly lower as compared to the baseline (p-value <0.001).

### Conclusion:

There is significant evidence of positive effect of PRP in knee osteoarthritis in present study. There is definite evidence of waning off effect of PRP towards end of 9 months.

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### Keywords:

Osteoarthritis, PRP, WOMAC score

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## Introduction

Osteoarthritis (OA) is a chronic degenerative disease causing articular cartilage damage [1]. It is one of the most common rheumatologic disease prevalent worldwide. Females are affected more than men [2,4] with a significantly higher prevalence in the elderly [2,3]. In the

knee, medial compartment is involved earlier [3]. Prevalence of OA is as high as 22% to 39% in India [2]. In females with OA over 65 years of age, 70% have evidence of radiological damage and 45% are symptomatic [2]. OA can be disabling owing to the pain and deformity it ensues.

There are conservative as well as surgical modalities of treatment for OA of the knee which aims to reduce symptoms and improve joint function [4]. The conservative treatment includes aerobic and strengthening exercises, physical activity, weight loss with the aim to reduce BMI less than 25 and acupuncture. Other conservative measures include electrotherapeutic modalities, valgus directing brace (medial compartment unloader) and lateral wedge insoles for symptomatic medial compartment osteoarthritis. The pharmacologic therapy in practice consists of Glucosamine, Chondroitin sulphate, NSAIDs, Acetaminophen, Opioids, Analgesic patches, intraarticular corticosteroids and Hyaluronic Acid injections.

The most common side effect with chronic use of NSAIDs is gastrointestinal bleed. Intra-articular corticosteroid injection is associated with a higher incidence of secondary infection [5].

OA can involve all structures of the knee joint but hyaline articular cartilage loss remains the pathologic hallmark of the disease. The loss of cartilage is focal and non-uniform initially and becomes widespread and uniform as the disease advances. Since hyaline cartilage is an aneural structure, pain is likely to arise from damage to structures outside the cartilage [1]. Limited perfusion and innervation leads to decreased self regeneration ability of cartilage. Also, there is reduced systemic compensation in response to degeneration of cartilage [3]. Therefore, intra-articular injection of drugs or drug combination with the ability to restructure the cartilage tissue has been the focus of research in OA of the knee. Examples include the use of hyaluronic acid and irritants such as dextrose and erythropoietin with different mechanisms of action and efficacy levels [6].

Platelet-rich plasma (PRP) is a limited volume of plasma containing concentrated platelets and growth factors which enhance wound healing and promote tissue regeneration. It has been used in early OA for chondral repair [7]. Intra-articular autologous platelet-rich preparations deliver growth factors (GFs) and proteins stored in the alpha granules of platelets. These GFs and proteins promote articular cartilage repair [8] which is incapable of that because of its avascular, aneural and hypocellular nature. Growth factors released by platelets include platelet-derived growth factor, transforming growth factor beta, vascular endothelial growth factors, endostatins, platelet factor 4, angiopoietins, and thrombospondin 1 [9]. Analgesic property of PRP is credited to protease-activated receptor

4 peptides [10]. Therapeutic dose of PRP is considered 2 to 6 times higher than the normal platelet count [11, 12]. Although there is paucity of Indian literature for the use of PRP in knee OA, multiple studies worldwide have reported the short and long term efficacy of PRP in OA using various scales albeit with inconclusive results [4]. There seems to be an equipoise among researchers regarding the efficacy of PRP in OA.

Therefore, we performed a single-arm (intervention only) quasi-experimental study evaluating the change in OA outcomes measured on WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) questionnaire administered before and at 3, 6 and 9 months after two doses of intraarticular PRP administered one month apart. Our study population included knee OA patients aged 40-60 years seeking care at a tertiary care urban orthopedic outpatient clinic. We envision this study as hypothesis generating for the future testing of efficacy of PRP in knee OA in a well-powered randomized controlled trial.

## Methods

### Study Design

A single arm (intervention only) quasi-experimental study with a pre and post intervention design was conducted on 50 patients (66 knee joints) seeking care in outpatient department of orthopedics in a tertiary care hospital from January 2018 to September 2019 (a study duration of 21 months). The inclusion and exclusion criteria are reported in Table 1.

We needed 57 knee joints to achieve a power of 80% and a level of significance of 5% (two tailed), for detecting a mean of the differences of 5 between the WOMAC score at baseline and 6 months, assuming the pooled standard deviation of the differences to be 13.14 (sd1= sd2=15). Following formula was used to arrive at above calculated sample size-

$$n = \frac{2(Z_{1-\alpha/2} + Z_{\beta})^2 \times \sigma^2}{d^2}$$

Informed consent was obtained from all participants.

### Procedure

All patients received a baseline WOMAC score prior to PRP administration. WOMAC score is composed of three components: 1) Pain (5 items); 2) Joint stiffness (2 items); and 3) Knee function (17 items). Scoring in each case ranges from 0 to 4, and the total score of the scale varies from 0 to 96.

After performing routine cardiac monitoring (blood pressure, heart rate) and blood oxygen saturation, 20ml of patient's blood was taken intravenously under sterile conditions in 4 EDTA blood collection bottles and placed in

**Table 1: Inclusion and Exclusion Criteria of the Study**

INCLUSION CRITERIA	EXCLUSION CRITERIA
1. Age 40 to 60 years	1. Rheumatoid Arthritis
2. Degree 1 and 2 of Kellgren and Lawrence scale	2. Hemophilia
3. BMI < 30	3. History of previous knee surgery
4. Stable knees without malalignment or maltracking of the patella	4. Use of Anticoagulants and NSAIDs in past 7 days.
5. Informed consent.	

the REMI centrifuge (Figure 1) for PRP preparation. This was centrifuged at 3200 rpm for 2 minutes. Five ml of plasma at the top of buffy coat was taken for intra-articular injection. The intra-articular injection was performed by injecting 5 ml of PRP from lateral parapatellar approach into the knee joint space under sterile conditions. At the end of the procedure, the patient's knee was flexed and extended few times, to allow the PRP to distribute itself throughout the joint. The patient was observed for 1 hour to monitor any emerging side effects. Subsequently, patients was sent home with instruction to limit the use of the intervened lower limb for at least 24 h and to use cold therapy ice on the affected area for to contain the drug in the joint. During this period, the use of NSAIDs were prohibited and tablet Tramadol 50 mg and tablet Paracetamol 500mg was advised for the pain relief. The same procedure was repeated one month later.

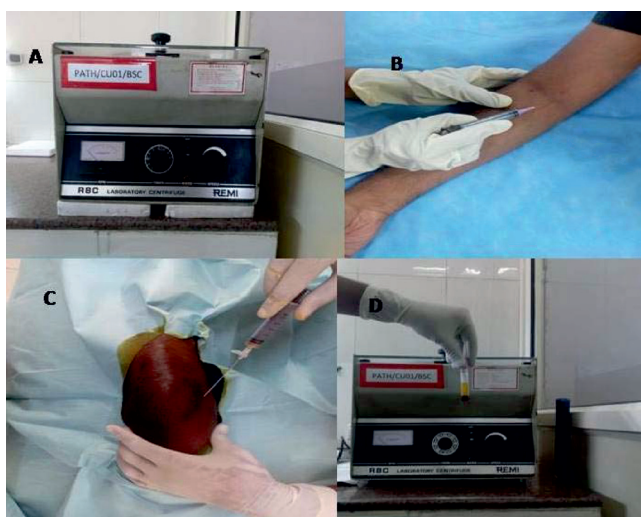


Figure 1 (In clockwise direction): REMI centrifuge- a table top variety used in the study (A), 20 ml of blood drawn from anti-cubital vein for PRP preparation (B), Prepared autologous PRP with supernatant on the top and buffy coat below (C), Administration of PRP in the affected knee by lateral parapatellar approach (D).

### Outcome Ascertainment : Follow Up

The condition of patient's knee was assessed at baseline (immediately before the first injection) and then at 3

months, 6 months and 9 months using WOMAC questionnaire. The adverse drug events were also recorded at these time points.

### Statistical Analysis

The data was analyzed in RStudio version 1.1.456 © 2009-2018 R Studio, Inc. Descriptive statistics were performed summarizing continuous data using means and standard deviations and categorical or binary data using frequency, percentages and counts. The paired sample t-test was used to determine whether the mean difference between two sets of WOMAC score was zero. All T-tests were two-tailed with an alpha of 5% (a p-value of less than 0.05 was considered statistically significant). Bonferroni correction was applied for multiple hypothesis testing to control for inflation in Type 1 error. Since the study tested five paired comparisons; the Bonferroni correction tested each individual hypothesis at  $\alpha = 0.05/5 = 0.01$ .

### Results

A total of 66 knee joints were enrolled for the study and 2 doses of autologous PRP were administered 1 month apart. A total of 5 knee joints were lost to follow up and analysis was done on 61 joints.

Demographic profile of participating knee joints is summarized below in the Table 2.

**Table 2: Baseline Variable**

Variables	N=61
Age in years (mean(sd))	46.0(6.2)
Female (%)	42(68.9%)
Male (%)	19 (31.1%)
Right knee (%)	32(52.5%)
Left knee	14 (23%)
Bilateral knee	15 (24.5%)
Homemaker	40 (66%)
Army Personnel	21 (44%)
Duration of pain in months (mean(sd))	22.2(25.8)
Radiological score(Kellgren and Lawrence)	
1	15 (24.5%)
2	46 (75.5%)

## Effect of PRP in treatment of Osteoarthritis on WOMAC Questionnaire

Mean WOMAC score at baseline, 3 months, 6 months and 9 months was 50.6, 35.9, 35.4 and 40.5 respectively in 61 knee joints (Figure 2).

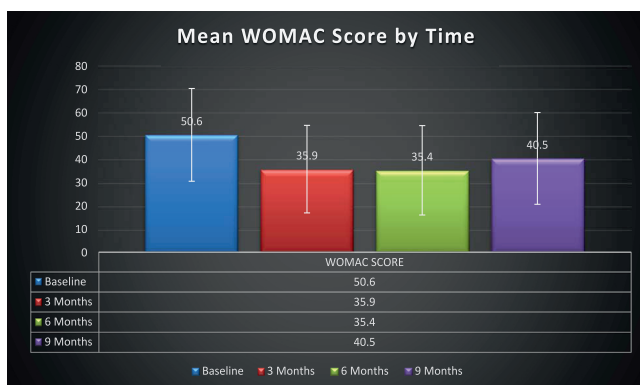


Figure 2: Trend of mean WOMAC scores at study time points

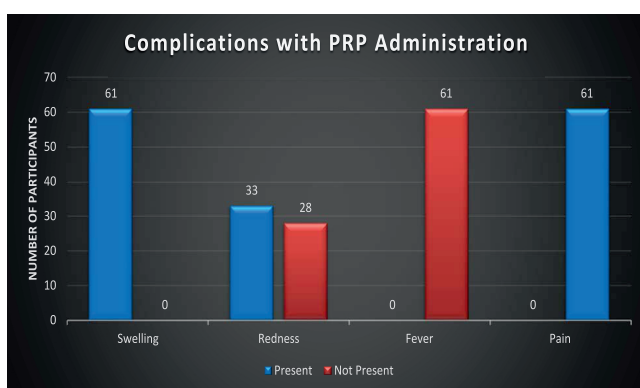


Figure 3: Complications observed following PRP administration

**Table 3: Comparison of effect of PRP on WOMAC score before and after administration**

Time-points Compared	Mean Difference	P-value	95% CI
Baseline – 6 months	15.2	<0.001	11.0, 19.2
Baseline – 3 months	15.4	<0.001	12.0, 18.8
Baseline – 9 months	10.0	<0.001	4.8, 15.4
3 months – 6 months	-0.3	0.82	-2.4, 1.9
6 months – 9 months	-5.0	<0.01	-8.6, -1.6

## Comparison of effect of PRP on WOMAC score before and after administration

WOMAC score decreased from baseline to 3 months and slightly more at 6 months, however the trend was reversed from 6 months to 9 months when the WOMAC score

started to increase again.

All comparisons between WOMAC score time points were statistically significant except between 3 months and 6 months.

## Complications with PRP administration

Minor side effects were observed after administration of PRP. Swelling was present in all of the patient post injection which continued for 7-10 days. Redness was present in 33 knee joints (54%) and it subsided in 3-5 days. Pain was present in all of the patients; however, fever was not present in any patient.

## Discussion

We observed that PRP administration was associated with a decline in the WOMAC score from baseline to 3 months post-administration, with the effect sustained at 6 months in an outpatient population of knee OA patients. WOMAC score at 9 months was higher as compared to 6 months during follow up, however, the value remained less than the baseline.

A similar observation was derived by Filardo et al in 2012 when they observed improvement in symptoms, pain, activity of daily life and sports during follow up at 2 months, 6 months and 12 months after 3 injections of PRP at 3 weekly intervals. They also saw that effect of PRP at 12 months was waning off as compared to 6 months, but still higher than 6 months [14].

Elvira Montanez Haredia in 2016 administrated 3 PRP injections at 1 monthly interval in 58 patients and observed similar improvement in scoring system at 3 months and 6 months [15]. Again, Lana et al in 2016 similar trend on 60 patients during follow up at 1, 3, 6 and 12 months after 3 intra-articular injections with 2 weeks interval [16]. Alberto Gobbi did a case series of 50 patients by giving 2 intra-articular injections and following up at 6 and 12 months. At 12 months, KOOS and IKDC score increased as compared to 6 months [17]. Patel et al tried with 2 intra-articular injections and saw declining trend of score at end of 6 months [18].

Studies done till now shows positive effect of PRP in terms of improvement in different scoring systems. However, different dosing schedule has been used in all studies – 2 doses, 3 doses and multiple doses with different spacing interval between the two dosages, which might explain the different duration of effect of PRP before it weans off. Also, there is still no standard method of PRP preparation. Currently, PRP preparation kits are of 2 types – cell saver/separator and table top PRP devices. We have used REMI- a table top device but there are a lot of devices in market by different manufacturers [13].

Most of the studies have confined themselves to patients with early OA (KL I, II and III). So, in our study with 2 PRP intra-articular injections with spacing of 1 month shows sustained effect for 6 months and decline thereafter.

Most of the side effects observed were expected and mild. No serious adverse events warranting medical attention or intervention were seen. Overall PRP seemed to be a safe agent in our study population.

We find these results encouraging for planning a future investigation of the use of intra-articular PRP in the knee OA population. The improvement in the WOMAC score was found to be both clinically and statistically significant at all the three study time points (i.e 3, 6 and 9 months) when compared against the baseline. Our low dropout rate, overall favorable side-effect profile and ease of administration of PRP makes it a lucrative and promising intervention for future studies. Based on our work, a future randomized placebo-controlled trial should be designed to test the efficacy of PRP in knee OA population.

However, our study is limited by the lack of a control group, which limits attributing the effect entirely to PRP administration. Our small sample size and single-institution recruitment makes the results less generalizable. Finally, we did not collect any patient-centered outcome measures eliciting the values and preferences of knee OA patients for their acceptability of this novel intervention.

## Conclusions

Our study shows a promising trend of the beneficial effect of PRP in knee osteoarthritis. Owing to the waning effect of PRP, future studies should focus on multiple doses given at carefully selected time points to optimize the effect and achieve sustained symptom relief. The pharmacokinetic properties of PRP should drive these choices and standardizing the methods of preparing and administering PRP should be considered for any future work. If PRP is proven to be feasible, acceptable and effective for patients in knee OA, it has the potential to become a major player in the standard of care of this population.

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<b>Ethics:</b>	There is no ethical violation as it is based on voluntary anonymous interviews
<b>Funding:</b>	No external funding
<b>Guarantor:</b>	Maj . (Dr.) Rupesh Prasad will act as guarantor of this article on behalf of all co-authors.

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