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Comparison of intra articular autologous platelet rich plasma with steroids in osteoarthritis knee.

Dr. Pragadeeshwaran G, Senior Resident, Department of Orthopaedics,
ACS Medical College & Hospital, Chennai, Tamil Nadu.
Corresponding Author: Dr. Pragadeeshwaran G.

Abstract

Background: Intra-articular (IA) platelet-rich plasma (PRP) is a promising treatment option for knee osteoarthritis (OA). It accelerates the process of healing, ligament repair, cartilage regeneration, and bone formation when given in supraphysiological doses. The aim of this study was to compare the efficacy of IA PRP versus IA methylprednisolone acetate (MPA) in patients with knee OA.

Methods: Open labeled prospective observational study was conducted on 60 patients with Kellgren-Lawrence Grade 2 and 3 OA knee, who fulfilled the ACR classification criteria for knee OA. Thirty patients were given IA PRP (6 ml) and 30 received IA methyl prednisolone (80 mg) at baseline line, which was repeated at 12 weeks. The primary endpoint was an improvement in Western Ontario and McMaster Universities Index (WOMAC) and 100 mm Visual Analog Scale (VAS) pain at 24 weeks postinjections.

Results: The mean change in VAS pain and total WOMAC score from baseline to 24 weeks was 32.9 ± 12.1, 31.8 ± 14.7 for PRP group, and 12.9 ± 5.9, 7.5 ± 5.5 for MPA group, which was statistically significant ($P < 0.0001$).

Conclusions: Treatment with IA PRP showed sustained improvements in WOMAC and VAS scores compared to IA steroids. PRP is an effective treatment for functional status and pain in moderate knee osteoarthritis.

Introduction

Osteoarthritis (OA) knee is the most common degenerative joint disease worldwide. The main goals of management are directed to reduce pain, improve function, quality of life, and limit disease progression.[1] Unfortunately, there are no agents currently available that can halt the progression of knee OA.[2] Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) have suboptimal effectiveness; surgical treatment can reduce pain and improve joint mobility and function; however, it is associated with significant cost and potential morbidity.[3,4] Intraarticular (IA) corticosteroids and hyaluronic acid (HA) injections provide short-term reduction in pain of OA.[5] Recently, placebo-controlled studies have shown that IA injection of platelet-rich plasma (IA PRP) can relieve pain, improving knee function and quality of life.[6,7] The most likely mechanism by which PRP reduces pain and stiffness of OA is by stimulating the natural healing cascade and tissue regeneration by a "supra-physiological" release of platelet-derived factors directly at the site of treatment.[8] Despite numerous studies and metaanalyses, the efficacy of IA PRP in patients with knee OA remains debated and uncertain worldwide.[9-11] The aim of this study is to compare the efficacy of IA PRP versus IA depot MPA in mild-to-moderate knee OA.

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Methods

Study design

This was a prospective, observational study, comparing IA PRP injection versus IA MPA in patients with mild-to-moderate knee OA. The two groups were treated with either IA PRP (6 ml) or IA methylprednisolone (80 mg) at baseline, which was repeated at 12 weeks, and results were compared.

A study by Cerza *et al*.[9] found the mean total Western Ontario and McMaster Universities Index (WOMAC) score at the end of 24 weeks was 36.5 ± 17.9 and 65.1 ± 10.6 in groups that were treated by IA PRP and HA, respectively. Based on the above study, the mean difference between PRP and MPA groups (WOMAC scores) was assumed to be 50% between the groups, with a power of 80% and 95% confidence interval, it would be necessary to include a total of 60 patients (30 patients per group). We enrolled 30 patients in the PRP group and 30 patients in the MPA group. Type I error probability associated with this test of the null hypothesis is 0.05.

Statistical data analysis was carried out using SPSS (version 19.0; IBM Corp). Categorical variables were described by percentages and frequencies, whereas continuous variables were described by means, standard deviations, medians, and minimum and maximum values. The analysis of primary and secondary variables was accomplished using the intention to treat principle. Shapiro–Wilk and Kolmogorov–Smirnov tests were used to test the normalcy of data, and it was found that data were not normally distributed (Visual Analog Scale [VAS], WOMAC); hence, non-parametric test Mann–Whitney was used to compare mean scores between groups. Categorical variables were compared using Chi-square tests. A value of $P < 0.05$ was taken as statistically significant.

The severity of OA was defined by Kellgren-Lawrence (KL) grading.[12] Patients with clinical and radiological diagnosis of knee OA either KL Grades 1, 2, or 3 without knee deformity were eligible if they have continued pain despite conservative management with NSAIDS, and be symptomatic for at least 6 months with pain of >40 mm on a 100 mm as per VAS pain despite standard of care treatment. Patients were excluded if they had KL Grade 4 or severe mechanical deformity or received IA injection of HA in the past 6 months. Patients who had received either oral, injectable (intramuscular or IV) or IA steroid during the 3 months before the study, or blood dyscrasias or immunosuppressive, anticoagulant treatments, uncontrolled diabetes mellitus, secondary knee OA were excluded. The use of analgesics, physiotherapy was not restricted for both groups during the study period for both groups. Efficacy was assessed using WOMAC 5-point Likert scale,[13] and the VAS for pain on a 100 mm scale. Both parameters were assessed at baseline12 weeks, and 24 weeks follow up.

Outcome measures

Primary outcome was the mean difference in total WOMAC score and VAS pain score between PRP and MPA groups from baseline to end of 24 weeks, and secondary outcomes included the differences in various components of WOMAC score (pain, joint stiffness, and physical function) from baseline to the end of 24 weeks.

Platelet-rich plasma preparation

About 100 ml of venous blood drawn under aseptic precautions from the antecubital vein a traumatically

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in an effort to avoid irritation and trauma to the platelets. The blood was collected in a 100-ml bag with citrate phosphate dextrose and adenine 1 as an anticoagulant. The procedure is completely performed inside the biosafety cabinet. The final PRP is assessed for platelet count and supplied for injection. PRP was prepared freshly and administered at two points of time (baseline and 12th week), and no PRP was stored.

Interventional procedure

The patient was placed in the supine position with the knee in full extension. Under aseptic conditions, either IA PRP 6 ml or Depo-medrol® (MPA) 2 ml was injected to knee joint through superolateral approach with an 18G needle without local anesthetic under ultrasound guidance. 0.5 ml of CaCl2 (M/40) was injected for every 6 ml of PRP to activate platelets. The knees were immobilized for 10 min after injection. Some patients who reported dizziness or sweating were observed for 2–3 h and discharged once they recovered.

Results

The study population consisted of 60 patients with mild-to-moderate OA knee, as shown in Table 1. The mean and 57.0 ± 7.2 years for the MPA group, with a range of 41–72 years. The majority 47% and 43% of patients belonged to 51–60 years of the age group in PRP and MPA groups, respectively. Mean body mass index (BMI) of cases was 26.0 ± 2.3 kg/m^2 for PRP and 25.8 ± 2.4 kg/m^2 for the MPA group, and all patients had bony crepitus. Kellgren and Lawrence grade of knee OA-maximum patients (49 out of 60) had Grade 3 OA, and 11 patients had Grade 2 OA. Our study group has not included Grade 4 knee OA, and none of our patients had retropatellar knee OA.

Table 1: Baseline characteristics of the study groups

Characteristics	Mean±SD		*P*
	PRP (*n*=30)	MPA (*n*=30)	
Age (years)	53.3±7.9	57.0±7.2	0.06
Sex (male/female)	9/21	11/19	0.584
Duration of OA (years)	7.3±4.0	8.0±4.4	0.505
BMI (kg/m²)	26.0±2.3	25.8±2.4	0.748
Received previous intra articular interventions	6	6	-
Bony swelling	23	11	0.002
Knee effusion	4	5	0.508
KL grade of OA			
Grade 1	0	0	
Grade 2	5	6	
Grade 3	25	24	
Grade 4	0	0	

PRP: Platelet-rich plasma, MPA: Methyl prednisolone acetate, BMI: Body mass Index, SD: Standard deviation, OA: Osteoarthritis, KL: Kellgren-Lawrence

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At baseline mean VAS pain score, WOMAC (total, pain stiffness, and functional) score in PRP and MPA group were as shown in Table 2. The mean change in VAS pain from baseline to 24 weeks was 32.9 ± 12.1 for the PRP group and 12.9 ± 5.9 for the MPA group, which was statistically significant ($P < 0.0001$). Mean changes in total WOMAC score between PRP and steroid groups from baseline to 24 weeks were 32.8 ± 14.7 for PRP and 7.5 ± 5.5 forthe MPA group ($P < 0.0001$).

Table 2: Baseline visual analog scale pain score and Western Ontario and McMaster Universities Osteoarthritis Index scores in the study patients

	PRP (*n*=30)	MPA (*n*=30)	*P*^
VAS score	78.40 (9.24)	77.17 (8.78)	0.551
WOMAC scores			
Pain	16.0 (2.03)	16.3 (1.44)	0.619
Physical function	53.77 (6.55)	54.33 (6.18)	0.807
Stiffness	5.83 (1.34)	6.30 (0.79)	0.255
WOMAC total	75.60 (9.14)	76.6 (7.57)	0.801

^Mann–Whitney test: $P>0.05$; not significant. PRP: Platelet-rich plasma, MPA: Methyl prednisolone acetate, VAS: Visual analog scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Mean changes in the WOMAC scale and subscales between PRP and steroid (MPA) groups from baseline to 24 weeks were statistically significant ($P < 0.0001$), as shown in Table 3. For all the outcome parameters, i.e., VAS pain, WOMAC pain, stiffness, function, and total scores, a statistically significant difference from baseline was seen as earlyas 6 weeks in both groups. These significant differences in treatment response from baseline were sustained for the entire duration of follow-up till 24 weeks in the PRP group when compared to the MPA group ($P < 0.0001$). The decrease in pain VAS and WOMAC scores were significantly greater for the group receiving IA PRP.

Within the PRP group, comparison of treatment response at week 6, 12, and 24, we found that VAS, WOMAC (pain, stiffness, function, and total) scores, there was a significant difference between week 6 and week 12 scores ($P < 0.05$) and between 12 and 24 week scores ($P < 0.0001$). Within the steroid (MPA) group, VAS pain and WOMAC, there was a decrease in efficacy at 12 weeks as compared to peak response at 6 weeks, which was statistically significant but significant decrease in efficacy at 24 weeks (Table 3).

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Table 3: Comparison of Western Ontario and McMaster Universities Osteoarthritis Index/visual analog scale scores inintra-articular platelet rich plasma and methyl prednisolone acetate groups

Characteristic	`12 weeks			24 weeks		
	PRP (*n*=30), mean±SD	MPA (*n*=30), mean±SD	*P*^	PRP (*n*=30), mean±SD	MPA (*n*=30), mean±SD	*P*^
VAS score	47.50±14.75	55.40±6.11	0.0025	45.47±14.64	64.27±6.30	<0.0001
WOMAC scores						
Pain	9.77±3.56	12.33±1.92	0.0007	9.00±3.86	14.10±1.47	<0.0001
Physical function	34.77±10.87	44.00±6.52	0.0005	32.17±12.63	49.53±6.85	<0.0001
Stiffness	3.20±1.58	4.87±0.68	<0.0001	2.67±1.90	5.60±0.62	<0.0001
Total	47.47±15.19	61.03±7.48	0.0001	43.83±17.88	69.07±7.59	<0.0001

DISCUSSION

Table 4: Comparison of visual analog scale and Western Ontario and McMaster Universities Osteoarthritis Index scores with other studies

	Study design	Number of patients	VAS and WOMAC Scores at baseline		VAS and WOMAC at the end of follow-up	
			VAS Total	WOMAC	VAS Total	WOMAC
Present study	Prospective, observational	60 (PRP - 30; MPA - 60)	PRP - 78.4 (9.2) MPA - 77.2 (8.8)	75.6 (9.1) 76.6 (7.6)	45.5 (14.6) 64.3 (6.3)	43.8 (17.9) 69.1 (7.6)
Cerza *et al*.[9]	RCT	Total - 120 PRP - 60 (4 doses PRP) HA - 60	PRP HA	76.9±9.5 75.4±10.7	- -	36.5±17.9 65.1±10.6
Patel *et al*.[10]	RCT	Total - 78 PRP-A (27) PRP-B (25) NS- (26)	PRP-A 4.56±0.61 PRP-B 4.64±0.56 NS - 4.57±0.62	49.5±17.8 53.2±16.1 45.5±17.2	2.16±1.54 2.54± 1.71 4.61± 0.74	27.18 30.18 53.09
Raeissadat *et al*.[11]	RCT	Total - 160 PRP - 87 HA - 73	PRP - 49.9±24.77 HA - 45.45±20.5	39.5±17.06 28.6±16.6	- -	18.44±14.35 27.46±16.36
Kavadar *et al*.[14]	RCT	Total - 102	Group 1: 77±10	91.4±2.0	72±2	87.6±1.9

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		Group 1: 34	Group 2: 77±12	81.6±3.0	64±2	74.5±2.4
		Group 2: 34	Group 3: 84±12	89.9±1.7	45±12	75.1±1.7
		Group 3: 34				
Ghai *et al*.[17]	Double-blind randomized comparative	Total - 20 (40 knees)	PRP: 8.40±0.883	PRP: 37.5±3	4.85±2.48	18.1±11
		PRP - 20	NS: 7.15±0.93	NS: 26.65±2.9	5.7±2.9	26.45±2.9
		NS - 20				
Sánchez *et al*.[19]	RCT	Total - 176	PRGF: 9.5±3.0	PRGF:	9.5±3.0	PRGF -
		PRGF - 89	HA: 9.1±3.2	121.8±44.4	9.1±3.2	74.0±42.7
		HA - 87	(Lequesne index)	HA: 115.6±45.1 (normalized WOMAC score)	(Lequesne index)	HA: 78.3±48.1
Joshi Jubert *et al*.[21]	RCT	65	PRP - 75.14±10.11	KOOS pain	38.2±24.8	KOOS pain
		PRP - 35		PRP - 35.1±17.9	46.3±29.8	53.09±22.15
		CSA - 30 (betamethasone)	CSA - 75.00±9.38	CSA - 38.8±18.9		49.52±23.70

PRP in OA of the knee is far better in patients with OA of radiological KL Grade 1 and 2 than Grade 3 and 4. 37% of patients showed excellent prognosis, 30% good and fair prognosis. In contrast, only 3% of people showed poor prognosis after a follow up of 9 months duration.[15] Chinder *et al*.[16] showed statistically significant improvements in WOMAC scores in all patients treated with IA PRP in a prospective observational study in 50 patients with KL Grade 1 and 2 knee OA. This was consistent with our study as majority (80%) population in both the study groups (PRP and MPA) were Grade 3 OA, and IA PRP was effective in improving pain and physical function. In a double blind randomized comparative study by Ghai. comparing PRP and normal saline in early OA knee, showed a decrease in mean pain score after 2 weeks of injection in PRP knee. At 6 months, pain reduction in PRP knee was 49%, as compared to only 21% decrease in NS knee.[17] There was also a significant decrease in stiffness and improvement of physical activity in the plateletrich plasma knee as compared to the normal saline knee. Kadam *et al*.[18] in an observational study to assess the effects of PRP application on pain in OA knee, showed that that average mean VAS score was decreased from 6.0 to 4.13 after followup of

3 months after a single dose of IA PRP. Sánchez *et al*. performed a retrospective cohort study comparing IA plasma rich in growth factors (PRGF) and HA and reported better improvement in pain and quality of life with PRGF injection.[19] Chang *et al*. demonstrated that PRP led to significant functional improvement in patients with knee cartilage pathology, and the effects lasted for 12 months.[20] Similarly, our study demonstrated significant improvement in pain and function in the PRP group and the effects were more sustainable, lasting >6 months compared to the MPA group. In a randomized control study by Joshi Jubert et al. comparing PRP and corticosteroid in late stage OA knee, at 1st month, results showed a decrease in VAS in both groups, the VAS for the corticosteroid with local anesthetic (CSA) group

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worsened at 3 months while it improved in the study (PRP) group.[21] This result was consistent with our study, with peak treatment response in the MPA group was noticed at 6 weeks after that there was a marginal decrease in efficacy at 12 weeks, which further decreased at 24 weeks.

In our study, we observed that IA MPA was not efficacious at 24 weeks in comparison with IA PRP; these findings were consistent with the study by Forogh *et al*., which compared a single injection of PRP with CSA.[22] Several factors could explain the greater improvement of IA PRP group results in our study compared with previous randomized trials: the lesser degree of knee OA, no bony deformity, younger mean age of participants and average mean BMI–few risk factors for symptomatic knee OA. Despite its wide application in clinical practice and the positive findings reported in many clinical trials, almost all the questionnaires were based on subjective findings. Therefore, conducting a study based on objective parameters such as joint inflammatory biochemical markers, imaging assessment with magnetic resonance imaging knee to look for the morphology of articular cartilage would determine the clinical improvement or OA progression. IA PRP injections were well tolerated by almost all patients and were least painful. There were no serious local or systemic adverse events in any patient during the study duration, which would require immediate intervention or discontinuation of PRP. Strengths of the study, none of the patients lost follow-up, PRP preparation technique was standardized by our transfusion medicine department, and we were able to get a standardized concentration of platelets for all cases. All investigations and treatment offered free of the cost being government institute. There were no financial implications confounding the study. The limitation of this study was, it was an open-label, observational study; both treating physicians and patients were aware of the treatment administered, which could have led to bias. There was no randomization done, and patients who choose PRP were more likely to exhibit higher placebo effects. The use of analgesics by the patients was not restricted, which might have interfered with the assessment of treatment response. Our study was lacking the objective evaluation of the effects of IA PRP treatment on the morphology of the cartilage, soft tissue, and other intraarticular and peri-articular structures of the knee.

Conclusion

Two injections of IA PRP, 3 months apart, would be effective in patients with symptomatic OA of the knee, with sustained improvement in VAS pain and WOMAC scores. PRP is a novel option in the management of OA knee with promising results.

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