Original Research Article

Comparison of the clinical effect of intra-articular injection of platelet-rich plasma and methylprednisolone in primary osteoarthritis of knee: a randomized controlled trial

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ABSTRACT

Background: Osteoarthritis of knee is one of the commonest musculoskeletal disorder causing mobility impairment affecting 3.3% in urban areas and 5.5% in rural areas. Intra-articular injection of Platelet-Rich Plasma (PRP) delivers activated platelets that may reduce inflammation, provide pain relief, improve function and stimulate possible cartilage regeneration at the site of worn cartilage area of the knee.

Methods: Eighty patients with primary osteoarthritis of the knee fulfilling inclusion and exclusion criteria were recruited in the study conducted in the Department of Physical Medicine and Rehabilitation, RIMS, Imphal from October 2014 to September 2017. Six ml of PRP prepared by conventional bench top centrifugation system was injected intra-articularly, two weeks apart in the PRP group. Steroid group received 80mg of methylprednisolone, two weeks apart by the same technique. The outcome variables (VAS and WOMAC score) were measured before starting intervention (baseline) and at 8 and 24-weeks post-intervention follow up.

Results: Significant improvement seen in VAS, WOMAC-pain, stiffness and physical function and total scores in both the groups at 8- and 24-weeks follow-ups (p<0.001). Steroid group showed better result than the PRP group in VAS (2.78±0.76 vs 3.58±1.03) and WOMAC-total (30.42±6.85 vs 36.25±10.87) scores at 8 weeks respectively (p<0.001). But at 24 weeks follow-up, PRP showed significantly more effective than the steroid group in reducing pain (2.0±.0.87 vs 2.45±0.78) and disability (22.95±3.78 vs 25.25±6.67) respectively (p<0.001).

Conclusions: Intra-articular injection of methylprednisolone was found to be more effective in reducing pain and disability in primary knee osteoarthritis of KL grade 2 and 3 at the end of 8 weeks whereas 2 doses of PRP intra-articular injection 2 weeks apart was significantly more effective than methylprednisolone at the end of 24 weeks. However, the long-term benefit of PRP is to be determined by studies with a larger sample size and longer duration of follow-up.

Keywords: Osteoarthritis, Platelet rich plasma, Tabletop centrifugation, Visual analogue scale, Western ontario and mcmaster universities osteoarthritis index

INTRODUCTION

Osteoarthritis is the most common form of arthritis, and a major cause of morbidity, activity limitation, physical disability, excess healthcare utilization, reduced health-related quality of life, and excess mortality, especially in people aged 45 years and above.[1] Approximately 10% of the world's population who are 60 years or older have

symptomatic problems that can be attributed to OA.[1] Framingham Study reported the prevalence of radiographic knee OA as 19.2% in adults above 45 years and, in those over 80 years, the figure rose to 43.7%.[2] Fast track model of COPCORD Bhigwan model reported 13% prevalence of degenerative osteoarthritis of knee in an identified village of Manipur, India in the year 2008.[3] Forty-five percent of women over the age of 65 years have symptoms while radiological evidence is found in 70% of those over 65.[1] in the Version 2 estimates for the Global Burden of Disease 2000 study published in the World Health Report 2002, OA is the 4th leading cause of Years Living with Disability (YLDs) at global level, accounting for 3.0% of total global YLDs.[4]

Causes of OA are not known; however, current evidence indicates that it is multifactorial. The typical progression of OA involves the following events: (1) loss of cartilage matrix, which makes the joint more susceptible to further injury, (2) alterations to underlying bone associated with wear on the cartilage, with affected joint, (3) cartilage breakdown associated with synovial inflammation, which can lead to release of cytokines and enzymes that exacerbates the cartilage damage.[5]

There are different methods used for alleviating the symptoms of patients with knee OA, including non-pharmacological modalities like rest, weight loss, physical therapy and exercises, orthosis, heat and cold therapies, Transcutaneous Electrical Nerve Stimulation (TENS), laser therapy, dietary supplements (glucosamine, and chondroitin-sulfate), arthritis education and support; pharmacological therapy like pain relief medications, NSAIDs, intra-articular injections (glucocorticoids, hyaluronic acid) and surgical interventions like arthroscopy and joint irrigation, realignment, fusion, joint replacement, cartilage shaving.

Intra-articular corticosteroid injections are frequently used to treat acute and chronic inflammatory conditions.[6] Especially during the OA flare, when there is evidence of inflammation and joint effusion, steroid injections decrease acute episodes of pain and increase joint mobility. Also, when the correlation of chondrolysis with the OA flare is considered, the intra-articular steroid injection for the short-term treatment of disease flares is recommended.[7]

The current therapeutic approaches focus on preventing or at least delaying the structural and functional changes of OA. Research into the biology of bone, ligament, and tendon healing has led to the development of a variety of products designed to help stimulate biologic factors and promote healing. Platelet-Rich Plasma (PRP) is an example of one such autologous product that has been utilized and studied since the 1970s. When platelets become activated, growth factors are released and initiate the body's natural healing response.[8] The study was conducted with an aim to assess the clinical results, with regard to decreasing pain and improving healing and function, of autologous PRP compared with steroid therapy in primary osteoarthritis knee.

METHODS

A prospective, randomized controlled study on 80 patients with primary osteoarthritis of knee attending OPD at Physical Medicine and Rehabilitation Department, Regional Institute of Medical Sciences, Imphal was conducted from October 2014 to August 2017. Approval from the Research Ethics Board, RIMS, Imphal was taken before the start of the study and written informed consent was obtained from all the subjects.

Sample size was considering 80% power to detect a difference of 10-point improvement in VAS scoring between the groups, two-sided t test $\alpha=0.05$ and 10% drop out rate a total sample size of 80 was fixed (40 in each group).

Inclusion criteria

- Patients fulfilling the ACR criteria of OA Knee, between 40 and 65 years, Body Mass Index (BMI) <30, with OA Grade 2 and 3 (KL Grading), normal complete hemogram, unilateral knee joint involvement, stable knee, normal tibio-femoral alignment ($\leq 5°$) and patellar tracking were included in the study.

Exclusion criteria

- Patients with inflammatory joint diseases, metabolic bone diseases, known blood diseases, systemic metabolic diseases including uncontrolled diabetes, immunodeficiency, hepatitis B or C, HIV positive, systemic and local infection, h/o recent intra-articular steroid or hyaluronate, medication that could interfere with platelet aggregation <7 days prior to the day of intervention, severe cardiovascular disease, uncooperative and cognitive impaired patients were excluded.

Group allocation

Patients were assigned to two groups: PRP and steroid groups by using block randomization technique (Figure 1). PRP and steroid groups received intra-articular Inj. PRP and Inj. Methylprednisolone acetate 80 mg respectively. The participants and physician who conducted follow-up examination were masked to the treatment received.

Interventions

Patient's baseline complete hemogram was performed. Twenty-six ml of peripheral venous blood was drawn in a 30 ml syringe containing 4 ml of Citrate Phosphate Dextrose (CPD) anticoagulant. Thirty ml of anticoagulated blood was dispensed into six vacutainer

tubes. The tubes were subjected to a centrifugation of 12 minutes at 3000 rpm (Figure 2). The blood column in each vacutainer tube formed 3 layers: lower RBC layer, middle buffy coat layer and upper plasma layer. Buffy coat layer and 1 ml of plasma just above the buffy coat layer was pipetted out from each tube. This yielded 6 ml of PRP. One ml was sent for platelet concentration examination. Platelet activation was done by adding 1 ml of $CaCl_2$ (molar conc. M/40). After taking proper antiseptic and aseptic precautions intra-articular injection knee joint with 6 ml of activated PRP was performed through a marked point inferior to the patella and lateral to the patellar tendon in a 90° flexed knee using a 21G needle (Figure 3).
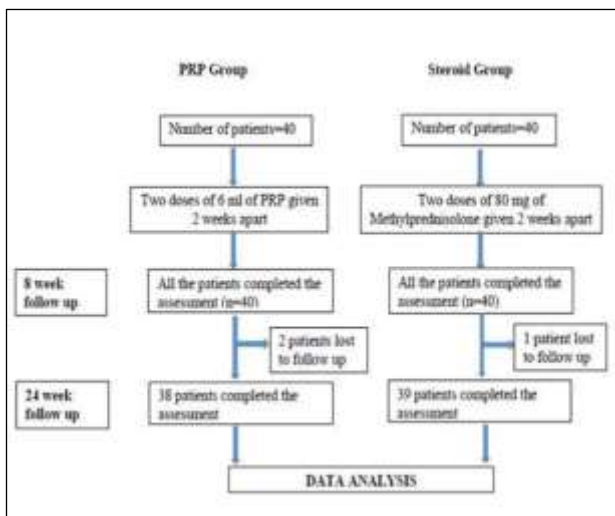
Figure 1: Study algorithm.

Figure 2: Centrifugation at 3000 rpm for 12 minutes.

Outcome measures

The treatment outcome was assessed with WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) score and VAS for pain; WOMAC version 3.1 in Likert scale was used, consisting of three subscales: pain (5 items), stiffness (2 items), physical function (17 items). Each item was measured in five-point Likert scale, with minimum WOMAC score 0 and maximum 96.

Using a 10 cm line, VAS for pain was assessed with two endpoints representing "no pain" and "worst pain imaginable." Patients were asked to rate their pain by placing a mark on the line corresponding to their current level of pain. The distance along the line from the "no pain" mark is then measured with a ruler giving a pain score out of 10.

Outcome variables were measured at baseline before PRP and steroid injection. Follow up assessments were done at 8 and 24 weeks. Patients were asked to stop medications 48 hours prior to follow up assessment.

For the steroid group, methyl-prednisolone acetate 80 mg of the same brand was given by the same technique.

In both the groups, knees were mobilized 3 times and then immobilized for 10 minutes. Patients were kept under observation for half an hour. Patients were advised to avoid the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Tablet tramadol 100mg was given as and when required. Any adverse reactions were deal with.

Figure 3: Intra-articular injection of PRP.

Statistical analysis

Data were entered and analyzed by using SPSS version 21. The baseline characteristics between the PRP and steroid group were studied by chi-square test for categorical variables. Mann-Whitney U-test was used for significant test between group comparison of mean scores. The differences in the changes of the mean scores at different time points were compared by repeated-measure analysis of variance. A post hoc Bonferroni test was used to compare the change in different parameter from baseline to 8 and 24 weeks. p-value <0.05 was taken as significant.

RESULTS

A total of 46 females and 34 males were included in the study. PRP group consisted of 19 males and 21 females with mean age of 51.60±6.06 year while the steroid group consisted of 15 males and 25 females with mean age of 49.73±4.54 year. There were no statistically significant

differences between the groups in terms of baseline characteristics (Table 1). Majority of the patients, 23(57.5%) in PRP group and 26(65%) in steroid group had involvement on the right side. Osteoarthritis of KL

grade 3 constituted 60% (n=24) and 67.5% (n=27) in the PRP and steroid group respectively. Majority of the patients had osteoarthritis affecting the right knee (61%) as compared to the left knee (39%).

Table 1: Baseline characteristics of the study groups.

Characteristics		PRP group (n=40) (mean±SD) (n, %)	Steroid group (n=40) (mean±SD) (n, %)	p-value
Mean age (year)		51.60±6.059	49.73±4.535	0.121
Sex	Male	19	15	0.369
	Female	21	25	
Religion	Hindu	18	16	1.000
	Christian	9	14	
	Muslim	9	6	
	Others	4	4	
Side affected	Right	23	26	0.494
	Left	17	14	
Duration (months)		4.60±1.172	4.83±1.259	0.411
Occupation	Manual laborers	17	14	0.496
	Government employee	10	11	
	Housewife	9	10	
	Businessman	3	3	
	Others	1	2	
Kl grading	Grade 2	16	13	0.488
	Grade 3	24	27	
BMI		27.03±2.65	27.62±1.83	0.817

Table 2: Changes of outcome measures after intra-articular PRP injection (n=40).

Outcome measures	Mean±SD			p-value (RMA)	Mean difference from baseline (95% CI) (post hoc bonferroni test) [b]	
	Baseline (n=40)	8 weeks (n=40)	24 weeks (n=38)		8 weeks	24 weeks
VAS	5.85±0.77	3.58±1.03	2.00±0.87	<0.001	2.27(1.84-2.70)	3.85(3.38-4.31)
WOMAC-pain	10.42±3.13	6.45±2.78	4.22±1.36	<0.001	3.97(3.18-4.76)	6.20(5.02-7.37)
WOMAC-stiffness	4.65±1.21	3.37±0.92	2.60±0.67	<0.001	1.27(0.82-1.72)	2.05(1.71-2.38)
WOMAC-physical function	38.3±9.25	26.42±9.07	16.12±7.12	<0.001	11.87(8.75-14.9)	22.17(18.17-26.1)
WOMAC- total	53.37±10.88	36.25±10.87	22.95±3.78	<0.001	17.12(13.5-20.7)	30.42(25.9-34.9)

Values are expressed as mean±SD. Difference in mean change at intervals from baseline are expressed as mean change (95% CI).
Statistical test: repeated measures analysis of variance (RMA)a with post hoc Bonferroni test b within the groups.
CI, confidence interval

Table 3: Changes of outcome measures after intra-articular steroid injection (n=40)

Outcome measures	Mean±SD			p-value (RMA)	Mean difference from baseline (95 CI) (post hoc bonferroni test) [b]	
	Baseline (n=40)	8 weeks (n=40)	24 weeks (n=39)		8 weeks	24 weeks
VAS	5.53±0.67	2.78±0.76	2.45±0.78	<0.001	2.75(2.28-3.21)	3.07(2.83-3.31)
WOMAC-pain	10.43±2.61	5.58±2.48	4.10±1.08	<0.001	4.85(3.86-5.83)	6.32(5.29-7.35)
WOMAC-stiffness	4.80±1.40	3.03±0.89	2.48±0.90	<0.001	1.77(1.32-2.22)	2.32(1.75-2.89)
WOMAC-physical function	39.13±9.19	21.83±5.21	18.68±6.17	<0.001	17.3(13.08-21.5)	20.45(17.1-23.8)
WOMAC-total	54.35±10.52	30.42±6.85	25.25±6.67	<0.001	23.92(19.1-28.6)	29.1(25.3-32.8)

Values are expressed as mean±SD. Difference in mean change at intervals from baseline are expressed as mean change (95% CI).
Statistical test: repeated measures analysis of variance (RMA)a with post hoc Bonferroni test b within the groups.
CI, confidence interval

Table 4: Comparison of mean VAS and WOMAC-Total scores between the groups.

Outcome measures	Time	PRP group (mean±SD)	Steroid group (mean±SD)	p-value[c]
VAS	Baseline	5.85±0.77	5.53±0.67	0.126
	8 weeks	3.58±1.03	2.78±0.76	<0.001
	24 weeks	2.00±0.87	2.45±0.78	0.001
WOMAC- total	Baseline	53.37±10.88	54.35±10.52	0.685
	8 weeks	36.25±10.87	30.42±6.85	0.013
	24 weeks	22.95±3.78	25.25±6.67	0.021

Mann- Whitney U test[c]
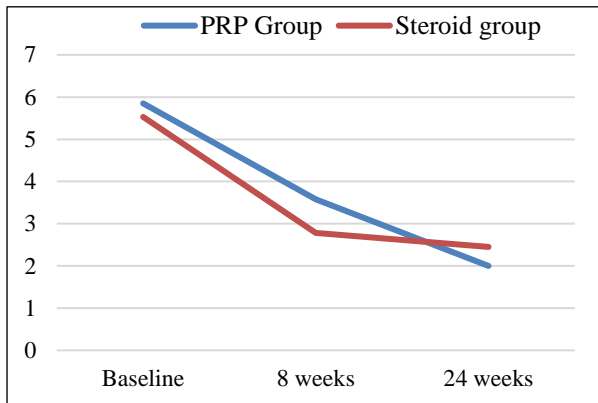
Figure 4: Changes in vas scores over time.
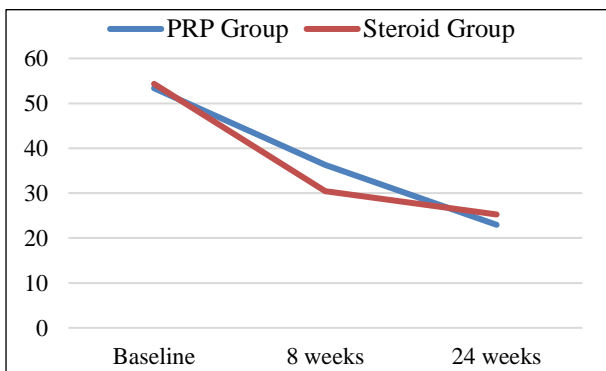
Figure 5: Changes in WOMAC-total scores over time.

There is no statistically significant difference in VAS (5.85±0.77 vs 5.53±0.67) and WOMAC-total (53.37±10.88 vs 54.35±10.52) scores between PRP and steroid group respectively at baseline (p>0.05) (Table 4).

Significant improvement was seen in VAS, WOMAC-pain, stiffness and physical function and total scores in both the groups at 8 and 24 weeks follow ups (p<0.001) (Table 2 and 3). Steroid group showed better result than the PRP group in VAS (2.78±0.76 vs 3.58±1.03) and WOMAC-total (30.42±6.85 vs 36.25±10.87) scores at 8 weeks (p<0.001) (Table 4). But at 24 weeks follow-up, PRP showed significantly more effective than the steroid group in reducing pain (2.0±.0.87 vs 2.45±0.78) and

disability (22.95±3.78 vs 25.25±6.67) (p<0.001) (Figure 4 and 5).

DISCUSSION

Mean age of the study population was 51.60±6.06 and 49.73±4.54 year in PRP and steroid group respectively. Overall male: female ratio is 0.7:1. The finding that the females are affected more than the males comply with the previous studies.[9] Previous studies have found that female gender is also a strong risk factor for incident KL ≥2 knee OA, possibly implicating the involvement of muscle strength to compensate for mechanical stress.[9] As men generally have more muscle strength than women, muscle strength involvement may compensate for the mechanical stress on the joint, which reduces the risk of occurrence of the disease in men. However, the Research on Osteoarthritis Against Disability (ROAD) study has reported that female gender is not a significant risk factor for incident KL ≥3 knee OA or progressive knee OA.[10]

Majority of the patients had osteoarthritis affecting the right knee (61%) as compared to the left knee (39%). The present finding is in compliance with those observed by Neame R et al.[11] They observed more global tibiofemoral joint osteoarthritis and higher ostephyte scores on the right side. This contrasts with the Zoetermeer Survey, in which global OA was equally distributed between the right and left knees.[12]

Kneeling and squatting are common postures in daily life; this lifestyle factor could obscure the association between knee OA and the occupational activities of kneeling and squatting.

Obesity is a strong risk factor for incident knee OA, possibly because of the accumulation of mechanical stress on the knee joint. The mean Body Mass Index (BMI) of the PRP and steroid group were 27.03±2.65 and 27.62±1.83 kg/m^2 respectively, which falls in the obesity group in the continuum of BMI for the Asian population.[13]

Excess weight affects OA severity and pain. With regard to OA severity and BMI, researchers have found that obesity is the main modifiable trait in helping reduce knee OA effects. Excess weight increases the risk of knee

OA even after controlling for smoking, diet, alcohol, Heberden's nodes and socio-economic status.[14]

The mean platelet concentration of the PRP group at baseline is (2.53±0.54) x105/ml. Platelet rich plasma was prepared by the conventional bench top centrifugation system. The mean concentration achieved after preparation of PRP by centrifugation is (5.26±0.90) x105 /ml. The platelets are concentrated on an average of 2.08 times the initial concentration which is less than the recommended concentration of 3 to 5 times the baseline platelet concentration.

In the present study there was significant improvement in the mean score of all the outcome measures; Visual Analogue Scale (VAS), WOMAC- Pain, Stiffness and Physical function and Total score in both the groups at 8- and 24-week follow-ups (p<0.05). When both the groups are compared, the steroid group is better than the PRP group in terms of improvement in mean VAS and WOMAC scores at 8 weeks follow-up (p<0.05). This can be explained by the rapid short-term effects of the corticosteroids.

Corticosteroids inhibit prostaglandin synthesis and decrease the activity of collagenase and other enzymes. Their major mechanism of benefit in osteoarthritis, however, remains unclear. Saxne et al, measured the release of proteoglycans into synovial fluid to monitor the effects of therapy on cartilage metabolism.[15] Their data strongly suggest that intra-articular corticosteroid injections reduce the production of interleukin-1, tumor necrosis factor alpha and proteases that may degrade the cartilage.

In the present study, the improvement of the mean scores of the outcome measures; VAS, WOMAC- Pain, Stiffness and Physical function and Total score in the PRP group was more than the steroid group at 24 weeks follow-up.

PRP relieves symptoms owing to its three known biological properties. Firstly, PRP has an anabolic effect on chondrocytes, Mesenchymal Stem Cells (MSCs) and synoviocytes with resultant increases in cell proliferation, cartilaginous ECM accumulation, and HA secretion. Secondly, PRP may act as a bioactive cell scaffold to fill defects and enhance cartilage regeneration. Thirdly, PRP has the potential to inhibit inflammation and alleviate OA symptoms with a clinically acceptable safety profile.[8]

There were no major adverse effects following intra-articular PRP injection. Three patients had mild burning pain at the injection site, swelling of the knee, local rise of temperature. These were treated symptomatically. No systemic symptoms and infections were noted in the present study.

The limitations of the study are platelet concentration yield by conventional bench top centrifugation system

(average 2.08 times the baseline concentration) is slightly less than the recommended concentration, non-blinding of the study and shorter duration of follow-up period.

To sum up, studies indicate that PRP is promising for relieving pain, improving knee function and quality of life. But there is no data that PRP will cause osteophytes to regress or cartilage and meniscus to regenerate in patients with substantial and irreversible bone and cartilage damage. More promising results are shown in younger patients, and in mild OA cases. The study shows that 2 doses of PRP injection 2 weeks apart significantly reduce pain and disability in primary osteoarthritis knee of Kellgren-Lawrence grade 2 and 3 at 24 weeks, however long-term benefit is to be determined by studies with a larger sample size and longer duration of follow-up.

CONCLUSION

Intra-articular injection of methylprednisolone was found to be more effective in reducing pain and disability in primary knee osteoarthritis of Kellgren-Lawrence grade 2 and 3 at the end of 8 weeks whereas 2 doses of PRP intra-articular injection 2 weeks apart was significantly more effective than methylprednisolone at the end of 24 weeks. However, the long-term benefit of PRP is to be determined by studies with a larger sample size and longer duration of follow-up.

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