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Efficacy of Autologous Intra-articular Platelet Rich Plasma Injection as a Biological Adjuvant in Early Primary Osteoarthrosis Knee—A Prospective Study

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ABSTRACT

Introduction: Classical characteristics of osteoarthrosis are reduction or loss of articular cartilage, new bone formation, accompanied by synovial proliferation resulting in pain, loss of joint function, and disability. Platelet rich plasma (PRP) has been used to provide stimulus for local regeneration and healing. The present study was conducted with the aim of evaluating the clinical outcome and efficacy of injecting PRP intra-articularly in early primary osterarthrosis knee.

Objective: Prospective study was conducted with the aim of evaluating the clinical outcome of efficacy of injection of PRP in early primary osteoarthrosis knee with respect to pain, stiffness, function and quality of life, in short-term follow-up. Attempt was made to standardize protocol and formulate PRP.

Materials and Methods: Patients were divided into two groups: one treated with two autologous PRP injections at 2 weeks interval and second received symptomatic treatment with physiotherapy. Patients were prospectively evaluated at baseline and then at 1 month, 3 months, and 6 months of follow-up using the visual analog scale (VAS) score, Western Ontario and McMaster Universities osteoarthritis index (WOMAC) score, and range of movements.

Results: There was reduction in VAS score in group 1 patients compared with group 2 patients with the *p*-value <0.0001 which was highly significant. There was a significant improvement in WOMAC score at 1 month, 3 months, and 6 months in group 1 compared with group 2 patients.

Conclusion: Autologous PRP in osteoarthrosis of knee has emerged as a simple technique, sensitive procedure, and cost-effective treatment option. Administration of intra-articular PRP injections reduced the VAS score significantly and also a significant improvement in the WOMAC score was observed in patients who were treated with PRP injection. The two doses of injection of PRP were found to give adequate relief in short term of 6 months and further long-term studies are required.

Keywords: Osteoarthrosis, Platelet rich plasma, Intra-articular, VAS score, WOMAC score

INTRODUCTION

Osteoarthrosis (OA) is the most common articular disease of the developed world and a leading cause of chronic disability.[1] It is characterized by a progressive loss of articular cartilage accompanied by new bone formation and often synovial proliferation that may culminate in pain, loss of joint function, and disability.[2] OA is a chronic disorder of synovial lined joints where there is progressive softening and disintegration of articular cartilage accompanied by new growth of cartilage and bone at the joint margins, cyst formation and sclerosis at subchondral regions

of bone, mild synovitis, and capsular fibrosis. Risk factors such as age, sex, trauma, overuse, genetics, and obesity can each make contributions to the process of injury in different compartments of the joint. Such risk factors can serve as initiators that promote abnormal biochemical processes involving the cartilage, bone, and synovium, which over a period of years result in the characteristic features of OA: degradation of articular cartilage, osteophyte formation, subchondral sclerosis, meniscal degeneration, bone marrow lesions, and synovial proliferation.[2] The process of articular cartilage degeneration in OA has several mechanisms with many still unknown but the process can be divided into the three overlapping stages: (1) cartilage matrix alteration; (2) chondrocyte response to tissue damage; (3) decline of the chondrocyte synthetic response and progressive loss of tissue.[3–5] The loss of articular cartilage leads to secondary changes in synovium, ligaments, capsules, and muscles that move the involved joints. The earliest microscopic changes in joint degeneration include fraying and fibrillation of articular cartilage superficial zone extending into the transitional zone. Some investigators have postulated that stiffening of a subchondral bone as a result of remodeling precedes and causes articular cartilage degeneration and that progression of cartilage degeneration requires stiffening of subchondral bone.[6] Enzymatic degradation of matrix simultaneously decreases the cartilage volume further eventually; the progressive loss of articular cartilage leaves only dense and often necrotic, eburnated bone.[7,8]

Recent trends in treatment focus on cartilage tissue repair processes including mesenchymal stem cell therapy, autologous chondrocytes implantation, use of matrix metalloproteinase inhibitors, gene therapy, and growth factors. Presently, different researches and systematic reviews have been performed on the effect of platelet rich plasma (PRP) in knee OA. The present study is a prospective observational study with control group to investigate the effect of PRP on pain, stiffness, function, and quality of life of patient suffering from knee OA.

Aims and objectives

Ortho-biologic is an emerging branch of medicine and PRP has shown promising results in various fields of medicine. Since it is an emerging technique in OA knee, there are some research gaps.

The present study was conducted to:

1. Evaluate the clinical efficacy and outcome of intra-articular injection of PRP in early primary OA of knee.
2. Study the use of PRP without activators using two spin technique in early OA of knee.
3. Evaluate frequency of doses whether two injections of PRP are adequate at 2 weeks interval for short-term favorable clinical results.
4. Compare two PRP injections to conventional conservative treatment on clinical outcome of pain, stiffness, and function of knee.

MATERIALS AND METHODS

The prospective study was performed in a tertiary care government hospital (Government Medical College Nagpur) in Department of Orthopaedics from July 2018 to June 2020.

Patients presenting to our institution with knee joint pain of more than 3 months, restriction of movement, and swelling were evaluated clinically and radiologically. Those with OA were classified by KELLGREN LAWRENCE classification. Eighty-four patients with OA grade I, II, and III were alternatively allocated into two groups on the basis of alternative allocation method according to their inclusion criteria in the study. In total, 84 patients were calculated as considering confidence level 95% with margin of error within ± 10.7% in 50% population proportion. Patients in first group were given two autologous PRP injections at 2 weeks interval and in second group were received symptomatic treatment with physiotherapy. Data was obtained for parameters like age, height, weight, BMI, sex, visual analog scale (VAS) score, Western Ontario and McMaster Universities osteoarthritis index (WOMAC) score, and range of movements. Consent from the patients and ethical committee clearance was obtained.

Inclusion criteria: Symptomatic patients of OA having arthralgia from 3 months between age 50 and 70 years with normal blood profile having radiologic evidence of OA were included.

Exclusion criteria: Patients with uncontrolled diabetes, collagen vascular disease, septic arthritis, inflammatory arthritis, active wound over knee, patients on treatment with anticoagulant medications 10 days before injection, patients using non-steroidal anti-inflammatory drugs 3 days before injection, and patients with unstable knee were excluded.

Methodology

In Group 1, after explaining the procedure, 40 mL venous blood was collected from cubital vein with the help of a 18-gauge needle. Blood was collected in two centrifuge tubes in equal amount (20 mL in each). PRP was prepared by two spin method by using centrifuge machine. Blood collected in two tubes was centrifuged at 2,800 rpm for 10 minutes. Centrifugation gave three layers, upper layer composed

of plasma platelets and some WBCs, intermediate layer or buffy coat composed of WBCs, and bottom layer of RBCs. The upper layer was separated with pipette. Blood was again centrifuged at 3,500 rpm for 10 minutes; the upper half of the plasma volume with platelet poor plasma was removed and the remaining volume of plasma rich in platelet was collected. The final product was 3 to 4 mL of plasma containing higher concentration of platelets. No exogenous factors were used for activation. PRP was injected using 22-gauge needle through a classical approach for intra-articular injection (supra-patellar or medial) into affected knee immediately in sterile conditions. Patients were asked to actively flex and extend their knees after a waiting period of 15 to 20 minutes to spread PRP evenly across the joint space. The patients were advised limited weight bearing for 24 to 48 hours post injection. Cold therapy was advised thrice a day for 10 minutes each. Tab paracetamol 500 mg was advised for pain, if required. The patients resumed daily activities on second day with subsequent increase in activity as tolerated. Exercises were started at 1 week and gradually increased in intensity. In the control group, exercises were started immediately with tab paracetamol as and when required.

Clinical evaluation of patients was done using: (1) WOMAC score for pain, stiffness, and functional outcome; (2) VAS score for pain and 3—range of movement.

Statistical analysis

The data was collected and analyzed by using SPSS version 20 (IBM Inc.). Reliability test was conducted for the study. Cronbach's α-value was found to be 0.92. The data collected was found to be reliable as any value above 0.70 in reliability study is acceptable. Validity test and data adequacy test were conducted. Data was found to be both valid and adequate. The data was collected and analyzed by descriptive statistics method. Continuous variables were presented as mean SD and compared by independent *t*-test. Pre- and posttreatment VAS score was compared by paired *t*-test. Posttreatment changes between two groups were compared by independent *t*-test. Changes in WOMAC score at 1, 2, and 6 months from baseline (pre-treatment) between two groups were compared by independent *t*-test. All the tests were two sided. $p < 0.05$ was considered as statically significant. We compared the two groups at 1 month, 2 months, and 6 months of follow-up in terms of pain, stiffness, and functional capacity. The reductions in pain, VAS, and total WOMAC score were higher in PRP treated group (group 1).

RESULTS

The efficacy of intra-articular injection of PRP in early OA knee patients was evaluated.

Mean age and BMI of patients in this study: Maximum number of patients presented in age group of 50 to 70 years with a mean of around 60. There was a consistent association between OA and increased BMI. No correlation was found in male and female population [Table 1].

The mean total VAS score changes between the two groups after treatment had a significant difference. The table showed comparison of mean change in pain score between group 1 (PRP) and group 2 (control) after post-injection. The *p*-value is <0.0001 (HS) [Table 2].

Table 3 shows a mean WOMAC score at different follow-up period in PRP-treated group.

Table 4 shows a mean WOMAC score at different follow-up period in control group.

On repeated measured ANOVA test, no improvement was seen in initial follow-up periods at 4 weeks and 2 months of treatment, but at 6 month, improvement in WOMAC was seen in both the groups. Significant improvement was present in PRP group compared with control group patients [Table 4].

Comparison of changes in WOMAC score at 4 weeks, 2 months, and 6 months from baseline between group 1 and group 2 is seen in [Table 5].

Table 1: Mean age and BMI of patients in this study.

Variables	PRP group	Control group	*p*-value	Test of significance
Age, mean ± SD	61.02 ± 10.23	59.33 ± 9.68	<0.05	Significant by independent *t*-test
BMI, mean ± SD	28.23 ± 4.1	27.30 ± 3.27	<0.05	

Table 2: Mean change in VAS score after injection.

	Mean VAS Pre-injection	Mean VAS Post-injection	Mean change in VAS score	*t*-value	*p*-value	Test of significance
Group I (PRP)	7.07 ± 0.99	3.04 ± 1.22	4.02 ± 1.3	9.6455	<0.0001,	Highly significant by paired *t*-test
Group II (CONTROL)	6.85 ± 0.81	5.05 ± 0.89	1.83 ± 0.79			

Table 3: Mean WOMAC score at different follow-up period in PRP-treated group.

Performance measurement factors	Pre-injection score	WOMOC-score at 4 weeks	WOMAC score at 2 mo	WOMAC score at 6 mo	By repeated measured ANOVA test
Age					
40–60 y	1.67	2.5	2.5	1.67	
47–53 y	2.25	2.75	2.5	1.50	
54–60 y	2.00	2.70	2.5	1.90	
61–67 y	1.78	2.44	2.22	1.33	
68–75 y	2.15	2.23	2.15	1.23	
F-test (ratio)	0.601	0.423	0.355	0.868	
Sig.	0.664	0.791	0.839	0.492	

Table 4: Mean WOMAC score at different follow-up period in control group.

Performance measurement factors	Pre-injection score	WOMAC score at 4 wk	WOMAC score at 2 mo	WOMAC score at 6 mo	By repeated measured ANOVA test
Age					
40–46 y	3.00	2.83	2.83	2.50	
47–53 y	2.85	3.57	3.00	2.00	
54–60 y	2.00	2.50	2.25	1.50	
61–67 y	2.85	3.31	2.54	1.92	
68–75 y	2.50	3.08	2.67	2.00	
F-test (ratio)	1.62	0.922	0.544	0.869	
Sig.	0.189	0.462	0.704	0.492	

Table 5: Comparison of change in WOMAC score at 4 weeks, 2 months, and 6 months from baseline between group 1 and group 2.

	Group 1	Group 2	*t*-value	*p*-value	Test of significance
	Mean ± SD	Mean ± SD			Highly significant by independent *t*-test
At 4 wk	11.38 ± 4.51	6.02 ± 3.86	5.8403	<0.0001, HS	
At 2 mo	26.26 ± 7.22	7.95 ± 3.02	15.1413	<0.0001, HS	
At 6 mo	39.67 ± 7.05	3.83 ± 3.17	30.0220	<0.0001, HS	

Comparison of change in WOMAC Score at 4 weeks, 2 months, and 6 months from baseline (pre-injection) between PRP and control group is seen in [Table 5].

DISCUSSION

Various treatment modalities available for treatment of OA can be divided into (1) non-pharmacological methods that include physiotherapy, acupuncture, transcutaneous electrical nerve stimulation (TENS), electromagnetic therapy and other aides and devices; (2) Pharmacological treatments like oral non-steroidal anti-inflammatory drugs (NSAIDS) and opioids, topical NSAIDS, capsaicin, and nutraceuticals; (3) Intra-articular injections used like steroids, hyaluronic acid, PRP, and combinations of these[9]; (4) Surgical treatments like arthroscopic debridement, proximal femoral osteotomy (PFO)/high tibial osteotomy (HTO), and total knee replacement (TKR). No available treatment options except osteotomies alter the course of the disease.

The use of PRP is quick, minimally invasive, and relatively low-cost therapeutic strategy. Classically, PRP is considered as a volume of plasma containing higher concentration of platelets compared with blood basal level. Platelets contain different growth factors and cytokines and plasma contains proteins and bioactive molecules which play an important role in cellular repair process. In OA, the mechanical properties of articular cartilage change due to change in cellular and biochemical process. Progression is due to predominance of pro-inflammatory over anti-inflammatory cytokines causing cartilage destruction. Balance between destruction and repair mechanism is disturbed. There is an increased expression of pro-inflammatory cytokines, matrix metalloproteinase, aggrecanase nitric oxide, and prostaglandin that ultimately lead to joint destruction. Injected platelet may act at different levels like joint homeostasis, reduction of synovial membrane hypoplasia, and modulation. PRP is a regenerative treatment, that stimulates cell proliferation and cartilage matrix and

regulates expression of chondrocyte phenotype. PRP has a role in preventing catabolism of articular cartilage. Various factors, such as transforming growth factor β, raise the chondrocyte–phenotype expression and initiate mesenchymal stem cells differentiation. Platelet-derived growth factor causes cell proliferation and increased synthesis of glycoproteins. Vascular endothelial growth factors induce cartilage and fibroblast and hepatocyte growth factors cause regeneration of articular cartilage metabolism.[10] It is postulated that injection of PRP results in efficient delivery of these factors to maintain their high concentrations and promote healing.

Several ortho-biologic products are coming up for treatment of chronic diseases like OA and sports injuries. They are organic ortho-biologic products like bone marrow aspirate concentrate, mesenchymal stem cells, and PRP and synthetic ortho-biologic products likes bone void fillers, visco-supplementation products, and synthetic bone marrow proteins.[11]

Four main families of autologous blood preparation can be defined depending on their content of platelets and fibrin architecture as pure platelet rich plasma (P-PRP) or leucocyte poor PRP, leucocyte rich PRP (L-PRP), pure platelet rich fibrin or leucocyte poor PRP, and leucocyte and platelet rich fibrin or second generation PRP.[12]

The basic principle of autologous PRP is differential centrifugation. Two common methods are used, the double spin method uses two centrifugation and gives a PRP which has a minimum or no leucocyte (P-PRP) and which can be used for intra-articular injection; buffy coat method with single hard spin which gives L-PRP and used in conditions like planter fasciitis. We have used two spin centrifugation method for the preparation of PRP and no activator was used in this study.

Our study included patients in the range of 50 to 70 years of age with a mean age group 61.0 ± in group 1 and 59.33 ± 9.68 in group 2. Study conducted by Sánchez et al included 187 patients with age between 40 and 72 years and with a mean of 59.8 years.[13] The study of 20 patients by Hassan et al found age range from 40 to 70 years with a mean age of 50.4 ± 8.[14] A study by Jang et al included 65 patients with a mean age of 59.7 years and an age range of 32 to 85 years.[15] It was found that symptomatic OA is more prevalent in age group of 50 to 70.

Our study had a mean BMI of 28.23 ± 4.1 in group 1 and 27.30 ± in group 2. BMI of patients in a study by Sánchez et al was 27.9 = ± 2.9 in PRP group and 28.2 ± 2.7 in HA group. In a study by Hassan et al, BMI was 28.4 ± 7.2 and in a study by Patel et al BMI was 25 ± 3.[13–16] Increased BMI is associated with risk of OA. A Study by Jang et al showed that injection of PRP had effective results for longer period of time in young and low BMI patients.[15]

Table 6: Comparison between our study and other studies.

SR no.	Study name	Sample size	VAS score at baseline	VAS score at 6 mo
1	Our study (PRP group)	42	7.07 ± 0.99	3.04 ± 1.22
2	Our study (control group)	42	6.85 ± 0/81	5.02 ± 0.89
3	Hassan *et al.*	20	5.9 ± 1.3	3.9 ± 1.1
4	Patel *et al.* (group B)	78 (27)	4.64	2.54
5	Jang *et al.*	65	7.4	4.2

No correlation was found in patients with different sex groups in our study as well as in other studies except a study by Sánchez et al which found OA is more prevalent in female patients.

The average VAS score shows significant improvement from baseline to 6 months of follow-up periods in group 1 patients compared with group 2 patients. A study by Hassan et al, Jang et al, and group B in Patel et al showed similar results as mentioned in [Table 6].[14–16] Study conducted by Jang et al continued his study up to 12 months of follow-up period and concluded there was deterioration in VAS score from 9 months onward. He calculated accurate relapse time for pain in OA patients treated with two injections of PRP.

In our study, we found significant improvements in WOMAC score such as 73.28 ± 4.54 at baseline to 33.61 ± 7.97 at 6 months in group 1 patients compared with 70.02 ± 4.61 to 66.19 ± 5.17 in group 2 patients. In Patel et al's study, 78 patients with bilateral knee involvement were divided into three groups as group A: 27 patients treated with single PRP injection, group B: 25 patients with two doses of injections, PRP in interval of 3 weeks, and group C: with normal saline (placebo). WOMAC score was used only in a study by Patel et al which showed similar results as our study with improvement from 53.20 to 30.48 at 6 months follow-up period in group B patients (PRP-treated group)[16] [Table 6].

Emerging concepts like intra-osseous infiltration of PRP in severe OA knee has been studied by Sánchez et al in subchondral area of tibia, femur, and patella along with intra-articular use for which they coined the term "local biologic joint centric approach."[13]

Complications

We encountered mild swelling and mild local rise in temperature around knee with some pain which lasted for 10

to 12 days in 6 patients out of 42 patients. In a study by Jang et al of 65 patients, there was a mild swelling and mild local heating around knees in 10 patients which was relieved within 14 days.[15] Mild pain to moderate pain in six patients and bruising at knee joint in two patients were found in a study of 20 patients conducted by Hassan *et al*.[14] In a study by Patel et al, there were systemic complications likes syncope, dizziness, headache, nausea, gastritis, sweating, and tachycardia in some patients after second dose of PRP injection.[16] We did not encounter any systemic complications.

This was a short-term study and further large randomized multicentric studies would help to throw light on various emerging concepts and trends in use of PRP and ortho-biologics.

CONCLUSION

Autologous PRP has emerged as efficacious treatment option in early OA knee. It is simple, cost effective but a technique-sensitive procedure. Administration of two PRP injection 2 weeks apart resulted in significant VAS score reduction and improvement in WOMAC score in a period of 6 months. The injections were effective in reduction of pain, stiffness, and symptoms and improved quality of life of the patients without any severe complications. The maximum effect was seen in patients who presented earlier with OA symptoms.

Conflict of interest

None declared.

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