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ORIGINAL ARTICLE

Effectiveness of Platelet Rich Plasma for the Management of Knee Osteoarthritis: A Randomized Placebo Controlled Trial

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ABSTRACT

Aim: To determine impact of platelet rich plasma therapy for the management of knee osteoarthritis.
Study design: Prospective double-blinded, add –on randomized, placebo-controlled trial
Place and duration of study: Department of Orthopedics, Shaikh Zayed Hospital Lahore from 1st January 2019 to 30th June 2019
Methodology: Fifty volunteer participants fulfilling inclusion criteria were enrolled. One hundred knees of patients were randomly allocated into two groups. Knees were assigned either of the two groups. Platelet rich plasma group which was assigned to receive 5ml of platelet rich plasma and normal saline (NS) group which was assigned to receive 5ml of NS labeled as control group. All patients given 3 successive intra-articular injections of 5 mL of autologous platelet rich plasma or 5ml of normal saline was given at weekly intervals. Patients were blinded and subjected to a standardized injection protocol and the intensity of pain was assessed on visual analog scale (VAS) for pain.
Results: The VAS scores decreased from 50.9±14.7 at baseline assessment to 43.6±16.2 at 1-month follow-up after completion of therapy for PRP group (p<0.0203). The improvement was maintained from the end of the therapy to 3 and 6 months' follow-up, as measure of VAS score as 30.54±11.8 and 20.2±8.6 respectively (p<0.0001). In normal saline group, there was very slight decrease in VAS score from baseline i.e. 49.8±19.5 to 48±22.7, 44±16.6, and 42±21.7 at 1, 3 and 6 months interval.
Conclusion: Platelet rich plasma therapy can provide effective pain control up to 6 months post injection in knee osteoarthritis.
Key words: Platelet rich plasma (PRP), Knee osteoarthritis (OA), Pain score

INTRODUCTION

Osteoarthritis is a degenerative joint disease. In this condition the regular cushioning cartilage between the articulating surfaces of the large synovial joints in the body erodes away gradually due to age related wear and tear. In due course of the disease, the denuded articular surfaces of the joints start to rub against each other abrasively and cause pain, swelling, stiffness and a diminished capacity to move.[1]

Osteoarthritis (OA) knee is a frequently diagnosed issue in the US. Symptomatic knee OA is found in 10% men and 13% women over 60 years. The number of individuals influenced with symptomatic OA is probably going to increase in the recent future as the demography suggest, there is an expected increase in life expectancy and also an increase in fraction of population, who are overweight. The etiology of OA is multi-factorial and still a bit elusive. It is associated with advancing age, predominantly in females and people who are overweight. However it is also seen as a familial (genetic) predisposition, secondary to trauma, repetitive miss use of steroids have also been seen to be associated with osteoporosis, muscle, weakness and joint laxity.[2]

Knee Osteoarthritis is a very common condition requiring frequent OPD follow-ups, prolonged medical therapies before ending up in expensive invasive treatments, like joint replacement surgeries.[3] Still very little is known about the prevalence of these pathologies in our society. Assessing the actual incidence requires apparatuses that enable specialists to screen huge samples drawn from the overall population and to distinguish people well on the way to have this disease.[4] However people are diagnosed now after a thorough clinical examination by a doctor followed by a conclusive X-ray evaluation.[5]

Symptomatic OA is commonly characterized by agonizing pain, stiffness, difficulty in movements (loss of motion) and deformity in late stages along with all radiographic features of OA. According to Framingham subject ≥26 years had the incident of hand and knee OA, as 6.8% and 4.9% respectively. But knee OA was 16.7% among subjects age ≥45 in the Johnston County Osteoarthritis Project, a lot higher than Framingham Study. Furthermore, in light of the fact that OA is a disease of the old people who are simultaneously suffering from different ailments makes direct estimation of the rate of OA troublesome.[6]

Treatment with PRP was helpful in improving pain, mobility and regenerative capacity of the joints. The examiners found out that knee scores estimated by a standard test called the Western Ontario and McMaster Universities Arthritis Index, improved with a decrease of 41.7% at a half year and 55.9% at one year. On commonly

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utilized pain scale called the Visual Analogue Scale, pain decreased by 56.2% at a half year and 58.9% at one year. Functional scores improved by 24.3% at one year. Movement of Daily Living Scores likewise demonstrated a noteworthy increment at both a half year (46.8%) and one year (55.7%).[7]

MATERIALS AND METHODS

This study was a prospective double-blinded, add –on randomized, placebo-controlled trial was conducted at Department of Orthopaedics, Shaikh Zayed Postgraduate Medical Institute from January 2019 to June 2020 after approval from Ethical Committee. The participating individuals and the treating physician who were involved in outcome assessment were blinded to treatment arm. All the participants were counselled to carry on with physiotherapy and remedial knee exercises. A maximum one gram Paracetamol as per requirement was recommended as a supportive medicine. The trial was amenable with consolidated standards of reporting trials (CONSORT). All patients of both gender aged more than 35 years already diagnosed cases of knee osteoarthritis with clinical history of knee pain lasting between 6 and 24 months, resistant to NSAID, and associated with radiological findings of knee osteoarthritis (OA) were included. Previous hyalournic acid (HA) Knee injections if performed more than 12 months were not enrolled. Patients with previous knee surgery at the affected knee, severe knee deformities following knee fractures, severe dysplasia, breastfeeding, diabetes mellitus, rheumatoid arthritis, severe cardiovascular diseases, infections and immune-compromised, current consumption of drugs other than NSAID, hematological diseases, coagulopathies, therapies with anticoagulant, hemoglobin levels less than 11 mg/dL or platelet levels less than 150,000/μL, and previous ipsilateral hip prosthesis were excluded.

One hundred and twenty eighty knees of patients were randomly allocated into two groups; PRP group assigned to the group receiving 5ml of platelet rich plasma (PRP) and NS group was assigned to receiving 5ml of normal saline (NS) were labelled as control group. Randomization of knees guaranteed the comparable baseline characteristics of the two groups with respect to age, gender, weight, height, body mass index (BMI), and pre-injection visual analogue scale (VAS) scores.'

Platelet-rich plasma preparation: 20mL of venous blood was taken from each patient and collected in a syringe containing 0.5ml of Heparin. After shaking it is transferred into 3 sterile vaccutainers, in equal proportions. It is then given 2 spins in a centrifuge. The first cycle was run at 1800 rpm for 15 minutes to separate erythrocytes. The supernatant was segregated in a separate tube along with the Buffy layer and spun again. The second cycle was run at 3500 rpm for 10 minutes to concentrate platelets. Then the upper Platelet Poor Plasma (PPP) is wasted and lower Platelet Rich Plasma (PRP) is taken in a sterile syringe for injection. Just before the injecting the PRP is activated with few drops of 10% calcium chloride.

Treatment procedure: Each patient was placed supine with the knee in approximately 90 degree of flexion. The lateral eye of the Patella is palpated and injection needle of 20 gauges is introduced into the knee in caudal and medial direction. At the end of the procedure, the patient moved the knee a couple of times to encourage the circulation of the infused substance in the joint. The patient was then counseled to restrain utilization of the leg for a couple of hours and afterwards advised to perform light exercises. Nonsteroidal anti-inflammatory drug (NSAID) utilization was prohibited for first 48 hours after treatment. NSAID utilization was taken into consideration, together with all conceivable post treatment symptoms. All patients given 3 successive intra-articular injections of 5 mL of antilogous PRP or 5ml of normal saline was given at weekly intervals.

Patient's evaluation and follow-up: Patients were blinded and subjected to a standardized injection protocol and the intensity of pain was assessed on visual analog scale (VAS) for pain. The average pain recorded using the 100 mm VAS before the treatment (at baseline) and at3 times (1 month, 3 months and 6 months) after completed course of three injections. VAS score "0" was considered no pain and 100 was severe pain. Patients were also assessed for treatment related adverse effects. All patients were evaluated by the evaluator who was blinded to the treatment arm.

Treatment outcomes: The treatment was tagged as "effective" when pain relief was >50% from baseline after 6 months. The primary outcomes were significant improvement in the visual analogue scale (VAS) score from baseline on follow-up at 1 month, 3 months and finally on 6 months following treatment procedure.

All data was entered and analyzed using SPSS 22.0. Effectiveness was compared between the groups by applying Chi-square test. A p value ≤0.05 was considered as statistically significant

RESULTS

Mean pain score on visual analogue scale (VAS score) was 50.1±14.7 among participants of PRP group and was 48.8±12.6 among NS group. The difference between baseline VAS score in both groups was statistically in-significant (p=0.636) (Table 1). The data was stratified according to age, gender, grading of osteoarthritis (OA), duration of disease, and BMI of the study participants and their frequencies and percentages were determined. The characteristics of participants shows no statistically significant difference between groups (p>0.05). (Table 2)

A 100mm Visual Analogue Scale was used to document average pain score of knee of each participant at baseline, 1, 3, and 6 months follow up time. The VAS scores decreased from 50.9±14.7 at baseline assessment to 43.6±16.2 at 1-month follow-up after completion of therapy for PRP group. The difference in VAS score from baseline to 1 month follow up was found statistically significant (p<0.0203). The improvement was maintained from the end of the therapy to 3 and 6 months' follow-up, as measure of VAS score as30.54±11.8 and 20.2±8.6 respectively. The decrease in VAS score was highly significant at these time intervals (p<0.0001). For the participants in NS group who were receiving injections of normal saline (NS) in addition of Paracetamol and physiotherapy, there was very slight decrease in VAS score from baseline i.e. 49.8±19.5 to 48±22.7, 44±16.6, and 42±21.7 at 1, 3 and 6 months interval. The decrease in VAS score was statistically in-significant with p value equal to 0.6715, 0.1125, 0.0616 at follow up of 1, 3, and 6 months respectively. This shows benefit in pain reduction as measured by VAS score was significant in PRP group as compared to NS group (Fig. 1).

The treatment was tagged as "effective" when pain relief was >50% from baseline after 6 months. It was observed that intervention with platelet rich plasma (PRP) in addition to paracetamol and physiotherapy was effective in 46 participants

having more than 50% relief in pain from baseline. Whereas participants who received injections of normal saline (NS group) in addition to paracetamol and physiotherapy, only 15 participants could get benefit of treatment showing >50% pain relief. Chi-square test was used to show the association of effectiveness of treatment with type of intervention. It was observed that PRP therapy was more effective than NS and the difference was statistically significant with p<0.0001.

Data was stratified and association of effect modifiers with effectiveness of treatment was calculated. It was observed that age < 50 years, female gender, osteoarthritis grade III, duration of disease less than 5 years was significantly associated with treatment effectiveness with p value <0.0001, 0.021, 0.04, 0.03 respectively. Furthermore no statistically significant association was found between BMI and treatment effectiveness (p = 0.511) [Table 4].

Table 1: Baseline characteristics of study participants

Characteristics	PRP Group	NS Group	P value
Age (years)	60.03±4.7	58.7±3.9	0.133
Weight (Kg)	82.12±7.6	79.6±6.7	0.082
Height (cm)	163.02±9.9	159.97±8.1	0.095
BMI	29.7±4.7	31.2±6.7	0.198
Duration of Disease	9.3±3.6	8.5±3.1	0.237
Baseline VAS score	50.1±14.7	48.8±12.6	0.636

Table 2: Frequency of study participants

Variable	PRP Group	NS Group	Total	p-value
Age (years)				
<50	19	24	43	0.419
≥50	31	26	57	
Gender				
Male	17	20	37	0.681
Female	33	30	63	
Osteoarthritis grade				
II	13	9	22	0.27
III	18	26	44	
IV	19	15	34	
Duration of disease (years)				
<5	32	38	70	0.28
≥5	18	12	30	
Body mass index (kg/m^2)				
Normal	6	4	10	0.81
Over weight	10	25	35	
Obese	34	21	55	

Table 3: Association of treatment effectiveness with type of Intervention

Group	Effectiveness of treatment		Total
	Yes	No	
PRP group	46	4	50
NS group	15	35	50
Total	61	39	100

p <0.0001

Fig. 1: Comparison of Mean VAS score of study groups at different time interval

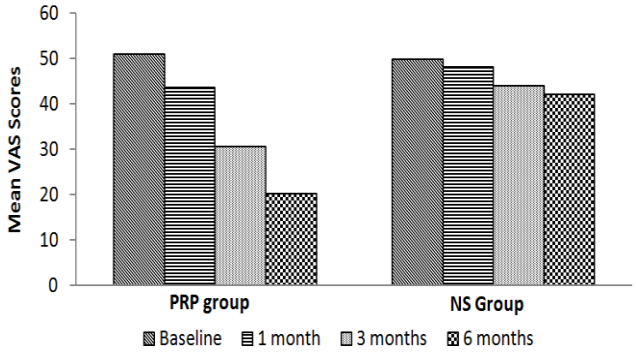

Table 4: Association of effect modifiers with effectiveness of treatment

Variable	Effectiveness of Treatment		Total	p-value
	Yes	No		
Age (years)				
<50	37	6	43	<0.0001
≥50	24	33	57	
Gender				
Male	28	9	37	0.021
Female	33	33	63	
Osteoarthritis grade				
II	16	6	22	0.04
III	30	14	44	
IV	15	19	34	
Duration of disease (years)				
<5	48	22	70	0.03
≥5	13	17	30	
Body mass index (kg/m^2)				
Normal	6	4	10	0.511
Over weight	24	11	35	
Obese	31	24	55	

DISCUSSION

Platelet rich plasma, ordinarily alluded to as "PRP', is a very good natural regenerative agent, recently quite in vogue. It is being frequently used to augment healing in tendon injury/repair, ligaments sprains, tears and non-specific inflammatory conditions like tendinitis and anesthopathies. Platelets contain many α-granules. These are powerhouses of numerous growth factors and important chemotactants that help in promoting tissue repairs. It contains high levels of BMP-2, BMP-7, TGF-β1, VEGF and PDGF. When infused in an enhanced concentration at a site, these factors promote healing and repair at a far rapid pace than usual. This hastens recovery and the biological response of the injured tissue.[8]

The potential advantages of organically improved recuperating ability have prompted an ongoing enthusiasm for the utilization of PRP in orthopedic sports injuries. It is being used for muscle strains, tendinopathies including tendon injuries. In Cruciate ligament and Meniscal l reconstruction of the knees and Shoulder labral and cuff repairs, it is being used as an adjunct. Despite the recent exponential increase in its utilization, substantial evidence in its support is still in their outset.[9,10] The joint exposed to repetitive wear stresses and the slowing of the regenerative capacity in advancing age leads to the attrition of the joint cartilage. To assist the cartilage to recovery remains a challenge.[11] Various investigations have been conducted to see the effect of PRP on chondrocyte activation and cartilage regeneration. In an examination it was noticed that there was impressive enhancement in the pain score of patients who have been given intra-articular PRP therapy as compared with Hylarounic Acid infusion.[12]

Although Patel et al[10] compared the PRP with normal saline as a placebo. Study participants were given two PRP injections 3 weeks apart and found to have significant improvement in WOMAC parameters within 2 to 3 weeks and pain relief lasted up to 6 months with marginal worsening noted at 6 months follow up, while decline in WOMAC scores were noted in NS group. In this study different scoring system was used but results are quite comparable to our study.

Forough et al[13] compared the results of Intra-articular corticosteroids with PRP. His study revealed considerable better pain score in the group with PRP as compared to Corticosteroid at the end of 6 month period. In this study a more prominent difference in favor of PRP is noted. Jubert et al[14] also compared corticosteroid and PRP; though a decrease in the pain score was noted in both groups but the difference was not significant. This distinction might be due to the higher

grade of OA in their investigated sample (K-L grades III-IV), in contrast to the present examination. Another prospective study from India assessed the effect of single injection of PRP at one and 6 months interval and found that improvement of symptoms began 2 weeks after the treatment and remained statistically significant up to 6 weeks follow up. Assessment was again done by utilization of WOMAC scores but results are close to what we have observed in our study.[15].

Bansal et al[16] compared effect of PRP versus Hylarournicacid (HA) and it that showed significant improvement in WOMAC scores from baseline in both PRP and HA groups (P<0.001). Intergroup comparison showed significant better composite scores in PRP group in comparison to HA group at 3 (P<0.001), 6 (P<0.001) and 9 months (P < 0.01) and 1 year (P<0.001) respectively.

In terms of side effects Taniguchi Yu et al[17] studied effect of PRP in the treatment of knee osteoarthritis in Japanese population and found to have only minor adverse effects after the injection which settled after 48 hours. This observation is also quite comparable to current study in which only one patient from PRP and two from NS reported minor pain and swelling which was subsided after 2-3 days. Various clinical trials from the literature have suggested that PRP injection in comparison with HA is proved to be better treatment modality in young age groups.[18-21] These results are consistent to findings in our study.

In a study by Jubert et al[14], patients with older ages (mean 67 years), higher BMI value (31 kg/m^2), and higher grades of OA (III or IV) were evaluated, which could justify the lower effectiveness of PRP in their study. These results are in quite in agreement with our observations in terms of age, grade of osteoarthritis but no significant association was found between BMI and treatment effectiveness.

Hence, in the light of above discussion, it is recommended that the patients irrespective of the age, gender and BMI could be managed effectively by using PRP to treat osteoarthritis. Patients with the older age and high grade of OA may have indulged in the long treatment time but they will still have better results as compared to the conventional HA, corticosteroid injection treatment. It can be presumed that PRP promotes regeneration and induce at least reversal of some symptoms. It is the plethora of Growth Factors (GF) in the platelets that induces chondrocyte in the articular-cartilage to regenerate and improve joint function.

CONCLUSION

Platelet rich plasma is a feasible treatment option which can be offered for significant symptomatic improvement in patients with knee osteoarthritis. The treatment effectiveness was notable in young adults of less than 50 years, female gender, presence of grade 3 osteoarthritis and disease duration less than 5 years.

Conflict of interest: Nil

REFERENCES

1. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage 2013;21(1):1621.
2. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. Best Pract Res Clin Rheumatol 2014;28(1):5-15.
3. Melzer D, Guralnik JM, Brock D. Prevalence and distribution of hip and knee joint replacements and hip implants in older Americans by the end of life. Aging Clin Exp Res 2003;15(1):60-6.
4. Roddy E, Thomas MJ, Marshall M, Rathod T, Myers H, Menz HB, Thomas E, Peat G. The population prevalence of symptomatic radiographic foot osteoarthritis in community-dwelling older adults: cross-sectional findings from the clinical assessment study of the foot. Ann Rheum Dis 2015;74(1):156-63.
5. Cedraschi C, Delézay S, Marty M, Berenbaum F, Bouhassira D, Henrotin Y, Laroche F, Perrot S. "Let's talk about OA pain": a qualitative analysis of the perceptions of people suffering from OA. Towards the development of a specific pain OA-Related questionnaire, the Osteoarthritis Symptom Inventory Scale (OASIS). PLoS One 2013;8(11):e79988.
6. Yelin E, Callahan LF. The economic cost and social and psychological impact of musculoskeletal conditions. National Arthritis Data Work Groups. Arthritis Rheum 1995;38(10):1351-62.
7. Chang KV, Hung CY, Aliwarga F, Wang TG, Han DS, Chen WS. Comparative effectiveness of platelet-rich plasma injections for treating knee joint cartilage degenerative pathology: a systematic review and meta-analysis. Arch Phys Med Rehabil 2014;95(3):562-75.
8. Jang SJ, Kim JD, Cha SS. Platelet-rich plasma (PRP) injections as an effective treatment for early osteoarthritis. Eur J Orthop Surg Traumatol 2013;23(5):573-80.
9. Middleton KK, Barro V, Muller B, Terada S, Fu FH. Evaluation of the effects of platelet-rich plasma (PRP) therapy involved in the healing of sports-related soft tissue injuries. Iowa Orthop J 2012;32:150-63.
10. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Medd 2013;41(2):356-364.
11. Ayhan E, Kesmezacar H, Akgun I. Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. World J Orthop 2014;5(3):351-61.
12. Raeissadat SA, Rayegani SM, Hassanabadi H, Fathi M, Ghorbani E, Babaee M, Azma K. Knee Osteoarthritis Injection Choices: Platelet-Rich Plasma (PRP) Versus Hyaluronic Acid (A one-year randomized clinical trial). Clin Med Insights Arthritis Musculoskelet Disord 2015;8:1-8.
13. Forogh B, Mianehsaz E, Shoaee S, Ahadi T, Raissi GR, Sajadi S. Effect of single injection of platelet-rich plasma in comparison with corticosteroid on knee osteoarthritis: a double-blind randomized clinical trial. J Sports Med Phys Fitness 2016;56(7-8):901-8.
14. Joshi Jubert N, Rodríguez L, Reverté-Vinaixa MM, Navarro A. Platelet-rich plasma injections for advanced knee osteoarthritis: a prospective, randomized, double-blinded clinical trial. Orthopa J Sports Med 2017;5(2):2325.
15. Karra B, Sreeja K, Raviteja V. Role of intra articular injections of autologous platelet rich plasma in osteoarthritis of knee joint. Int J Med Sci Clin Inven 2019; 6(3): 4373-80.
16. Bansal H, Leon J, Point JL, Wilson DA, Bansal A, Agarwal D, et al. Platelet rich plasma (PRP) in osteoarthritis (OA) knee: correct dose critical for long term clinical efficacy. Sci Reports 2021;11:3971
17. Taniguchi Y, Yoshioka T, Kanamori A, Aoto K, Sugaya H, Yamazaki M. Intra-articular platelet-rich plasma (PRP) injections for treating knee pain associated with osteoarthritis of the knee in the Japanese population: a phase I and IIa clinical trial. Nagoya J Med Sci 2018;80(1):39-51.
18. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med 2013;41(2):356-64.
19. Filardo G, Kon E, Pereira Ruiz MT, Vaccaro F, Guitaldi R, Di Martino A, Cenacchi A, Fornasari PM, Marcacci M. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. Knee Surg Sports Traumatol Arthrosc 2012;20(10):2082-91.
20. Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, Fornasari PM, Giannini S, Marcacci M. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy 2011;27(11):1490-501.
21. Montanez-Heredia E, Irizar S, Huertas PJ, et al. Intra-articular injections of platelet-rich plasma versus hyaluronic acid in the treatment of osteoarthritic knee pain: a randomized clinical trial in the context of the Spanish national hea