Efficacy of Intra-articular injections of Platelet Rich Plasma (PRP) in Osteoarthritis Knee.

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ABSTRACT

Objective: To determine the effectiveness of intra-articular injections of Platelet Rich Plasma (PRP) in early Osteoarthritis knee in terms of pain reduction and improvements in functional outcome.

Methods: This descriptive study was conducted in Department of Orthopedics Surgery Punjab Rangers Teaching Hospital Lahore/ Rahbar Medical and Dental College Lahore from 23rd March 2018 to 23rd March 2021.All patients with early osteoarthritis knee fulfilling the inclusion criteria were administered two intra-articular pure PRP injections. Follow up assessment was done at 6 weeks, 3 months, 6 months and one year for pain reduction measured on Visual Analog Scale (VAS) and functional improvement assessed with Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire. The pre and post injection WOMAC and VAS values were compared P value calculated with Student-t test. *P* value <0.05 was considered significant.

Results: Two intra-articular injections of PRP were administered to 84 knees in 61 patients. Female patients were 35(57.37%) and male 26(42.62%). The mean age was 61.5±2.3 years. Majority (60.71%,n=51) of knees had grade II Osteoarthritis while 33(39.28%) knees had grade I Osteoarthritis. In each follow up visit a significant improvement (P <0.05) in pain reduction(VAS) and functional outcome(WOMAC) was observed which persisted till last follow up visit at one year follow up. No complication was reported.

Conclusion: Two intra-articular PRP injections in early Osteoarthris knee yielded significant reduction in pain and improvement in functional outcome.

Keywords: Intra-articular injection, Knee, Osteoarthritis, Platelet-Rich Plasma.

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INTRODUCTION

Knee Osteoarthritis is responsible for pain and disability of 10% population globally. [1] More than 50 million people in the United States have symptomatic Osteoarthritis and accounting for over 100billion dollars spent annually on treatment and lost wages.[2] Conservative treatment of knee osteoarthritis include nonsteroidal anti-inflammatory drugs(NSAIDs),activity modification, physical therapy, intraarticular injections of steroid, Hyaluronic acid and Platelet-Rich Plasma (PRP).[3] Platelet Rich plasma (PRP) is produced after centrifugation of whole blood sample and is preferred over others because of its cost effectiveness, safety and long term efficacy.[4] The α- granules of platelets contain Platelet Derived Growth factor (PDGF), Platelet Derived Epidermal Growth factor (PDEGF), Epidermal Growth factor (EGF), Transforming Growth factor- β (TGF- β), Insulin like Growth factor-1 (IGF-1), Fibroblastic Growth Factor (FGF), Vascular Endothelial Growth Factor (VEGF), Hepatocye Growth Factor (HGF), Cytokines and Chemokines.[5-7] PRP is an Orthobiologics autologous plasma with higher concentration (4 to 5 times) of platelets than plasma itself and release growth factors which are responsible for stimulation of cells and chondrocytes and enhances the repair and regeneration of damaged articular cartilage.[8] Moreover PRP

increases Hyaluronic acid and increases Aggregan, an anti-inflammatory marker while pro-inflammatory markers like Cyclooxygenases, Interlukin-1, Metalloproteinases, Interferon gamma, Disintegrins, Selectins and Tumor Necrosis factor alpha are inhibited.[9] PRP injections have been shown to provide more pain relief and improved functional outcome at one year follow up than Hyaluroinc acid, placebo or controls.[10-12] In addition statistically significant improvement has been detected on MRI in the volume of patellofemoral cartilage, lateral and medial meniscal disintegrity and synovitis in patients treated with PRP injections.[13]

The objective of our study was to determine the effectiveness of intra-articular injections of PRP in early Osteoarthritis knee in terms of pain reduction and improvements in functional outcome.

METHODS

We conducted this descriptive study in Department of Orthopedics Surgery Punjab Rangers Teaching Hospital Lahore/ Rahbar Medical and Dental College Lahore from 23rd March 2018 to 23rd March 2021.Patients of either gender and age 40 to 70 years with BMI<30 and with symptoms of Osteoarthritis for more than 3 months were included in this study. The Osteoarthritis was diagnosed as per American College of Rheumatology(ACR)[14] criteria for knee Osteoarthritis. The radiological grades of Osteoarthritis included were grade I and grade II as per Kellgren-Lawrence grading system.[15] Patients with knee instability, infection, rheumatoid arthritis, diabetes, Coagulapathy, post traumatic arthritis, pregnancy, lactation, arthroscopic lavage, previous knee surgery or injections were excluded. Patients who had Platelet count below 150000/cu mm and Hemoglobin level < 9 gm were also excluded. It was ensured that patients had not taken any NSAIDs in the previous 10 days. The study protocols were approved by the ethical committee of our hospital. Informed consent was taken from all the patients for administration of PRP injections and publication of results. In the included subjects complete history was taken followed by physical examination and relevant investigations. Pre injection assessment included Visual Analog Scale (VAS)[16] and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionaire.[17]

PRP preparation technique

For PRP preparation 40 ml of venous blood was obtained from the forearm vein with 18 gauge needle. For complete blood count 1ml of this blood was sent to laboratory. To the remaining sample anticoagulant was added and centrifuged at 1800 RPM initially for 15 minutes and erythrocytes were separated. The second spin was set at 3500 RPM and platelets were concentrated.[18] The PRP was filtered through a Leucocyte filter(Imugard III-PL,® Terumo Penpol Ltd, India) so that the final PRP was 4 to 5 ml and without leucocytes. For platelet and leucocyte count 0.5 ml was sent to laboratory for analysis. About 0.0425 ml of 10% Calcium Chloride per ml of PRP was added to the sample for activation of platelets. This PRP sample was injected with 22 gauge needle through anterolateral approach with extended knee in supine position under ascetic protocol in the operation theatre. The patient was instructed to actively flex and extend the knee few times so that the injected PRP spread out in the joint. All the patients were discharged home after a rest period of 20 to 30 minutes. They were instructed not to use any NSAIDs except Actaminophen and cold packs for pain. The second injection was administered after 2 weeks following the same identical protocol. For bilateral knees the more painful knee was injected first. The patients were followed in the out patient department at 6 weeks,3 months,6 months and 1 year for assessment of pain measured with VAS and functional outcome measured with WOMAC questionnaire. The VAS consists of 0 to 10 equal distance spaces on a 10 cm line with 0 indicating no pain and 10 indicating unbearable pain. The WOMAC questionnaire consists of 24 questions with 5 questions assessing pain,2 questions assessing stiffness and 17 questions assess physical function. A likert scale of 1(none) to 5(very high) is used to calculate WOMAC subgroup score or total score. Post injection assessment was done by a senior Orthopaedic consultant who was not part of the study group.

The data was analysed with SPSS version 23. Frequency and percentage was calculated for qualitative variables while mean and standard deviation was calculated for quantitative variables. The pre and post injection WOMAC and VAS values were compared and P value was calculate with Student-t test. *P* value <0.05 was considered significant. The data was presented in table where necessary.

RESULTS

We treated 84 knees in 61 patients with two PRP injections. Unilateral knee Osteoarthritis was treated in 38(62.29%) patients while bilateral knees were treated in 23(37.70%) patients. Female patients were

35(57.37%) and male 26(42.62%). The mean age was 61.5±2.3 years(range 40 to 70 years). Majority (60.71%,n=51) of knees had grade II Osteoarthritis while 33(39.28%) knees had grade I Osteoarthritis. Before first injection the mean platelet concentration in the whole blood of patients was 221322.11±61398 per microliter. The first injection of PRP had platelet concentration of 1253440.41±412213.31. There was 5.21±1 fold increase of platelet concentration in first injection of PRP. The mean leucocytes count in the first PRP injection was zero. The blood samples of the patients before the second injection of PRP showed mean platelet concentration of 219723.32±60187 per microliter. The second injection of PRP had platelet concentration of 1298113.81±433391.61. The platelet concentration had increased 5.812±1.4 fold in PRP. The mean leucocyte count in the second PRP injection was zero. In each follow up visit a significant improvement (P <0.05) in pain reduction (VAS) and functional outcome(WOMAC) was observed which persisted till last follow up visit at one year follow up.(Table I).The mean follow up period was 14.5±5 months(range 12.6±3 to 17.6±1 months). No significant difference was found in VAS and WOMAC when data was stratified for age, gender, body weight, side, grade of Osteoarthritis and laterality.(P>0.05).No immediate or delayed complications relating to PRP injection were noted.

Table I: Outcome of PRP injections as measured with VAS and WOMAC questionnaire.

Clinical Parameter	Pre-Injection	Post injection follow up time				*P* value
		6 weeks	3 months	6 months	1 year	
VAS	7.10±1.11	6.21±3.20	4.13±2.11	3.51±1.07	1.13±2.23	0.03
WOMAC Pain	16.11±3.2	10.30±1.23	8.53±2.22	4.72±1.10	2.31±1.11	0.001
WOMAC Stiffness	6.43±2.23	5.72±1.01	3.31±2.45	2.70±3.20	2.13±4.12	0.01
WOMAC Function	60.32±7.44	43.10±4.45	23.67±3.21	17.45±1.612	7.34±3.01	0.001

DISCUSSION

In our study we administered 2 PRP injections(Leucocyte depleted) to 84 knees in 61 patients. Follow up visits at 6 weeks,3 months,6 months and one year showed statistically significant pain reduction(VAS) and functional improvement (WOMAC). The VAS score improved from pre injection value of 7.10±1.11 to post injection 1.13±2.23 at one year(P=0.03). The pre injection WOMAC pain score improved from 16.11±3.2 to 2.31±1.11 (P=0.001). The WOMAC stiffness improved from pre injection 6.43±2.23 to post injection 2.13±4.12(P=0.01).The WOMAC function score improved from 60.32±7.44 to 7.34±3.01(P=0.001). Rai and Singh[19] treated 98 patients of knee Osteoarthritis with two injections of PRP at 3 weeks interval. The pre injection WOMAC pain score was 15.51±1.45 and at 1 year it was 13.14. The WOMAC stiffness was 5.51 initially and at one year it was 4.96.The WOMAC function score was 57.96 pre injection and 54.57 at one year. The pre injection VAS was 6.06 and post injection VAS at one year was 4.80. Outcome with WOMAC Questionnaire and VAS showed statistically significant improvement at 6 weeks,3 months and 6 months and slight improvement at 1 year. Grade 1 and 2 Osteoarthritis had more pain relief than grade 4 or 5.These authors concluded that PRP is a safe and effective therapy for osteoarthritis knee. Kavadar[18] treated 120 patients of osteoarthritis with single PRP injection (group 1), two PRP injectio n (group 2) and three PRP injections (group 3).Post injection follow up assessment at 1 month,3 months and 6 months with VAS and WOMAC questionnaire showed significant improvements in all the three groups but more in group 2.These authors advocated to use minimum of two PRP injections. Guillibert and Charpin[20] treated 57 patients of Osteoarthritis knee with a single injection of pure PRP and noted significant pain reduction (from 37.5±25.1 to 12.9±20.9) and improvement in Knee Injury and Osteoarthritis Score(from 43.5±14.3 to 66.4±21.7) at six months follow up. Cole and colleague[21] treated 49 patients of Osteoarthritis knee with leucocyte depleted PRP and 50 with Hyaluronic acid(HA). No difference was noted in the primary outcome WOMAC score between the two groups. However the secondary outcome, the International Knee Documentation Committee(IKDC) score was significantly higher in PRP than HA at 24 weeks and 52 weeks. Similarly the VAS was statistically lower in PRP group at 24 weeks and 52 weeks. These authors attributed the beneficial effects of PRP to a significant decrease of Interlukin-1b and Tumor Necrosis factor alpha in the synovial fluid of PRP patients at 12 weeks.

We found two interesting meta-analysis on PRP treatment of Osteoarthritis knee. In One meta-analysis of 3463 patients in 30 randomized trials by Migliorini *et al* [22] PRP injection was compared with

steroid, Hyaluronic acid and Placebo. At one year follow up PRP had better WOMAC scores followed by placebo, HA and steroid injections. The VAS scores of PRP at 12 months was reduced significantly followed by steroid, placebo and HA. In an another meta-analysis by Shen[23] on 1423 patients in14 randomized trials PRP injection was compared with saline, HA, Ozone and steroid injections. At 12 months PRP injection had significantly better WOMAC scores than others.

Contrary to the above studies Halpren *et al* [24] treated 22 patients of 30 to 70 years of age with early Osteoarthritis knee with PRP injection, At one year follow up pain score was decreased while WOMAC score was increased. MRI at one year showed no significant structural change in 73% patients. Patel[25] also documented significant improvement in WOMAC scores at 2 to 3 weeks and lasted for final follow up at 6 months but with small worsening of some of the WOMAC scores. Kon[26] noted slight worsening(but not significant) of IKDC score at 2 to 6 months.Bottegoni[27] observed an initial improvement in VAS, IKDC and KOOS followed by significant worsening at six months follow up. The possible reasons for these differences in outcome could be attributed to the differences in technique of PRP preparation, fresh versus stored PRP, frequency and duration of PRP injections because no standardized procedure for PRP could be found in literature. [19] We used Leucocyte depleted double spin fresh PRP with 5 times platelets concentration for injection. Our relatively better and consistent results are attributed to our technique of PRP preparation. The effective concentration of platelets in the PRP is also controversial. Tate[28] is of the opinion that the effective platelet concentration in PRP should be 4 to 6 times and that platelet concentration of less than 4 times and more than 8 times has no beneficial effects.

In our study we did not document any complication relating to the use of PRP injections. Rai and Singh [19] reported headache, dizziness, sweating and syncope lasting for about 20 to 30 minutes in 9(9.18%) of his patients following intra-articular PRP injection.Patel[25] was of the opinion that the adverse effects of PRP are due to higher platelets and $CaCl_2$.

Our study had small sample size, lacked randomization and had short follow up period. We could not performed biochemical analysis of PRP for growth factors. Cartilage health could not be confirmed with histology or MRI. We recommend further studies to address all such limitations.

CONCLUSION

Two intra-articular PRP injections in early Osteoarthris knee yielded significant reduction in pain and improvement in functional outcome.

Conflict of Interest: None

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