Effect of Platelet-rich Plasma Injection on Disability and Pain in Individuals with Osteoarthritis Knee: A Follow-up Study of Six Months

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Abstract

Objectives: To demonstrate the effect of autologous platelet-rich plasma (PRP) injections on pain and functional activities in patients with osteoarthritis (OA) knee.

Study design: Prospective interventional study.

Materials and methods: A detailed demographic data were collected, and each patient was examined clinically and radiographically. Complete blood counts, prothrombin time (PT)/international normalized ratio (INR), and X-rays of bilateral knees were taken. Radiological grading was done on Kellgren–Lawrence (KL grading) OA scale. Each individual was explained and informed consent was taken before the procedure. Three injections of PRP were given at an interval of 2 weeks. Detailed clinical examination was done at the end of 1 month and 6 months postinjection. Pain assessment was done on visual analog scale (VAS) and Western Ontario McMaster (WOMAC) OA index was used for comprehensive documentation of pain, stiffness, and overall disability experienced by the individual suffering from OA knee.

Results: The mean VAS score for pain was 6.53, 4.24, and 3.76 before treatment, 1 month posttreatment, and 6 months postinjection, respectively, in KL grades I and II individuals. On WOMAC scale, mean pain scores were 17.15, 7.90, and 7.39 before treatment, 1 month posttreatment, and 6 months postinjection, respectively. Mean stiffness scores were 5.56, 3.15, and 2.56 39 before treatment, 1 month posttreatment, and 6 months postinjection, respectively. Mean functional capacity scores were 46.49, 27.78, and 23.51 before treatment, 1 month posttreatment, and 6 months postinjection, respectively.

Conclusion: An overall reduction in pain and improvement in functional status were observed in all individuals suffering from OA knee of any grade. In the light of other studies, it can be concluded that the use of PRP injection has proven to be a promising treatment modality for OA.

Keywords: Osteoarthritis knee, Platelet-rich plasma, Visual analog scale, Western Ontario McMaster osteoarthritis index score.

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Introduction

Primary or secondary osteoarthritis (OA) of the knee joint is an extremely common disease entity affecting millions of individuals across the world. It causes significant functional impairment resulting in disability and handicap. In addition to its high socioeconomic cost, it is a major public health problem due to its impact on quality of life.[1]

Increase in general life expectancy of the population has increased the probability of diagnosis and individuals living with OA many a times over a period of years lead to a steep rise in the number of operative procedures on knee.

A wide-spectrum treatments are available, including strengthening exercises, nutritional supplements, and analgesic drugs, as conservative measures on one side of spectrum and more invasive operative procedures including total knee replacement, partial knee replacement, and various types of osteotomies on the other end. Minimally invasive procedures including steroid injections and viscosupplementation fall in the middle of the spectrum. If these procedures fail, then more invasive surgical approaches can be attempted to avoid metal resurfacing through the restoration of the mechanical balance and the regeneration of the articular surface, though the results are still controversial.[2,3] Some of these surgical treatments promise long-term relief in OA symptoms, but long postoperative rehabilitation and high cost of treatment along with unpredictable results over long-term limit their utility.[4,5]

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Most of these treatments are palliative and focus on management of symptoms, and none of these modify the biochemical environment of the joint. Autologous platelet-rich plasma (PRP) has emerged as a treatment option focusing on correction and restoration of biological balance within the joint.

Alsousou et al. have defined PRP as a volume of autologous blood having platelet levels above peripheral blood concentration.[6] Lee et al. hypothesize that greater concentration of platelets may provide a higher amount of bioactive growth factors along with

concentrated anti-inflammatory signals including Interleukin 1 ra, which is the focus of OA treatment.[7] Sampson et al. have labeled transforming growth factor-β to be responsible for chondrogenesis in cartilage repair in OA knee.[8,9] Sampson et al. demonstrated hard knobbles on magnetic resonance imaging, and histologic investigation and staining confirmed cartilage cultivation.[8,10] Anitua et al. demonstrated that PRP increased hyaluronic acid concentration, leading to stabilization of angiogenesis in 10 patients with OA knee.[11] Despite these convincing results of many PRP studies, the overall quality of outcome is affected because of the lack of literature and asymmetry of methods that are used to segregate PRP.

Our hypothesis was that intra-articular injection of PRP in patients suffering from knee OA might result in improvement of symptoms and ease of their daily activities. The aim of this study was to evaluate the effect of PRP on patient's pain and disability.

MATERIALS AND METHODS

Setting and Participants

The present study was conducted in the Department of Physical Medicine and Rehabilitation, Sawai Man Singh Hospital, Jaipur, from January 2015 to January 2016. A total of 46 individuals with OA knee were recruited during this period and were followed for 6 months from the first injection. There was a dropout of four patients, while 41 patients could complete the follow-up.

Inclusion Criteria

- Age greater than 40 years and less than 80 years.
- Clinical and X-ray confirmation of OA.

Exclusion Criteria

- Knee involvement because of inflammatory arthropathy.
- Currently on aspirin or any other blood thinner.
- Any surgical intervention on knee 6 months before the first visit.
- Age <40 years and greater than 80 years.
- Platelets less than 150,000/mm^3.
- Unilateral total knee replacement.
- Severe osteoporosis with T scores ≥ 2.5.

Evaluation of Study Subjects

Each patient was examined clinically and radiographically along with detailed demographic data compilation. Complete blood counts, prothrombin time (PT)/international normalized ratio (INR), and X-rays of bilateral knees were done. Radiological grading was done using Kellgren–Lawrence (KL grading) OA scale. Individuals were explained the entire procedure and informed consent was taken before the procedure.

An account of the total number of painkillers consumed during their follow-up was maintained. No nutritional supplements marketed for improvement in OA knee were prescribed to the patient. Paracetamol and diclofenac for mild to moderate pain and tramadol with or without aceclofenac for severe pain were the standard pain medications for all patients.

Treatment and Follow-up

On the procedure day, blood was collected in two, three acid-citrate-dextrose containing Vacutainer tubes of 8.5 mL capacity under aseptic precautions. Samples were taken to stem cell lab in a sterile box. Tubes were centrifuged at 700 rpm for 8 minutes under temperature control conditions, after which blood got separated into two fractions. The upper fraction (plasma) was obtained by pipetting under a laminar flow hood. The plasma was collected from both the tubes in plain red vials without acid citrate dextrose (ACD) and was again centrifuged at 400 rpm for 13 minutes. The lower fraction which amounted to around 3 mL was collected with a spinocaine needle of 18 G. This fraction obtained after double centrifuge was PRP and it was injected into the affected knee by a physical medicine and rehabilitation (PMR) specialist through lateral approach using aseptic precautions.

The PRP obtained was subjected to complete blood counts in initial few cases to set proper limits and standards of PRP used for injection. The standard was to obtain a platelet count of three to five times the normal count in blood.

Three consecutive PRP injections, at a gap of 14 days each, were given. Exercises were to continue throughout the treatment course, except on the day of injection. Each individual was given a 3-day course of antibiotic postinjection to avoid any iatrogenic infection.

Each patient was evaluated on the first visit, after each PRP injection and then at 1 month and 6 months after completion of treatment.

Independent Variables

The following baseline information were recorded in all patients: age, sex, weight, body mass index (BMI), current work status, education level, occupation, duration of pain, knee range of motion, thigh girth, associated illness, crepitations, blood investigations including complete blood count and erythrocyte sedimentation rate, radiographic staging on KL classification, VAS at admission, Western Ontario McMaster (WOMAC) index at admission, and the number of painkillers consumed per week.

Outcome Variables

Visual analog scale was used to measure the effect of PRP on intensity of pain. Score on this scale is between 0 (no pain) and 10 (worst pain).[12] All numbers mentioned on the scale separately depict the quality and intensity of pain in the form of emotes for better understanding of the individual to make it a good subjective measure.

Western Ontario McMaster is a self-administered health status measure that assesses the dimensions of pain, stiffness, and function (either separately or as an overall index) in patients with OA of the hip or knee. It is available in 5-point Likert, 11-point numerical rating, and 100 mm VAS formats.

Each question has been given a score of 0–4, where 0 is for none, 1 for mild, 2 for moderate, 3 for severe, and 4 for very severe problem. The WOMAC index has three subscales. (1) Pain that includes five questions, scores of which range between 0 (best) and 20 (worst). (2) Stiffness that includes two questions, scores of which range between 0 (best) and 8 (worst). (3) Functional disability includes 17 questions, scores of which range between 0 (best) and 68 (worst). The total WOMAC score may vary from 0 to 96.[13,14] The patient's response to each question produces a score that is then summed to derive an aggregated score for each dimension. It produces three subscale scores (pain, stiffness, and physical function) and a total score (WOMAC index) that reflects the overall disability.

Statistical Analysis

Assimilation of data was done on Excel sheet and complete statistical analysis was done on the latest version of Graph pad.

Continuous variables were summarized as mean and standard deviation, whereas nominal/categorical variables as proportions. Comparison between mean values of each scale from admission to each follow-up was done by using Student's paired t test. Significance was set at $p < 0.05$.

APPROVAL BY ETHICAL COMMITTEE

This study was approved by the Research Ethical Committee of SMS Hospital and is in accordance with the declaration of the World Medical Association.

RESULTS

A total of 68 knees in 45 individuals were injected with PRP. There were four dropouts after which 41 individuals could complete the follow-up of 6 months.

DEMOGRAPHICS

A total of 11 (23.91%) males and 35 (76.09%) females were included in the study. Thirty-five (78.26%) individuals were in the age-group of 45–65 years and 11 (26.09%) individuals were in the age-group of 66–80 years. The average age of the group was 59.74 ± 9.9. Current work status was active in 33 (71.74%) individuals of the group and 13 (28.26%) were not involved in active stream of life. Average BMI in these individuals was 27.40 ± 4.85. Unilateral knees were injected in 22 (47.83%) individuals and 23 (50%) individuals had PRP injections in bilateral knees. Duration of symptoms was less than 5 years in 33 (71.74%) individuals and greater than 5 years in 13 (28.26%) individuals. Duration is important as greater the pain duration, the more advanced is the disease; and it becomes more difficult to achieve pain relief. The chondropathy grade distribution was as follows: 19 (28.36%) had grades I and II, 26 (38.81%) had grade III, and 22 (32.84%) had grade IV OA. Platelet derived growth factor (PRGF) infiltration was done in 22 unilateral knees and 23 bilateral knees.

The mean VAS score for pain was 6.53, 4.24, and 3.76 before treatment, 1 month posttreatment, and 6 months postinjection, respectively, in KL grades I and II individuals. The mean VAS score was 6.70, 3.74, and 3.09 before treatment, 1 month posttreatment, and 6 months postinjection, respectively, in KL grade III individuals. The mean VAS score was 7.27, 4.82, and 4.05 before treatment, 1 month posttreatment, and 6 months postinjection, respectively, in KL grade IV individuals. Significant differences were observed at all time frames ($p < 0.0001$). The difference in mean scores of VAS is given in Table 1.

On WOMAC scale, the mean pain scores were 17.15, 7.90, and 7.39 before treatment, 1 month posttreatment, and 6 months postinjection, respectively. Mean stiffness scores were 5.56, 3.15, and 2.56 39 before treatment, 1 month posttreatment, and 6 months postinjection, respectively. Mean functional capacity scores were 46.49, 27.78, and 23.51 before treatment, 1 month posttreatment, and 6 months postinjection, respectively. Significant differences

were observed for all three items ($p < 0.0001$). The highest mean change was observed in KL grade III OA group because of higher start value and greater improvement followed by KL grade I–II patients and KL grade IV individuals. The difference in mean scores of WOMAC is given in Table 2.

DISCUSSION

Degenerative changes in joints have become a very common problem in the present scenario due to the increasing life expectancy. Over and above that, low healing potential of hyaline cartilage presents a greater problem in the treatment of knee articular cartilage lesions. Platelet-rich plasma is the latest treatment modality offering the possibility to deliver a high concentration of autologous growth factors and bioactive molecules in physiologic proportions, with low costs and in a minimally invasive way.[15] This could solve the problem by being a cartilage sparing, noninvasive, safe, and cost-effective method. Since its discovery in 1987 by Ferari et al., it has been used in a variety of applications for pressure sores and intraoperatively for repair of ligament injuries, tendinitis, and intra-articular injections in OA knee.[16]

Andia et al. mentioned that though the factors mediating the effects of PRP still remain unknown because platelets contain more than 300 proteins, this therapy could act as an endogenous source of chondroprotection by interfering with the early catabolic and inflammatory events and by subsequently promoting anabolic responses.[17] Growth factors are the main components of PRP, which induce differentiation of mesenchymal stem cells into chondrocytes and thereby increase cell proliferation.[4,16]

There is no standardization in the technique for extraction of PRP from whole blood, leading to variability in content and subsequently the performance of PRP. Giusti et al. proposed that the most efficacious platelet concentration for tissue healing is 1.5×10^6 platelets per microliter. A higher concentration or absolute number of platelets within PRP does not necessarily lead to an enhanced tissue healing effect, because of the inhibitory cascade that ensues once a sufficiently high concentration of platelets is reached.[18] On the other hand, some studies mentioned that PRP could be effective in musculoskeletal diseases only in platelet concentrations of 4–6 times, and concentrations of more than 8 times and less than 4 times had no such effect.[19]

In our study, target was to reach a concentration of platelets five times that of whole blood from which they were extracted, and it could be achieved with double centrifuge method. Some studies suggest that the device must use a double centrifugation technique to truly concentrate platelets from autologous blood.[20]

The PRP preparations are of various types depending on the leukocyte and fibrin content: pure PRP, leukocyte-rich PRP, pure platelet-rich fibrin, and leukocyte- and platelet-rich fibrin.[21] Due to the lack of consistency in formulation and randomized controlled studies, the superiority of one PRP formulation over another is questionable.[22] In our study, we did not separate leukocytes

Table 1: Difference in mean values of visual analog scale (VAS) scores

	VAS					
	1st visit to 1 month		1st visit to 6 months		1 month to 6 months	
KL grading	Mean change	p value	Mean change	p value	Mean change	p value
I–II	2.29	0.0003	2.76	0.0002	0.47	0.0413
III	2.96	0.0001	3.61	0.0001	0.65	0.0059
IV	2.45	0.0001	3.23	0.0001	0.77	0.0257

Table 2: Difference in mean scores of Western Ontario McMaster (WOMAC)

| | WOMAC | | | | | |
| | 1st visit to 1 month | | 1st visit to 6 months | | 1 month to 6 months | |
	Mean change	p value	Mean change	p value	Mean change	p value
Total pain score	9.24	0.0001	9.76	0.0001	0.51	0.1793
Total stiffness score	2.41	0.0001	3.00	0.0001	0.59	0.0166
Total functional score	18.71	0.0001	22.98	0.0001	4.27	0.0047
Total WOMAC score	35.93	0.0001	35.73	0.0001	−0.20	0.9202

from PRP, so ours was a leukocyte- and platelet-rich fibrin. This was advantageous, as some studies have stated that leukocyte-containing PRP could have some role in preventing injection site infection in addition to activating platelets and prolonging growth factor releasing time.[20]

The purpose of our study was to assess the effectiveness of intra-articular PRP injections in patients with OA knee in terms of pain and functional handicap. This study has documented the time course, amount of pain relief, and improvement in function in individuals with OA during the first 6 months after starting the PRP treatment. Initially 45 individuals were recruited for the study. Dropouts were four, so final sample size was 41.

In our study, the VAS showed extremely significant changes in the mean values from first PRP injection to 1 month postinjection. Significant differences were observed in mean scores from 1 month to 6 months, indicating the positive effect of PRP injections on pain reduction in OA knee. These findings are in agreement with other studies.[23–28]

In our study, the WOMAC scores (pain, stiffness, and functional scores) improved significantly from first injection to 1 month and from 1 month to 6 months. The maximum improvement seemed to be in first 1 month. The total WOMAC scores did not improve significantly from 1 month to 6 months. This is hypothesized to be due to a mixed effect of pain, psychological handicap, and limitation in function that have ensued over a period of time. This is in agreement with most other studies.[16,27,29–31]

Many studies have documented that PRP causes osteophytes to regress and cartilage and meniscus to regenerate in patients with substantial and irreversible bone and cartilage damage. Greater clinical benefits have been noticed in early OA and younger age-group. Thus, PRP is not very effective in the advanced stage of OA, which is in agreement with our study results. Despite these odds, a good number of studies have summed up their findings with the conclusion that PRP is promising for relieving pain and improving knee function and quality of life in all grades of OA.[4,25,27,32]

The total number of individuals with grades III and IV OA was more in group with BMI >24.9, which correlates with the finding that less improvement is seen in individuals with higher BMI and advanced stage of OA. It has been illustrated in Table 3. This is in agreement with the findings of other studies.[4]

We acknowledge some limitations of the present study, which include lack of randomization, absence of placebo control group, and evaluation of results only through clinical scores. Follow-up improvement could not be documented with the help of imaging and biological results due to the lack of funds and facility. Short follow-up for 6 months could also be regarded as a limitation. It has to be considered that per results of other studies, the effects of PRP start to reduce close to 12 months, leading to greater number of dropouts. Filardo et al. have documented that the median duration of clinical improvement with PRP was 9 months.[4]

Table 3: Distribution of number of patients according to body mass index (BMI)

| | BMI | | |
Grade of OA knee	≤24.9	25–29.9	>30
I–II	6	6	1
III	7	6	3
IV	1	5	6

Studies with a 2-year follow-up suggest that although improvement may be maintained at 2 years, there is a significant decline in outcome scores beyond 6 months.

The strength of this study was good sample size in terms of the number of knees injected and the near complete follow-up. The closed circuit system that we used contributed to the safety of the procedure. Platelet activation was not done in our study because activation could actually decrease their availability, compared with collagen activation of platelets.[33,34]

SUMMARY

At present, there is a lack of evidence to support the development of clear clinical guidelines in preparation and application of PRP. To our knowledge, till date no published studies are available on PRP effectiveness in OA from India. It is a step further toward standardization of techniques for preparation of PRP and its application in the treatment of large joint OA which will help a great deal in the management of pain-related conditions and reducing morbidity and disability caused by OA.

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