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Does Intraarticular PRP Injection improve function, pain and quality of life in patients with OA of knee? Case control study of 50 patients.

Dr. Manjiri Ranade¹, Dr. Kailash Kothari¹, Prof Hemant Pandit².

1: Pain Clinic of India

2: Professor of Orthopaedic Surgery, University of Leeds and University of Oxford, UK

Abstract

Knee osteoarthritis (OA) is a common debilitating chronic disease. Up to one in 5 people over the age of 45 suffer from knee OA and typical symptoms include significant pain, restricted mobility and difficulty to indulge in activities of daily living. Other than knee replacement, no other reliable treatment exists to manage symptomatic knee OA.

Platelet Rich Plasma (PRP) is a form of Prolotherapy and is increasingly used to manage OA patients, although the evidence is largely anecdotal. We conducted a case-control study to assess efficacy of PRP comparing it for pain relief in OA Knee.

We studied two groups of 25 patients each. One group of 25 patients was given therapeutic exercises and Acetaminophen for pain relief (control group). Second group of 25 patients (PRP group) was injected with two courses of intra-articular injection of Leucocyte rich PRP with interval of 6 weeks. WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) was recorded pre-intervention, at six months & one year post-intervention in both the groups. Change scores were assessed for statistical significance.

No complications were noted in both groups and none of the cases needed further surgical intervention during the follow up period. Mean changes of total WOMAC, in PRP group showed significantly better improvement than control group ($P < 0.05$) at all time intervals.

This study showed that intra articular PRP knee injection combined with therapeutic exercise can be more effective in pain reduction and improvement of stiffness and quality of life, compared with therapeutic exercise alone.

Keywords: platelet rich plasma, therapeutic exercise, knee osteoarthritis

Introduction

Osteoarthritis (OA) is a chronic disease defined by progressive degradation of the joint as well as loss of cartilage on joint surfaces. The degeneration that occurs in the joint leads to changes in the catabolic and anabolic activity of chondrocytes. As a result, other components of the joint get compromised which may lead to meniscus degeneration, bone deformity, sclerosis as well as subchondral tissue edema and

intermittent synovial inflammation. This condition impairs functional capacity and decreases quality of life (QOL) in patients by producing pain, stiffness and limitation in range of motion of the joint.¹

The weak potential of joint cartilage for repair which is related to its avascular nature has resulted in numerous researches focusing on cartilage repair processes during the last two decades. Common treatments for cartilage tissue repair procure relative satisfaction, but rarely achieve an ideal level of functional capacity for the patient.² Recently, innovative treatments for cartilage tissue repair have been introduced, including mesenchymal stem cell therapy, autologous chondrocyte implantation, use of matrix metalloproteinase inhibitors, gene therapy and growth factors.^{3,4}

In 1970, various studies were performed on different platelet concentrations in plasma. This was followed by work on the higher amounts of growth factors present in platelets, and from those years the first clinical applications of platelet rich plasma (PRP) were investigated.⁴ Classically, PRP is considered as a volume of plasma containing higher concentrations of platelets compared to blood base line level.⁵ In fact, this definition includes plasma and platelets. Platelets contain different growth factors and cytokines, and plasma is a liquid without cells containing proteins and bioactive molecules which play an important role in the cellular repair process.⁶ Today, the generic term PRP has progressed and includes various products. These products are categorized based on the PAW classification system (platelet concentration, white blood cells and activation method).⁷ Because PRP contains growth factors and plasma proteins, it can regulate anti-inflammatory signals and equilibrate angiogenesis.^{8,9} Based on this, its use in order to reduce the progression of OA has been suggested in some studies.^{10,11}

The aim of this case-control study is to assess the efficacy of PRP in reducing pain and stiffness and improve function and quality of life in patients suffering from knee osteoarthritis (OA).

Materials & methods

Study Design: case-control study

Study setting: Pain Clinic of India

Study period: 2014-2017

Inclusion criteria: Knee pain with minimum 3 months duration in adult patients presenting with evidence of Knee OA on plain x-rays (Kellgren-Lawrence Grade II or III).

Exclusion criteria:

- Age over 80 years
- Patients on immune suppressive therapy
- History of collagen vascular diseases,
- History of cancer or malignant disorders
- Presence of active infection or breach in the skin over the knee
- Recent history of severe trauma to knee (within the past 6 months)
- Auto immune platelet disorders

- Treatment with anti-coagulant and / or anti-platelet agents within ten days prior to injection
- Use of NSAIDs three days prior to injection
- History of intra articular cortisone within 3 weeks or use of systemic steroids within 2 weeks of proposed PRP injection
- Platelet count < 150,000 per micro liter
- History of vasovagal shock
- Pregnancy or breast feeding

Methodology: All consecutive patients presenting to Pain Clinic of India with Knee OA were considered for inclusion in this study. All patients were offered standardized physiotherapy and adequate oral analgesia. In addition, patients were provided with information about PRP and if willing to participate in the study, they were recruited. The study-arm patients were offered PRP in addition to routine treatment of physiotherapy and oral analgesia whilst the control arm patients were offered physiotherapy and oral analgesia.

Intervention (For the study group): For preparation of PRP sample all patients were referred to blood banks. 50 to 60 ml of blood was first collected from patient's upper limb cuboidal vein using 18G needle in a pre-added 5 ml of ACD – A bulb. 1 ml of blood was sent for blood count. The rest sample passed two stages of centrifuge (first with 1600 rpm for 15 minutes for separation of erythrocytes and next with 2800 rpm for 7 minutes in order to concentrate platelets). The final product was 8 to 10 ml of PRP containing leukocytes. The PRP concentration was 4 to 6 times the average normal value. As it was stated in some resources that anesthetic agents could not only have toxic effects on chondrocytes but could also influence the activation of platelet by changing the pH of the environment, therefore no local anesthetic agent was injected.¹⁴ The skin of injection site was prepped and draped and liquid PRP was injected in sterile condition using 24G – 1.5 inch needle through classic approach for intra articular injection (supra patellar or medial). All injections were fluoroscopy guided to know exact location of intra articular needle placement. After 15-20 minutes of rest, patients were asked to actively flex and extend their knees so that the PRP could spread evenly across the joint space. Then patients were sent home with a written order regarding the following issues. They were recommended to have relative rest 24 to 48 hours post-injection and limit weight bearing on the injected joint. Meanwhile for reducing pain and inflammation they were instructed to use cold therapy three times a day each time for 10 minutes. In the case of pain onset they had permission to use 650 mg of acetaminophen (up to 1.5 gm per day). However, they were strictly prohibited to take NSAIDs, Aspirin or any steroids. Generally patients were recommended to have mild to moderate levels of activity and increase it as tolerated. They could resume their usual activities of daily living (ADL) one week after injection. Exercises were started a week after injection with lower intensity in the first days and then it increased progressively to be continued on a normal level. PRP injection was repeated using the same precautions and technique at 6 weeks after the first injection.

Follow up: All patients were assessed at 3 months, 6 months and 12 months post initial consultation. Patients were requested to fill in WOMAC questionnaire and in addition joint swelling and range of movement were recorded at each visit.

Results:

The mean age of patients was 60.2 ± 9 years. Characteristics of both the groups are shown in Table 1.

Platelet rich plasma preparations in this study contained leukocytes (LR-PRP). Table 2 demonstrates the mean platelet concentrations and white blood cell in PRP and the mean platelet concentrations at base (whole blood); PRP concentration had no significant relation to the response to treatment ($P>0.05$).

Mean total WOMAC score from baseline to 6 months follow up improved significantly ($P = 0.005$) in both the groups. However the improvement in PRP group was significantly higher than in the control group at 6 months as well as at one year.

Table 1

The two treatment groups are homogenous for all the parameters evaluated.

Variables		PRP Group	Control Group
Age (Mean / SD)		60.12, +/- 8.75	60.36, +/- 9.30
Sex N,%	F	18(72)	19(76)
	M	7(28)	6(24)
KL Grade (%)	1	0(0)	9(36)
	2	12(48)	13(52)
	3	13(48)	3(12)
	4	0(0)	0(0)
Symptom Period	3-12M	15(60)	13(52)
	>12M	10(40)	12(48)

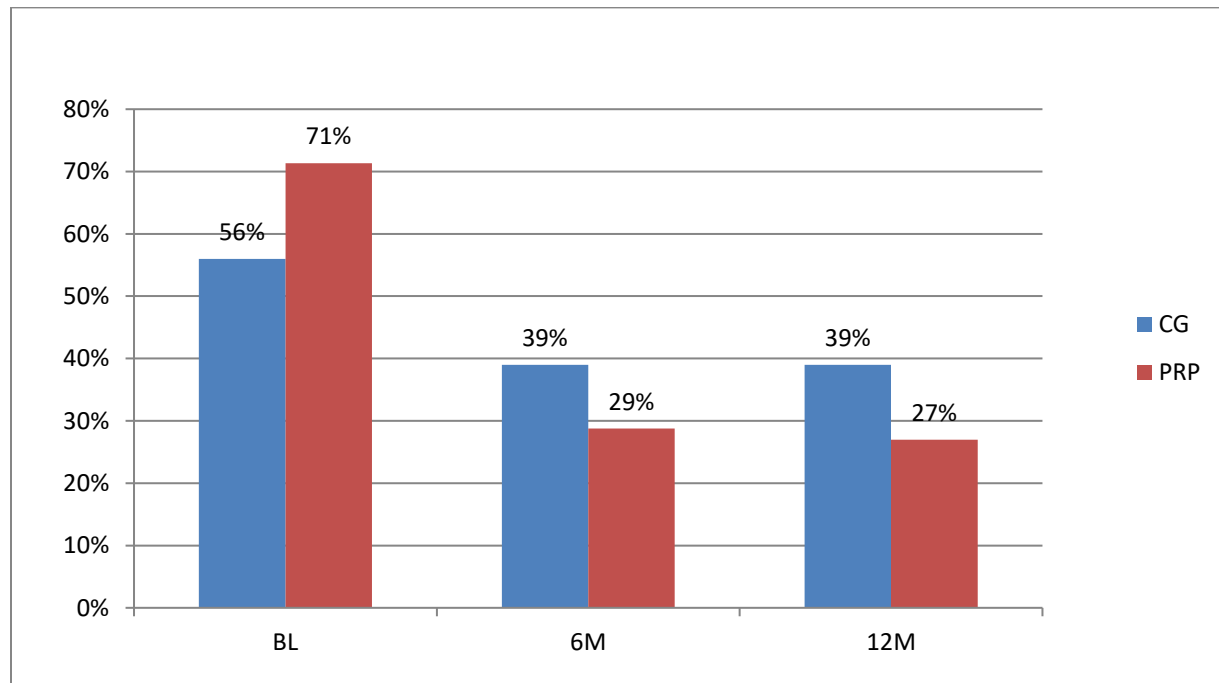
Table 2

Platelet rich plasma cytologic findings (mean \pm SD).

Parameters	Platelets concentration in whole blood [*]	Platelets concentration in PRP [*]	Platelets concentration in whole blood/PRP ^o	WBC count in PRP [*]
First injection	218643.80 \pm 85715.72	1346060.00 \pm 523291.05	5.68 \pm 1.17	240.00 \pm 203.65
Second injection	241166.14 \pm 51168.98	1367833.33 \pm 364955.38	5.62 \pm 1.65	388.89 \pm 489.76

*Per mL; ^ofold increase in platelet concentration.

Comparison of WOMAC Scores (Represented as percentage on Y axis) at different time intervals (CG: Control Group, PRP – Platelet Rich Plasma, BL: Baseline, 6M: 6 months, 12M: 12 months)



Discussion

In our study we found significant improvement in WOMAC score in group of patients who received two intra articular injections of PRP six weeks apart than control group. These improvements persisted at least for the first 12 months post-intervention.

There is no consensus about the standard regimen of PRP treatment in musculoskeletal disorders. In different study protocols, the average number of injections is two to three times at two to six week intervals.¹⁵ We chose two injections six weeks apart as a pragmatic approach. Second injection was performed the same way after 6 weeks. All patients were followed up at predetermined regular intervals after the treatment. Meanwhile they were evaluated for Paracetamol consumption, Pain, Joint swelling and Stiffness. Six months and one year follow up, WOMAC questionnaire were filled with the help of project executor. In our study after 6 months and one year pain stiffness functional capacity improved in

both PRP and Control group. Comparing with control group reduction in pain as well as total WOMAC score were significantly better in the PRP group.

Presently, various studies, including systematic reviews, have reported the effects of PRP on knee OA, and obtained results similar to our study.¹⁵ Patel et al. study, by comparing the effects of single injection or double injections of PRP and injection of normal saline (as a control group) in patients suffering from knee arthritis, showed that single injection was as effective as two times injections and both had better effects than normal saline injection. In their study, PRP obtained was lacking leukocytes with concentration of 2.5 million per micro litter with a single centrifuge turn.¹⁶ In our study, PRP used contained leukocytes after 2 turns of centrifuge with a platelet concentration of 5.6 times.

Kon et al. during a two year study investigating the short term (6 and 12 months) and long term (24 months) effects of PRP in knee osteoarthritis. In their studies using the IKDC questionnaire and VAS evaluation to assess patients' condition, results similar to our study were reported.^{17,18,19}

Sanchez et al. showed short term signs and symptoms improvement was correlated with severity of osteoarthritis (radiologic grading).²⁰ In our study also, PRP had better short term results compared to the control group even if in our study this finding didn't show any difference in various grades of OA. A reason for this difference may be related to fewer recruited patients in grades 1 and 4 compared to grades 2 and 3, exclusion of patients with severe genu varum and valgum and the small size of the sample.

The total amount of acetaminophen consumption during the 6 months follow up was higher in the PRP group than in the control group. By questioning patients, it appeared that in the PRP group due to prescription of before injection acetaminophen and because of intermittent pain 3 to 7 days after injection (because of the inflammatory process which is part of the PRP mechanisms), the highest amount of acetaminophen consumption occurred around the time of injection, but in the control group this amount was spread along the treatment period. Unfortunately, data regarding distribution of the time of acetaminophen consumption are unavailable to us. In further analysis, it appeared that there was no correlation between the amount of acetaminophen consumption and the amount of response to treatment. In the Patel et al. study, it was stated that increase in amount of platelet concentration in PRP leads to an increase in patient's pain after injection which can explain the increased consumption of pain killers the first few days after injection.¹⁶

Cellularity is one of the main aspects of PRP evaluation in different clinical applications. In our study the mean platelet concentration obtained for PRP in the first and second injection was 3-7.8 and 3.2-8.6 times respectively. No relation was found between improvement of pain, stiffness, functional capacity and QOL of patients and the platelet concentration. Some studies have indicated a positive effect of PRP in musculoskeletal diseases subject to concentrations of 4-6 times and others believe that concentrations higher than 8 times can jeopardize the repair process and induce an inhibitory effect on cellular proliferation.^{7,19} Up to now, we haven't been able to find a published study about the effect of PRP in knee OA based on platelet concentration.^{15,21} Also, in our study, the obtained PRP contained WBCs with a mean of 10-20% of blood white cells. Some believe, in the process of PRP preparation not only platelet but also monocytes as well as white cell stem cells become present. Some studies only consider PRP to be

appropriate when it is free of leukocytes. In their opinion, leukocyte secretion of proteases and reactive oxygen are unwanted.⁷ But certain researches mention the secretion of substances such as cytokines and enzymes to be effective in the processes of repair, platelet activation, prolonging the duration of growth factor release and prevention of infection (Staphylococcus aureus and Escherichia Coli).^{7,22} Up to now very few human studies have been published which had mean WBC of PRP in mind.^{1,5} In other studies it was also stated that presence of leukocytes increases pain after injection.

No significant complication (such as infection, atrophy, deep vein thrombosis, fever, hematoma and tissue hypertrophy) was observed except for transient increase in local pain and swelling. Other studies had the same reports. The most frequent patient complaint was injection site pain. In some cases pain lasted up to 10 minutes post injection, decreased gradually and continued as a dull pain at the injection site which lasted from 3 days to 2 weeks. Three patients complained of transient knee stiffness and feeling of swelling. These symptoms improved with oral analgesia and rest as needed.

This study has key strengths and some limitations. Use of a matched control group, assessment of functional outcome using validated scores and in depth evaluation of the PRP cytology are the strengths whilst relatively small sample size, predominance of female patients and limited follow up are potential weaknesses.

Overall, our study and other studies proposed the short term efficiency of PRP injection in comparison to control group in the treatment of patients suffering from OA. Details considered while choosing this treatment take into account age, gender, grade of arthritis and the duration of complaint from symptoms. These can affect the decision on the characteristics and best concentration of PRP, number of injection, their intervals as well as patient selection. The reduction of PRP effect with time indicates the lack of role of chondral remodeling alone. Therefore more studies are suggested to determinate PRP treatment patients' eligibility conditions, assessment of PRP real effects in the short and long term, and PRP cost benefit nature in a comprehensive and unique protocol.

Conclusions

Results obtained from this study showed that intra articular PRP knee injection can be effective in reduction of pain, stiffness and QOL improvement of patients in comparison to the control group in the short term.

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