Original Article

Effectiveness of Intra-articular Platelet Rich Plasma in Osteo-arthritis Knee

Puneet Nauwal[1], Mahima Agrawal[2], Mrinal Joshi[3]

Abstract

Objectives: To assess the effectiveness of intra-articular injection of autologous platelet rich plasma (PRP) on functional outcome in osteo-arthritis knee.

Study design: Prospective case control study.

Materials and Methods: A total of 113 individuals were recruited from outpatient door of Rehabilitation Research Centre, SMS Hospital, Jaipur. Out of which 59 individuals were kept in control group while 54 were taken in PRP group. Three PRP injections at a gap of fourteen days were applied to the affected knees in PRP group. Each individual was followed up to six months. WOMAC questionnaire was used as a functional outcome measure and pain was rated on numeric rating scale (NRS).

Results: There were a total of 113 individuals out of which forty-seven (41.6%) were male and sixty-six (58.4%) were female. On application of Mann-Whitney rank sum test on WOMAC between PRP group and Control group, there was no statistically significant difference ($p = 0.172$) at baseline. Up to 1 month the difference increased, but not statistically significant (p-value 0.068). At 3 and 6 months follow up, this difference became statistically significant (p- value 0.023) and (p-value <0.001) respectively.

Conclusions: Platelet rich plasma injections seem to be a promising alternative in the treatment and modification of disease course of osteo-arthritis. Though, further research and evidence is required to authenticate this statement.

Key words: **Platelet rich plasma, osteo-arthritis, WOMAC.**

Introduction:

Osteo-arthritis has a prevalence of 22–39 % in India, accounting for 30% of all joint disorders. It ranks among the top ten causes of disability worldwide and has a major impact on functioning and independence of a person[1].With the aging population, prevalence of osteo-arthritis is continuously on an increase.

Aetiology is multifactorial and includes both generalised constitutional factors (for example, aging, sex, obesity, heredity, reproductive variables) as well as local mechanical factors (for example, trauma, occupational and recreational micro trauma, misalignment, etc)[2,3].

Hyaline cartilage has limited intrinsic healing potential because it is avascular and has few specialised cells with a low mitotic activity. Once cartilage is injured, it gradually degenerates, leading to osteo-arthritis. None of the natural healing process is available for cartilage repair.

There is no curative treatment for osteo-arthritis. Several supportive treatments, both conservative and surgical, have been proposed to address cartilage pathology, but results are often only partially satisfactory and limited over time. Non-steroidal anti-inflammatory drugs have been the main pharmacological treatment, but have a high potential for side-effects on long term basis. Others like neutraceutical drugs have not been proven to be clearly effective [4].

Intra-articular injections of corticosteroids provide short-term relief in pain but do not change the natural history of the disease and may also have negative consequences. Intra-articular injections of hyaluronic acid produce an extended symptomatic improvement in patients with osteo-arthritis and can serve as an

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alternative to treatment with non-steroidal anti-inflammatory drugs and/or cortisone-based compounds. A relatively latest option is intra-articular platelet rich plasma injections[5].

Platelet rich plasma is defined as the plasma fraction with a platelet concentration greater than 2,00,000 platelets/µl). In recent years, autologous plasma rich in growth factors has been considered as a regenerative treatment for chondral tissue and a potential biological tool to treat soft tissue lesion. Presently, it is increasingly being used by pain physicians for the treatment of tendinopathy, acute and chronic ligament injuries,etc[6].The rationale for the use of platelet rich plasma is to stimulate the natural healing cascade and tissue regeneration by a "supra physiologic" release of platelet-derived factors directly at the site of treatment.

Activated platelets release growth factors contained in their α-granules. In this way, the plasma becomes a vehicle of growth factors such as transforming growth factor beta (TGF-ß), platelet derived growth factor (PDGF), epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF)[7]. These growth factors are known to induce biological changes in cell proliferation, regulating bone cell metabolism, stimulating the replication of stem cells and bone progenitor cells and promoting angiogenesis, epithelialisation and formation of granulation tissue; furthermore, they influence the activity of collagen, promoting endothelial and fibroblast proliferation in connective tissue. After PRP, the mechanical behaviour of full-thickness chondral injuries is similar to that of immature healthy articular cartilage[8]. Despite the promising preclinical findings and the huge interest in its clinical application, many questions on PRP applicability and efficacy remain unanswered.

This study intends to show that intra-articular injection of PRP in osteo-arthritis knee can improve patient's quality of life and functional capacity.

Materials and Methods:

The present study was conducted in the department of Physical Medicine and Rehabilitation, Sawai Man Singh Hospital, Jaipur, during the period of April 2012 to December 2013.

Inclusion Criteria:

Individuals with age greater than 45 years, clinical and radiological diagnosis of osteo-arthritis, pain duration greater than 6 months and those who gave informed consent were included in the study.

Exclusion Criteria:

Diagnosed cases of polyarticular inflammatory arthropathies, intra-articular injections within last 6 months, infection at injection site, platelet count <105x109/l were excluded from the study.

Evaluation:

Each individual underwent complete musculoskeletal examination in the outdoor setting of Rehabilitation Research Centre, SMS Hospital, Jaipur. Individuals willing for PRP treatment were included in the study group and similar matched patients who refused PRP treatment in control group.

Intervention:

In the study group, blood collection was done under aseptic precautions using 3 acid-citrate-dextrose containing Vacutainer tubes of 8.5ml capacity. Samples were taken to stem cell lab in sterile box. Tubes were centrifuged at 1800 rpm for 8 minutes under temperature control conditions, after which blood got separated in three fractions. PRP was obtained by pipetting the middle fraction under a laminar flow hood. It was injected in affected knee by a PMR specialist through lateral approach using aseptic precautions.

Three PRP injections were done at 2 weeks intervals for each knee. Pain killers were prescribed on basis of requirement and number was monitored at each visit. In control group, patients were on varied medications as prescribed by their respective physicians or were taken as over the counter medication.

Follow-up:

Assessment of patient's status on numeric rating scale, WOMAC index and amount of drug consumption were made at 15 days, 1 month, 3 months and 6 months from first injection.

Independent Variables:

The following baseline information was recorded in all patients: age, sex, weight, body mass index, 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 ESR, radiographic stage on Kellgren and Lawrence classification, numeric rating scale at admission, WOMAC index at admission, number of pain killers consumed per week.

Outcome Variables:

Numeric rating scale was used to measure the effect on pain in both groups. It measures the intensity of pain. Score on this scale is between 0 (no pain) to 10 (worst pain)[9].

WOMAC index was used to measure combined score of pain, stiffness and function disability in both the groups. Each question has been given a score of 0 for none, 1 for mild, 2 for moderate, 3 for severe and 4 for very severe problem. 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 seventeen questions, scores of which range between 0 (best) and 68 (worst). Total WOMAC score may vary from 0 to 96[10,11].

Statistical Analysis:

All individuals were divided into two groups and were analysed at admission, at 15 days, at 1 month, at 3 months and at 6 months from first visit on all scales as mentioned previously. Comparison between mean values of each scale from admission to each follow -up was done by using Wilcoxon signed rank test. Comparison between mean values of each scale in PRP and control group was done by using Mann-Whitney rank sum test. Comparison of dose of paracetamol in PRP group and control group from admission to each follow-up was done using Paired t-test.

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 & Analysis:

A total of one hundred and thirteen individuals were recruited for the study out of which fifty-nine were in the control group and fifty-four were in the PRP group. We had a complete follow-up of all individuals up to 6 months.

Demographics:

There were a total of 113 individuals out of which forty -seven (41.6%) were males and sixty-six (58.4%) were females. Of these 77 (68.1%) were in the age group of 45-65 years and 36 (31.8%) were in the age group of 65-85 years. Only 6 (5.3%) individuals had a body mass index (BMI) of < 20kg/m2, 71 (62.8%) had a BMI of 20-30 kg/m2 and 36 (31.9%) had a BMI of > 30kg/ m2. Duration of arthralgia was < 1 year in 15 (13.3%) individuals, 1-5 years in 43 (38.05%) individuals and >5 years in 55 (48.7%) individuals. In the control group, 2 (1.69%) knees were in grade I osteo-arthritis, 45 (38.14%) had grade II, 46 (38.98%) had grade III and 25 (21.19%) had grade IV OA, while in PRP group none of the individuals with grade I OA gave consent for intervention, 27 (28.13%) knees had grade II, 39 (40.62%) had grade III and 30 (31.25%) knees had grade IV OA. In the control group 30 (50.85%) individuals were involved actively in their work while 29 (49.15%) were not involved in active life. In the PRP group, 27 (50%) individuals were active workers while 27 (50%) were not.

Clinical Symptom Distribution:

As on NRS, 2 (3.39%) individuals had pain in the range of 0-5, 12 (20.34%) in the range of 6-10, 31 (52.54%) in the range of 11-15 and 14 (23.73%) in the range of 16-20. In the PRP group, 7 (12.96%) individuals had pain in the range of 6-10, 29 (53.70%) in the range of 11-15 and 18 (33.33%) in the range of 16-20 (Fig 1).

According to WOMAC score, in control group, 3

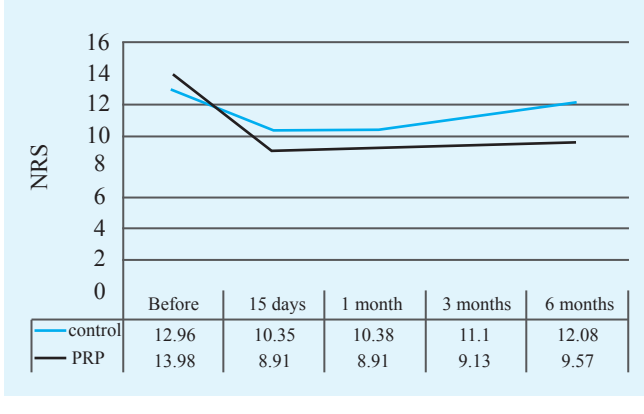

Fig 1- Comparison between PRP Group and Control Group on Numeric Rating Scale

(5.08%) had a score of 1-24, 14 (23.73%) had a score of 25-48, 29 (49.15%) had a score of 49-72 and 13 (22.03%) had a score of 73-96. In the PRP group, 2 (3.70%) had a score of 1-24, 9 (16.67%) had a score of 25-48, 27 (50%) had a score of 49-72 and 16 (29.63%) scored 73-96. More than 80% patients reported moderate to severe stiffness in their knees (Fig 2).

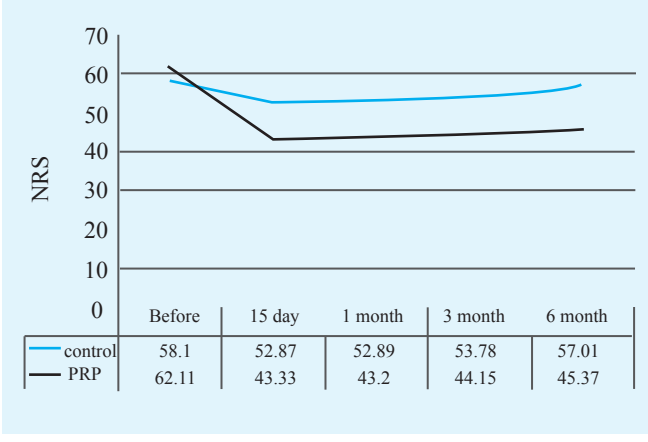

Fig 2- Comparison between PRP Group and Control Group on WOMAC Index

On application of Mann-Whitney rank sum test on WOMAC between PRP group and Control group, there was no statistically significant difference (p = 0.172) at baseline. Up to 1 month the difference increased, but was not statistically significant (p-value 0.068). At 3 and 6 months follow-up, this difference became statistically significant (p-value 0.023 and p-value <0.001 respectively).

Mean scores on pain and stiffness subscale of WOMAC index are given in Tables 1 and 2 respectively.

Comparison of mean scores of function in WOMAC between the two groups is given in Table 3.

Table 1: *Comparison between PRP Group and Control Group on Pain Subscale of WOMAC Index*

	Group	No of cases	Mean	Sd	P - value
Before	PRP	54	12.69	3.53	0.158
	Control	59	11.78	4.3	
15 days	PRP	54	8.04	3.45	0.026
	Control	59	9.85	3.63	
1 month	PRP	54	8	4.27	0.025
	Control	59	9.85	3.64	
3 months	PRP	54	7.98	4.11	0.009
	Control	59	10.07	3.68	
6 months	PRP	54	8.37	4.19	0.001
	Control	59	10.97	3.25	

Table 2: *Comparison between PRP Group and Control Group on Stiffness Subscale of WOMAC Index*

	Group	No of cases	Mean	Sd	P - value
Before	PRP	54	4.09	1.74	0.426
	Control	59	3.83	1.73	
15 days	PRP	54	2.93	1.9	0.125
	Control	59	3.41	1.55	
1 month	PRP	54	2.94	1.9	0.149
	Control	59	3.41	1.55	
3 months	PRP	54	3.04	1.91	0.246
	Control	59	3.46	1.55	
6 Months	PRP	54	3.09	1.8	0.067
	Control	59	3.73	1.39	

Table 3: *Comparison between PRP Group and Control Group on Function Subscale of WOMAC Index*

	Group	No of cases	Mean	Sd	P- value
Before	PRP	54	45.33	11.74	0.186
	Control	59	42.49	12.11	
15 days	PRP	54	32.37	10.32	0.007
	Control	59	39.61	11.21	
1 month	PRP	54	32.26	14.29	0.007
	Control	59	39.63	11.22	
3 months	PRP	54	33.13	14.04	0.006
	Control	59	40.25	10.96	
6 months	PRP	54	33.91	13.73	<0.001
	Control	59	42.31	10.24	

Mean dose of paracetamol at baseline was 8.75/week. It decreased to 5.28 at 15th day, 5 at 1 month, 5.09 at 3 months and 5.63/week at 6 months follow-up. Standard deviation of dose of paracetamol was 6.71 at baseline. It was 4.66 at 15th day, 4.47 at 1 month, 4.75 at 3 month and 5.07 at 6 months follow-up. Mean dose decreased at 15th day follow-up, then remained almost same up to 6 months follow-up. On application of Paired t-test between baseline and follow-ups, this difference was statistically significant (p value-0.005) at all follow-

ups. It started decreasing at 6 months follow-up (p value 0.028).

Two patients complained of mild fever on day 1 of PRP injection. Three patients complained of excessive pain during injection. In control group 10 patients complained of acid peptic disease. Fifteen patients of control group changed their drugs because of no relief.

Almost half patients had a diagnosis of hypertension or diabetes or both. Physical therapy modalities were advised by their physicians. But due to pain and stiffness secondary to osteo-arthritis knee, they could not follow the exercise regimen.

Discussion:

The use of growth factors has become increasingly popular to modulate the healing process in damaged tissues. Autologous PRP appears to offer an easy and promising solution for delivering multiple growth factors needed for tissue repair. PRP is the product of centrifugation of autologous whole blood to obtain plasma with an increased platelet concentration compared with whole blood[12,13].

The current literature is complicated by a lack of standardisation of study protocols, platelet separation techniques, and outcome measures. As a result, there is uncertainty about the evidence to support the clinical use of platelet rich plasma and autologous blood concentrates as a treatment modality.

The purpose of this study was to assess the effectiveness of intra-articular PRP injections in patients with osteo-arthritis knee in terms of pain and quality of life.

On comparison of NRS between study group and control group, there was no statistically significant difference (p value 0.172) at baseline, which suggests that both the groups were comparable. Up to 1 month, the difference in scores between the two groups increased, but was not statistically significant (p-value 0.068). At 3 and 6 months follow-up, this difference became statistically significant (p-value 0.023 and p-value <0.001) respectively.

Initially both groups showed improvement but in PRP group improvement was sustained up to 3 months. Then at the end of 6 months slight reduction in improvement was detected in the study group, which suggests that PRP should be repeated between 3 and 6 months for cumulative effect. This finding is in complete agreement with the literature. Napolitano *et al*[14] and Spakova *et al*[15] demonstrated improvement in NRS at the end of 3 months and 6 months in their study. But none of them used controls for comparison. Further research is required to support this statement.

Mean scores on WOMAC scale decreased dramatically at 15th day follow-up and remained at the same level up to 6 months. This difference was statistically significant (p-value <0.001) at all follow ups.

On comparison of WOMAC index between study group and control group, there was no statistically significant difference (p-value 0.18) at baseline. At 15th day the difference was statistically significant (p-value 0.011). At 3 and 6 months follow up, this difference became statistically significant (p-value 0.008 and 0.001 respectively).

Patel *et al*[16], showed similar improvement in mean WOMAC scores where it decreased from 49.86 to 27.18 at six months in group receiving single white blood cell filtered PRP injection and from 53.2 to 30.48 in group receiving 2 white blood cell filtered PRP injections at 3 weeks interval. But score worsened from 45.54 to 53.09 in group receiving single normal saline injection.

Cerza *et al*[17] conducted a comparative study between intra-articular PRP and hyaluronic acid group. Their results showed significant improvement in mean WOMAC scores in both PRP group (79.6 to 36.5) and hyaluronic acid group (75.4 to 65.1) at 24 weeks. This is in complete agreement with our results. Similar sustained improvement was seen by Spakova *et al*[15], Li *et al*[18], Sanchez *et al*[19] and Napolitano *et al*[14].

Mean score of PRP group on pain subscale of WOMAC index decreased dramatically at 15th day follow-up and remained at this level at 6 months follow-up. This difference was statistically significant (p-value <0.001) at all follow-ups. Mean scores of pain subscale of WOMAC in control group decreased up to 1 month follow-up, but started increasing at 3 months follow-up and increased further at 6 months follow-up also. This difference was statistically significant (p-value <0.001) up to 3 months follow-up, and became insignificant (p-value 0.47) at 6 months follow-up.

On comparison of pain subscale of WOMAC index between PRP group and control group, the difference was not statistically significant (p-value 0.158) at baseline. At 15th day the difference was statistically significant (p-value 0.026). At 3 and 6 months follow-up, the difference was statistically significant (p-value 0.009 and p-value 0.001 respectively).

Patel *et al*[16] showed similar improvement in mean pain score of WOMAC index. Filardo *et al*[20] reported significant improvement in pain scores on visual analogue scale and on International knee documentation committee score.

In our study, mean score of control group on stiffness subscale of WOMAC index decreased slightly up to 3 months follow-up, but started increasing at 6 months follow-up. This difference was statistically significant (p-value <0.02) up to 1 month follow-up, remained significant (p-value 0.001) at 3 months and became insignificant (p- value 0.555) at 6 months follow-up. Mean score of PRP group on stiffness subscale of WOMAC index decreased dramatically at 15th day follow-up and remained at this level at 6 months follow-up. This difference was statistically significant (p-value <0.001) at all follow-ups.

On comparison of stiffness subscale of WOMAC index between study group and control group, there was no statistically significant difference (p- value 0.426) at baseline. At 15th day the difference increased, but was not statistically significant (p- value 0.125). At 3 months follow-up, this difference decreased (p- value 0.246) but at 6 months follow-up, this difference increased, though was not statistically significant (p- value 0.067). Similar improvements were seen on function subscale.

All these results were in complete agreement with the previous literature. Patel *et al*[16] and Sampson *et al*[21] showed similar improvement in mean stiffness and function score of WOMAC index. Spakova *et al* [15],Cerza *et al*[17] and Sanchez *et al*[19] did not mention changes in subscales of WOMAC index.

We recorded a platelet concentration which was 2.3 times higher than patient's whole blood. PRP had 5.41 times less white blood cell and 81.89 times less red blood cells. Napolitano *et al*[14] used the PRP of 2.3 times higher platelet counts. Patel *et al*[16] used WBC filtered PRP of three times higher platelet counts.

Our results suggest that PRP not only was able to relieve pain but also improved the functional capacity of patients. But the effect of PRP lasted till 3 months and by the end of 6 months most of the scores started to come to baseline. Similar results were reported by Sampson *et al*[21].

The consumption of paracetamol at the start of study was 8.75per week, but at the end of 6 months mean dose decreased to 5.63 per week. This difference was statistically significant, indicating that the effect of PRP in reducing pain continued up to 6 months.

PRP infiltration shows marked improvement in pain and functional disability, but its effect on stiffness was inconsistent. In our study this improvement sustained up to 3 months. There was no carry over effect of PRP to more than 3 months. This study clearly suggess that PRP can effectively be used to manage osteo-arthritis knee, but further studies are required to standardise the treatment protocols and method of preparation of PRP for clinical purpose.

Conclusions:

PRP improves the pain and functional disability in early stage of osteo-arthritis knee over and above the standard conservative treatment. It shows better compliance and efficacy than any available treatment. The effect tends to taper off between 3 to 6 months. More randomised control trials are needed to standardise the treatment and include PRP infiltration as a part of standard regime.

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