Orthopaedics

EFFECT OF SINGLE INTRA-ARTICULAR INJECTION OF PLATELET RICH PLASMA FOR THE TREATMENT OF KNEE OSTEOARTHRITIS

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ABSTRACT

Purpose: To study efficacy of low cost minimally invasive intra-articular Platelet-Rich Plasma (IA PRP) injections in Osteoarthritis Knee(OA knee) by providing tissue regenerative growth factors. Assessment was done in terms of symptomatic improvement. **Methods:** This was a prospective study of 12 months in 40 patients. 4 were lost in the follow up –thus 36 only could be included in the study. All KOA patients of mild to moderately severity (Kellgren-Lawrence grades1 to 3) were treated with a single IA PRP. Clinical evaluation using NRS, KOOS and KSS scores were done at the first injection, 6 weeks, 6 months&12 months. Complications and adverse events were also recorded. **Results:** The36 patients included had amean age of 53.7 years, including 14 females and 22 males. There were 4 KL grade 1, 30 KL grade 2 & 2 KL grade 3 patients The mean KOOS, NRS and KSS after 6 weeks showed significant improvement with a plateau phase after 6 months and deterioration after 12 months but the final scores continued to remain above the baseline.All KOOS subscales [Symptoms, Pain, Activities of Daily Living (ADL), and Quality of Living (QOL)] except Sports & Recreational Activities had similar pattern as that of the mean total KOOS score. The KOOS subscale sports and recreation had a slightly different pattern i.e.a significant rise after 6 weeks, a fall after 6 month and a plateau phase after 12 months. **Conclusion :** IA PRP injections for OA Knee show promising results. A single injection of PRP gave significant relief in symptoms, pain, ADL, and QOL, and to a slightly lesser extent in Sports & Recreational Activities. The study was limited being a short study group, absence of a control group and a shortage of grade 1 and grade 3 patients.

KEYWORDS : IA PRP: Intra-Articular Platelet-Rich Plasma; OA Knee : OsteoarthritisKnee; KL grade : Kellgren-Lawrencegrading of KOA; KOOS score : Knee Injury and Osteoarthritis Outcome Score; NRS score : Numerical Pain Rating System; KSS score : American Knee Society Score; ADL : Activity of Daily Living; QOL : Quality of Living

INTRODUCTION

The primary OA usually starts after 40 years of age in 25 -30% population and progresses to affect about 60-90% population beyond 60 years of age because of certain precipitating factors like mechanical, structural, genetic, and environmental , involving medial compartment more frequently than the lateral one.[1]

Retrogressive sequence of cell and matrix changes are seen causing loss of articular cartilage structure and function along with cartilage repair and bone remodelling reactions.

The regeneration capability of cartilage is very poor .Pre-disposing factors like trauma, chronic overload, metabolic and biological factors lead to loss of articular cartilage resulting in joint damage. [2]

Platelet-rich plasma (PRP) is a thrombocyte concentrate obtained from the same individual having platelet concentration 5-6 times above baseline. It is generated by differential centrifugation of whole blood. RBCs are removed. It contains cytokines and various growth factors that enhance healing of soft tissue and joints. [3]

More recently, this form of treatment has led to advancement in the development of blood derived injections.In the knee, after surgical fixation, platelet-rich plasma (PRP) injection was first cited to enhance healing of a re-attached cartilage avulsion [4].

In tendinopathies like tennis elbow, plantar fasciitis, tendon & muscle injury & osteoarthritis, PRP injections have provensuccessful clinically.[5]

Claiming quick recovery from sports injuries in American athletes, the PRP has gathered immense media attention in field of sports medicine .[6]Other than nonpharmacologic therapy, pharmacologic therapy, Intra-articular injections – steroids and visco-supplementation are common methods of non-surgical treatment in patients of osteoarthritis.[6]

MATERIAL & METHODS

Type of Study -

The present study was held prospectively for a duration of 2 years. 40 patients were enrolled for a prospective study after fulfilling the inclusion and exclusion criteria. Out of them 4 patients did not turn up.

Inclusion criteria:
- All patients of both sexes with chronic knee pain (>4 months) with primary OA of knee as evidenced by Kellgren–Lawrence classification (KL Grade I to Grade III)
- Patients not being relieved with other conservative modalities.
- Completed informed consent.

Exclusion criteria:
- Patients with Hb <10gm/dl and platelets <1,50,000/cu.mm
- Patients having > 50 of varus and valgus malalignment.
- Patients suffering from secondary OA knee
- Haematological disorders – coagulopathies and patients on anticoagulant and antiplatelet therapy
- Immunodepression

Pretreatment evaluation

All patients were evaluated clinically in form of Numerical Rating Scale for pain (NRS, a modified version of VAS), Knee Injury & Osteoarthritis Outcome Score (KOOS Survey7) and American Knee Society Score (KSS).Weight bearing radiograph of both knees in AP view and each knee in 300 of flexion for lateral views for evidence of OA and degree of varus and valgus malalignmentand hematologically for Complete Blood Counts, Coagulation Profile were performed.

Technique

50 to 60 ml of blood is drawn into a collection bag with 7-8 ml Sodium

citrate under aseptic conditions in a blood bank.(Fig 1) Before collecting 50 to 60 ml of blood in blood bag, a sample for haemogram is also collected. Platelet Rich Plasma is obtained by the double spin technique. Collected blood was then transferred in to three 20ml syringes.(Fig 2) The first spin was done at 1500 rpm for 6 minutes causing the RBC layer to sediment down and plasma containing platelets forming supernatant with a whitish buffy coat in between the RBCs and plasma.(Fig 3) Supernatant plasma was transferred through an infant feeding tube to another syringe thus generating 10ml plasma in each syringe. The plasma undergoes a second centrifugation at 3500 rpm for 12 minutes causing platelets to sediment thus giving a pellet like appearance. The supernatant platelet poor plasma is disposed of with the help of an infant feeding tube and scalp vein needle generating a 2ml of platelet rich plasma from each syringe ie total of 6ml of PRP.(Fig 4) 1ml is sent for platelet count and TLC count. Before the injection, PRP is activated by 0.1 ml of 10% of Ca-chloride which is added to the PRP unit to activate the platelets.

 Single injection of 5ml Platelet Rich Plasma (PRP) is injected into knee joint using a suprapatellar site, aseptically in Minor OT.(Fig 5) Post infiltration the patient was advised to completely flex and extend the knee a few times to allow thorough distribution of PRP throughout the joint before forming a gel. The patients were then sent home with instructions to limit the use of the knee for at least 24 hours and to use ice packs/cold therapy on the infiltrated knee. The use of non-steroid anti-inflammatory drugs is avoided during this period and oral Paracetamol is given in case of pain. Quadriceps drill exercises and cycling were advised during the post injection phase. All the complications and adverse events were recorded.

Follow up was done at initial visit, 6 weeks, 6 months, and 12 months using Numerical Rating Scale (NRS), Knee Injury & Osteoarthritis Outcome Score (KOOS Survey), American Knee Society Score (KSS), while adverse effects were also recorded.

Statistical analysis
Quantitative variables were compared using paired t-test between the initial day of assessment and after 6 weeks of PRP application, after 6 months and after 12 months respectively. A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS version 25.0; IBM Corp).

Figure 1. Collection in blood bag(7)
Figure 2. Transfer from blood bag to 20ml syringe(7)
Figure 3. 20 ml syringe with RBC at the bottom and leukocyte rich supernatant after soft spin.Leukocyte rich portion is the buffy coat in between. [7]
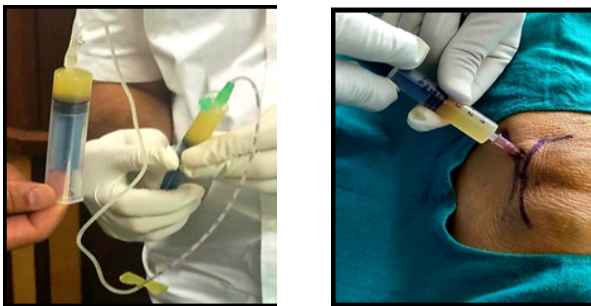
Figure 4. Upper portion of platelet poor plasma removed and lower 2ml of PRP with platelet at bottom after hard spin. [7]
Figure 5.Injection of PRP using classical suprapatellar approach.[7]

The above pictures are taken in the blood bank of Subharti medical college, meerut under the guidance of DrAvinash Rastogi

OBSERVATION AND RESULTS
A total 36 patients were enrolled for this study out of which 17 patients (47.2%) were between 51-60 years, 10 patients (27.8%) were between

the age of 41-50 years and 6 patients (16.7%) were more than 60 years and 3 patients (8.3%) were in between 31-40 years. Age of the patients ranged from 38 years to 70 years. The average age was 53.7 years. Out of 36 patients 22 were males and 14 were females and 30 (83.33%) were KL grade 2 OA, 4 (11.12%) were grade1 and 2 (5.55%) were grade 3 O.A.

KOOS score (8): The KOOS's was divided into five subscales: Pain (nine points), Symptoms (seven points), ADL(seventeen points), Sports and Recreation(five points) and Quality of life(four points). Five possible answer options from 0 (No problems) to 4 (Extreme problems) were available and each of the five scores is calculated as the sum of the points included.

Scores are transformed to a 0–100 scale, with zero representing extreme knee problems and 100 representing no knee problems.(8)

Table 1. Mean value of KOOS score and its subscales at initial clinical assessment, 6 week, 6 month and 12 month[9]

S No.	Parameter	Mean ± S.D			
		At initial clinical assessment	At 6 week follow up	At 6 month follow up	At 12 month
1	Symptoms	58.16 ±14.98	85.9±8.12	84.95±7.62	73.30±11.15
2	Pain	55.08 ± 17.72	91.06 ± 7.90	90.56 ± 7.91	75.45±9.58
3	Activities of Daily living(ADL)	58.83±18.02	92.00±4.22	89.83±6.50	75.89±9.58
4	Sports & Recreation Activities	40.50 ±18.04	81.17 ±8.88	64.17±14.76	61.66±11.95
5	Quality of Life(QoL)	44.42±11.57	76.08±8.29	76.08±8.29	65.72±3.46
6	Total	48.78±13.93	87.69±5.15	84.79±6.45	72.94±6.21

The mean KOOS scores were calculated before Injection PRP application, after 6 week, after 6 month and finally after 12 month. Mean Total KOOS score before PRP application was 48.7±14. There was significant improvement at the 6 week follow up which was 87.69±5.15. Then there was a plateau phase at 6 month follow up where total score was 84.793±6.5. At 12 month follow up there was deterioration in the mean total score which was 72.94± 6.21 but still above the baseline. KOOS subscales (symptoms, pain, ADL, sports & recreation and QoL) were also evaluated.(Fig 6) Symptoms, pain, ADL and Quality of life had similar pattern as that of mean KOOS score as seen in Table 1. The KOOS subscale (sports & recreation) had a slight different pattern where the mean score was 40.5±18.04 at baseline. At 6 week there was significant rise in the mean score which was 81.17±8.88 but at 6 month there was a fall in the mean score which was 64.17±14.67 but above baseline. By the time of 12 month there was a plateau phase where mean score was 61.66±11.95. (Table 1)
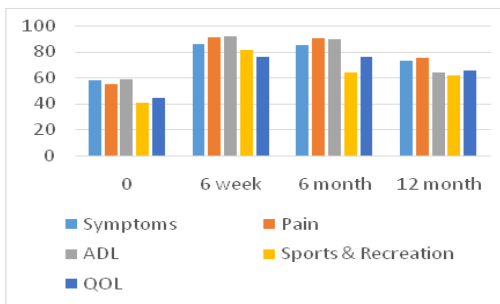
Figure 6. Pattern of KOOS subscales (Symptoms, Pain, ADL, Sports& Recreation &QoL) at baseline, 6 week, 6 month and 12 month(10)

In KOOS subscales decrease in all scores was seen at 12 month except sports and recreation subscale showed decrease at 6 month Similarly, the mean KSS and mean NRS were evaluated at the time of PRP application, after 6 week, after 6 month and finally after 12 month and found findings similar to that of mean KOOS (Table 2).

NRS score(11): The NRS is numeric version of the visual analog scale (VAS) in which a respondent selects a whole number (0–10 integers) that tells about the intensity of his/her pain. The common format is a horizontal bar or line.(Fig 7.)Pain increases in intensity as the score increases with 0 being no pain and 10 being worst pain.(11)
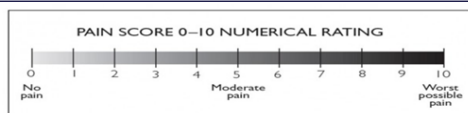
Figure 7. NRS score [11]

Table 2. Shows Total KOOS, NRS and KSS at baseline, 6 week, 6 month and 12 month respectively[9]

S. No.	Parameter	Mean ± S.D			
		At Initial Clinical Assessment	At 6 week follow up	At 6 month follow up	At 12 month
1	KOOS	48.78±13.93	87.69±5.15	84.79±6.45	72.94±6.21
2	NRS	5.89 ± 1.28	1.89 ± 0.52	2.06 ± 0.67	3.83 ± 0.81
3	KSS	52.22 ± 10.16	87.17 ± 5.05	84.25 ± 5.11	72.42 ± 5.61

For comparing mean values at initial assessment with effect of PRP after 6 week, 6 month and 12 month respectively paired t test was applied and p value for Total KOOS, KOOS subscales (Symptoms, Pain, ADL, QoL, Sports and recreation), KSS and NRS was <0.05 at 6 week, 6 month, 12 month respectively. Therefore the findings were significant at 6 week, 6 month and 12 month.

By applying paired t-test on mean KOOS with KL grade 1, 2 and 3a significant difference (p value <0.05) was found between baseline scores and those at 6 week, 6 month and also at 12 month respectively although scores at 12 month were lower than those at 6 month and deterioration was more in KL Grade 2 and 3 but still above the baseline. Similar findings were seen with the KOOS subscales- symptoms, pain, ADL and QoL at 6 weeks, 6 months and 12 months in all three grades of OA knee.(Fig 8)

The mean KOOS sports & recreation scores of patients with KL grade 1, 2 and 3 were found to be significant (p value <0.05) at 6 week, 6 month and 12 month with respect to baseline scores. Patients with KL grade 1 had deterioration of score by 12 month whereas patients with KL grade 2 and KL grade 3 showed deterioration at 6 month but scores still were significant (p value <0.05) with respect to baseline scores and at 12 month scores in all three grades showed deterioration but were well above the baseline. (Fig 9)
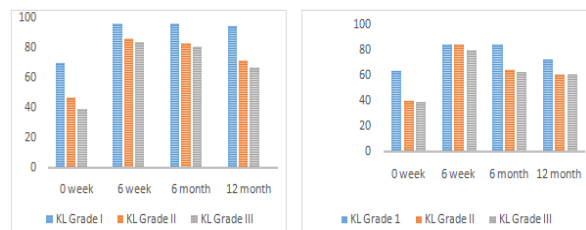

Figure 8. Mean KOOS of KL grade I, II and III at initial assessment, 6 week, 6 month and 12 month. [10]

Figure 9. Mean KOOS sports & recreation score at initial assessment, 6 week, 6 month and 12 month. [10]

DISCUSSION
Osteoarthritis (OA)also known as degenerative arthritis or hypertrophic arthritis, is a degenerative condition of the cartilage.Intra-articular injections – steroids and visco-supplementation are common methods of non-surgical treatment in patients of osteoarthritis.[6]

Recently the use of another biological product, PRP contain growth factors such as PDGF, TGF-β, IGF-1, FGF, cytokines, chemokines, etc, in their α–granules which promote tissue healing in a variety of applications. [12]

In this prospective study,36 patients were followed up after a single injection of Intra-articular PRP in KL grades 1-3 OA knee in terms of the improvement of the KOOS score, NRS scale and KSS score over a period of 1 year.

It was seen that most patients had significant improvement in pain, symptoms like stiffness, swelling, clicking or grinding sound on movement of knee and restriction of movement of knee, Activities of daily living (ADL), sports & recreational activities like squatting, running, jumping, turning, twisting on injured knee, kneeling& Quality of living at the time of 6 week follow up which remained constant at 6 month follow-up. However there was an exception in sports and recreation activities of most patients were deteriorated at 6 month follow-up but still were much better than what was at the time of initial assessment.

By the time of 12 month there was deterioration in the above mentioned parameters but still better than that at the time of initial assessment.

There was a marked improvement in symptoms, pain, ADL, sports and recreational activities and quality of life in patients with KL grade I of OA knee up to 6 months but deteriorated at the end of 12 month, however the condition was better than what was at the time of initial assessment. In patients with KL grade II and III similar results were seen in symptoms, pain, ADL and quality of life except that these patients had deterioration in sports and recreational activities at 6 month which remained constant at 12 month. But the result was better than what was at the time of initial assessment.

Among the published data, Filardo and co-workers (2010)[13] performed a pilot study consisting of ninety-one patients (115 knees) where he analysed results of three injections of IA PRP in the knee at 3 week interval. Follow up was done at 6 week, 6month, 12 month and 24 month. An overall reduction in all parameters was seen which was significantly lower at 24th month when compared to 12 month follow up but still the values were above the baseline.

The findings of this study were consistent with the findings of Filardo and co-worker's study but with only single IA PRP injection although this study is a short term study hence comments about long term results cannot be done.

Gobbi A and co-workers (2014)[14]did a prospective, randomized study consisting of 93 patients (119 knees) which were followed up for a period of 2 year and assessed the outcome of intra-articular PRP injections in patients with early stages of osteoarthritis and to determine whether cyclical dosing consisting of three injections of PRP given intra-articularly into the knee at an interval of 1 month would affect the end result. A marked improvement in scores was evident at 12 months which continued to improve until 18 months for those patients who received 2nd cycle. By 2 year, even the group that received 2 cycles at an interval of 1 year showed deterioration in results although the final mean was above the pre-treatment value and 12 months mean. The beneficial effects of the treatment peak within 6 month of injections and subsequently reduce but remain significantly higher at 12 month and even at 24 month after treatment.

More studies, and of longer duration (2 years) need to be done to compare multiple injections of PRP with single dose PRP, in larger controlled trials and different stages of OA Knee, to arrive at more definite conclusions.

The result of this study indicates that the improvement in the symptoms and function due to PRP start deteriorating by the end of one year, and raise hope that PRP injections if given repeatedly may relieve patients clinically.

PRP probably influences the overall joint homeostasis throughmodulation of the cytokine level and the reduction of synovial membrane hyperplasia, thus leading to the improvement in the clinical outcome, although for a short duration and may influence the deleterious effects in the tissues and progression of joint degeneration.[15,16]

This study has certain weak points such as- small sample size, few patients with KL grade I and KL grade III OA, follow-up was short term, synovial thickness was not evaluated, and no control was used.

Further studies needs to be done to also evaluate the synovial membrane thickness radiologically, to compare effect of different formulation of PRP like P-PRP, L-PRP on OA, single spinvs double spin PRP and longevity of single injection, and the effect of multiple injections of PRP on OA patients.

In the present study, there was no patient which presented with marked

pain response with swelling or any other adverse reactions but one patient came with complaints of nausea, vomiting and dizziness, however cause was unexplained.

CONCLUSION
• Intra-articular PRP injections into the knee for symptomatic osteoarthritis (KL Grade 1 to grade 3) are a useful treatment option and may benefit from yearly repeat of single injection.
• The limitation of this study are short study group, absence of a control, shortage of grade I and grade III patients, and no sonographic evaluation was done.

The advantages of PRP are its autologous nature, absence of side-effects, and possible role in healing and regeneration of cartilage.

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