Functional outcome of intraarticular platelet rich plasma in early osteoarthritis of knee joint: A prospective study

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Abstract
Aims: The effectiveness of Platelet rich plasma (PRP) is still controversial in osteoarthritis. We investigated the effect of PRP injection in patients with knee osteoarthritis based on improving function and decreasing pain. Our aim and objective is to assess the functional outcome of PRP in patients with early osteoarthritis, Kellgren-Lawrence Grade 1, 2 and to evaluate PRP as a treatment option for early osteoarthritis of knee joint.

Materials and Methods: This is a prospective study included 50 cases of osteoarthritis of knee of either sex fitting inclusion criteria which was conducted between November 2017 to June 2019. Patients underwent detailed history, clinical and radiological evaluation on first visit and were later followed up for a minimum period of 6 months. Autologous PRP extract prepared in Haematalogy lab and Intraarticular injections injected at 3 weeks interval at 3 sittings each. The outcome was assessed using International Knee Documentation Committee (IKDC) and Visual Analogue Scale (VAS) scores recorded prior to injections and at 2 and 6 months after the injection course.

Results: The mean age in our study is 52.48. The mean IKDC score increased from baseline of 38.63 to 59.68 at 6 month follow up, which is statistically significant (p value < 0.0001). The mean VAS score increased from 7.20 to 3.72 which is statistically significant (p value = 0.0001). After 2 month of follow up, there was significant improvement of VAS and IKDC score. The VAS and IKDC score showed improvement in all four age groups. Minor complications were reported.

Conclusion: Autologous PRP injections based on current evidence have effective pain reduction than other preparations with additional significant functional improvement in early osteoarthritis. More large studies with longer follow up are needed to confirm these early results and to test PRP injection as a part of management in osteoarthritis of knee.

Keywords: Osteoarthritis, platelet rich plasma (PRP), kellgren-lawrence grading, international knee documentation committee (IKDC), visual analogue scale (VAS)

1. Introduction
Osteoarthritis is the most common form of joint disease and among the top 10 causes of disability worldwide [1]. Felson et al. reported that about 1/3rd of all adults have radiological signs of osteoarthritis [2]. With an increase in life expectancy it is estimated that the need for knee arthroplasty would rise more than 6 times by 2030, causing significant economic burdens for pain control and rehabilitation of patients 3. Because of the high costs of knee osteoarthritis management therapeutic options that are effective on tissue healing have been taken into consideration in recent years in order to prevent the progression of osteoarthritis [4].

The healing potential of articular cartilage after damage is poor and capacity for cartilage regeneration is limited because of lack of systemic regulation and vascular deficiency [6, 7]. Platelets are natural source of growth factors and PRP helps in regeneration of articular cartilage. Growth factors are effective in chemotaxis, differentiation of mesenchymal stem cells, chondrocyte proliferation and synthetic activities of osseous and cartilaginous cells and remodeling of cartilage tissue [15]. The application of biologic treatments such as PRP in musculoskeletal disorders are growing significantly. It is used in muscular fibrosis, capsular relaxation in the shoulder, spinal fusions, pseudarthrosis, arthritis, synovitis, tendinous inflammations and lesions of meniscus and articular cartilage [16, 17].
The normal platelet count in human blood ranges from 150,000 to 350,000/μL whereas PRP is often defined as at least 10,000 platelets/μL suspended in plasma. PRP is an autologous blood product that can be injected into damaged areas to deliver platelet derived growth factors (GFs) and promote healing. The preparation process involves the extraction of blood which is anti-coagulated and then centrifuged to obtain a concentrated suspension of platelets. It is a two-stage centrifugation process to separate the solid and liquid components. The delivery techniques ranges from direct injection into the knee to application via a collagen membrane giving a gel-like consistency. Adverse events as reported in those receiving PRP injections include post-injection pain, swelling and limitation in activities which resolve by fourth day.

Platelets contain three types of granules: lysosomal granules, dense granules, and alpha granules. Alpha granules are the source of GFs, transforming growth factor (TGF-β), including platelet-derived growth factor (PDGF), insulin-like growth factor 1(IGF-1), fibroblastic growth factor (FGF), and epidermal growth factor (EGF); vascular endothelial growth factor (VEGF), platelet-derived epidermal growth factor (PDEGF), they also contain cytokines and chemokines, which are involved in stimulating chemotaxis, cell proliferation and maturation, modulating inflammatory molecules and attracting leukocytes. According to Sundman et al. there is positive correlations between platelet counts and both TGF-β1 and PDGF-AB concentrations within PRP preparations. TGF-β1 and PDGF-AB are considered to be anabolic growth factors. According to Lui et al. increasing platelet concentrations and acidic pH levels stimulate fibroblast proliferation and type I collagen production. As per various studies PRP treatment in knee osteoarthritis have promising clinical results with pain reduction, functional improvement, faster return to daily and sporting activities and consequent improvement of quality of life. With our focus on disease progression and pathogenesis of osteoarthritis and increasing availability of novel biological treatments such as Platelet rich plasma, there is a need to study the effect of this newer modalities of treatment.

1.1 Objectives
1. To assess the functional outcome of Platelet rich plasma in the patients with early Osteoarthritis Grade-1, 2.
2. To evaluate platelet rich plasma as a treatment option for early Osteoarthritis of knee joint.

2. Materials and Methods
This is a prospective study which was conducted in the department of orthopaedics, Sanjay Gandhi Institute of trauma and orthopaedics, Bangalore. This study consisted of 50 adult patients of either sex visiting outpatient department of the hospital. Patients diagnosed with early osteoarthritis knee were included in the study during the period from November 2017 to June 2019. The follow up visit was at 2 months and 6 months in this study.

2.1 Inclusion criteria
1. Pain and swelling of knee with duration of at least 4 months.
2. Confirmatory x-ray diagnosis (Kellgren-Lawrence classification Grade-1, 2. Kellgren-Lawrence grade 0 is no abnormalities. Kellgren-Lawrence 1 is defined as: doubtful narrowing of the joint space and possible osteophytic lipping. Kellgren-Lawrence 2 is defined as definite osteophyte with joint space narrowing.
3. All the patients who have understood the content and signed the written informed consent will be part of the study.

2.2 Exclusion criteria
1. Kellgren-Lawrence > Grade 2
2. Documented rheumatoid arthritis
3. Patients with anti-coagulants or anti aggregate medications (use of NSAIDS within 10 days before the injection and 5 days after the injection)
4. Intra-articular injection of steroids during past 3 weeks or systemic steroids during past 2 weeks
5. Immunodeficiency
6. Platelet count of < 1,50,000
7. Pregnancy or breast feeding
8. Previous knee operations
9. Participants who are not willing to sign the written informed consent after clearly understanding the content

A detailed clinical history of the patient was elicited. A general physical examination and Local examination of the affected knee was done and required basic investigations done.

2.3 Preoperative investigations
1. Routine Blood investigations: Complete haemogram, Erythrocyte Sedimentation Rate (ESR), Bleeding time (BT), Clotting time (CT)
2. C-reactive protein (CRP)
3. X ray Knee (standing Antero-posterior view in full extension and Lateral view in partial flexion of 20 degrees)

On the basis of the radiographs Kelligans-Lawrence grading was done. Before subjecting the patients for investigations and required procedure, written/informed consent was obtained from each patient/legal guardian. Pre injection IKDC score proforma and pain scaling with VAS score was done on the patients.

2.4 PRP preparation
The PRP extract was prepared in Haematology laboratory at our institute using double spin method which yields adequate concentration of platelets which is 4 to 5 times the baseline concentration. An 8.5 ml of venous blood is drawn from the cubital vein under aseptic precautions and mixed with acid citrate phosphate dextrose solution in vacutainer (Fig 1). The sample is then placed in a centrifuge and spin at 1200 rpm for 15 minutes (Fig 2 and Fig 3). Now using a sterile needle and syringe separate plasma from the vacutainer to a sterile container and then centrifuge this separated plasma at 1500 rpm for 10 minutes (Fig 4). So 4 ml of this sample is injected into the affected knee joint using a18 gauge needle under all aseptic precautions. Patient will be receiving one injection every 3 weeks and a total course of 3 injections.

2.5 Injection technique
The patient is placed in supine position, the knee being slightly bent with the help of popliteal cushion. Knee painted and draped. The infiltration technique used was superolateral approach and needle is inserted at an angle of approximately 45 degree towards the medial joint line until reaching the space between the patella and the femur (Fig 5). With a sterile syringe, joint effusion, if any was aspirated and 4 ml PRP was injected.
injected into the joint. Sterile dressing was applied at the injection site. After 15-20 minutes of rest, patient is asked to actively flex and extend their knee so that the PRP could spread evenly across the joint space.

2.6 Post op protocol and follow up

Patients will be advised relative rest for 24-48 hours after the injections and limit weight bearing over the joints. A strict vigilance was done in view of adverse reactions such as pain following injection, joint swelling or any systemic reaction. Patient will be advised to apply cold therapy three times a day for 10 minutes each time for initial 2 to 3 days. They will be allowed Tramadol (upto a maximum dose 300 mg per day) or Acetaminophen (upto a maximum dose of 2gm per day) for pain and prohibited from using any other analgesics, NSAIDS, steroids or medications influencing platelet count or function. Patients were asked to come 2 more injections each at 3 weeks apart to complete the course. All the subjects will be followed up at 2 months and 6 months after the course and will be assessed with IKDC score and VAS score.

3. Results

A prospective study involving 50 knees was undertaken and patients were followed up at 2 months and 6 months following the course. No patients were lost in follow up. Results were analyzed in terms of functional outcome with respect to age, sex and grades of osteoarthritis in the study. This study shows that the majority of patients were between 51-60 years old (36%) (Table 1). Most of the patients were females (76%) (Graph 1). Majority of patients in the study had Kellgren-Lawrence Grade 2 (80%) as compared to Grade 1(20%) (Table 2). Mean VAS score among the patients in the study reduced from baseline value of 7.20 to 5.08 at 2 months and 3.72 at 6 months follow up and this reduction in pain was found to be statistically significant (p = 0.001). The IKDC score showed highly significant (p< 0.001) improvement in patients with mean baseline IKDC of 38.6 to mean of 57.3 at 2 months and 59.6 at 6 months follow up. The VAS score showed decreasing trend in both males and females and a similar trend of increasing IKDC score from mean baseline to 6 month follow up was seen. The VAS score showed a decreasing trend in all four clusters of different age group, more in less than 40 years group which showed mean of 3.29 at 6 month follow up (Graph 2) (Table 3). The IKDC score showed an increasing trend in all four clusters of different age groups. However cluster one and two showed significant increase in IKDC score than cluster three and four at 6 month follow up (Graph 3) (Table 4).The mean VAS score markedly decreased from mean baseline to 6 month follow up in both the grades (Graph 4) (Table 5). The mean IKDC score showed increase from mean baseline to 6 month follow up in both the grades (Graph 5) (Table 6).

Table 1: Distribution of age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 Years</td>
<td>7</td>
<td>14.0%</td>
</tr>
<tr>
<td>41-50 Years</td>
<td>16</td>
<td>32.0%</td>
</tr>
<tr>
<td>51-60 Years</td>
<td>18</td>
<td>36.0%</td>
</tr>
<tr>
<td>&gt;60 Years</td>
<td>9</td>
<td>18.0%</td>
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</table>

Graph 1: Gender Distribution

Table 2: Distribution of Kellgren-Lawrence Grade

<table>
<thead>
<tr>
<th>Kellgren-Lawrence</th>
<th>Number of Patients</th>
<th>Percentage</th>
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<tr>
<td>Grade 1</td>
<td>10</td>
<td>20%</td>
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<tr>
<td>Grade 2</td>
<td>40</td>
<td>80%</td>
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</table>
Graph 2: Comparison of VAS with age

Table 3: Comparison of VAS with age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>&lt;40 Years</th>
<th>41-50 Years</th>
<th>51-60 Years</th>
<th>&gt;60 Years</th>
<th>Mann Whitney U Test P value</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Baseline VAS</td>
<td>6.57</td>
<td>.79</td>
<td>6.81</td>
<td>.75</td>
<td>7.44</td>
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<tr>
<td>VAS@ 2 month</td>
<td>4.86</td>
<td>.90</td>
<td>4.75</td>
<td>.58</td>
<td>5.28</td>
</tr>
<tr>
<td>VAS @6 month</td>
<td>3.29</td>
<td>.49</td>
<td>3.44</td>
<td>.51</td>
<td>3.61</td>
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</tbody>
</table>

Graph 3: Comparison of IKDC with age

Table 4: Comparison of IKDC with age.

<table>
<thead>
<tr>
<th>Age group</th>
<th>&lt;40 Years</th>
<th>41-50 Years</th>
<th>51-60 Years</th>
<th>&gt;60 Years</th>
<th>Kruskal Wallis Test P value</th>
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<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
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<tr>
<td>Baseline IKDC</td>
<td>43.5</td>
<td>1.91</td>
<td>41.6</td>
<td>2.3</td>
<td>36.9</td>
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<td>IKDC@ 2 month</td>
<td>62.1</td>
<td>2.4</td>
<td>60.1</td>
<td>2.4</td>
<td>55.8</td>
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<tr>
<td>IKDC@ 6 month</td>
<td>65.2</td>
<td>2.7</td>
<td>62.1</td>
<td>2.4</td>
<td>58.5</td>
</tr>
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Table 5: Comparison of VAS with Kellgren-Lawrence grade

<table>
<thead>
<tr>
<th>Kellgren-Lawrence Grade</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Man Whitney U test P value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Baseline VAS</td>
<td>7.00</td>
<td>.82</td>
<td>7.25</td>
</tr>
<tr>
<td>VAS@ 2 month</td>
<td>4.90</td>
<td>.88</td>
<td>5.13</td>
</tr>
<tr>
<td>VAS @6 month</td>
<td>3.90</td>
<td>.99</td>
<td>3.68</td>
</tr>
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Discussion

Osteoarthritis is the most common form of degenerative arthritis, affects the elderly resulting in physical, mental and social distress. Osteoarthritis most commonly affects the knee and is more common in elderly women. Many treatment options are available which include physiotherapy, life style modifications such as weight reduction and activity modifications, pharmacological therapy (NSAIDS, supplements, steroids, opioids) and surgeries like Osteotomies and Total knee replacement in whom all medical management have failed.

Intra-articular injectables include corticosteroids, hyaluronic acid viscosupplementation and autologous platelet rich plasma. Treatment modalities that reverse disease process and repair damaged tissues like intra articular autologous PRP which is a promising agent for cartilage healing in osteoarthritis of knee, also disease limiting activities and reduce pain. Treatment with PRP is cost effective.

Our study was conducted to find the efficacy of autologous intra-articular platelet rich plasma injection and its functional outcome in early osteoarthritis of knee.

We injected the freshly prepared 4 ml of PRP administered at 3 weeks interval. Filardo et al. used 2 injections of 5 ml volume at 4 weeks interval. Cerza et al. used 4 injections at 1 week interval of volume 5.5ml. Kon et al. used 3 injections at 2 weeks interval of volume 5ml [43]. Spakova et al. used 3 injections at 1 week interval with volume of 3ml [47]. The mean age in our study was 52.48 years and it is similar with other studies. The PRP prepared and used in this study had platelets amplified with an average of 4.2 times that of the baseline count. Aseptic precautions were followed in every step of PRP preparation. Spakova et al., in their study, had an average of 4.5 times amplification of platelet count [47]. In our study the mean baseline VAS was 7.20 and it was gradually reducing during follow up. The mean VAS score at 2 month follow up was 5.08 and was found to be significantly reduced at the 6 month follow up to 3.72. In the study by Ali Soliman Hassan et al. which was carried out on 20 patients with mild to moderate osteoarthritis knee, there was significant improvement in VAS from a baseline of 5.9±1.3 to VAS pain score of (3.9 ±1.1) at 6 month follow up [104].

Our study had baseline mean IKDC score of 38.63. There was...
increase in the IKDC score during follow up. The IKDC score at the 6 month of follow up was 59.68 which is a significant increase (IKDC- p value was < 0.0001). This is consistent with the study by Filardo in which IKDC score increased from 47% of normal and nearly normal knees before the treatment to 78% at the end, then to 73% and 67% at the 6 and 12 month follow-up, respectively, showing a statistically significant improvement (P < 0.0005) at all these follow-up times with respect to the basal level [31]. In our study from the 2nd month follow up, there was a significant reduction of VAS score (VAS score-p value was 0.0001).

In age wise comparison, individuals were divided into four clusters in our study-cluster one less than 40 years, cluster two 41-50 years, cluster three 51-60 years and cluster four more than 60 years. VAS shows a decreasing trend in all four clusters and IKDC shows an increasing trend in all four clusters. However cluster one & two showed a significant decrease in VAS than cluster three and four at the end of the study, similarly cluster one and two showed significant increase in IKDC score than cluster three and four at 6 month follow up.

In our study both males and females showed similar trend of decreasing VAS and increase in IKDC score from mean baseline to 6 month follow up.

Both Grade I and Grade II in this study, showed significant better outcome with PRP injections, VAS markedly decreased and IKDC increased from mean baseline to 6 month follow up in both the Grades. Filardo et al. in their study found that PRP had a better outcome in Grade I and II compared to Grade III and IV [102].

In our study there were no complications except moderate pain in 23 knees which lasted maximum up to 4 days. This is a cost effective minimally invasive therapy with better outcome improving the quality of life in patients which gives symptomatic pain relief and delays the need for surgical intervention.

5. Conclusion
Autologous PRP injections based on current evidence have effective pain reduction than other preparations with additional significant functional improvement in early osteoarthritis. More large studies with longer follow up are needed to confirm these early results and to test PRP injection as a part of management in osteoarthris of knee.

6. References