

# Functional Outcome of Early Knee Osteoarthritis Treated with Platelet Rich Plasma

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## ABSTRACT

**Introduction:** Osteoarthritis is a chronic degenerative condition of joint often associated with pain, deformity, disability in movement, and reduction in the quality of life. Study aimed to assess the utilization and efficacy of Platelet-rich plasma (PRP), for the management of early knee osteoarthritis.

**Material and methods:** Patients presenting with symptomatic early knee osteoarthritis were included in the study. They underwent infiltration of 5 ml PRP into the knee joint. Patients are evaluated 6 months after the procedure with Visual analogue scale (VAS) and range of motion assessment.

**Result:** In our study of 150 patients with early osteoarthritis of knee, 58.6% presented with Kellgren lawrance grade 2 and remaining were grade 1 osteoarthritis. At 1 month follow up, the procedure gave excellent results in 32% patients and good results in 26% patients, better with Kellgren lawrance grade 1 osteoarthritis. At 3 month follow up, PRP infiltration gave excellent results in 47.3% patients with early osteoarthritis and good results in 37.3%. At 6 month follow up, results were excellent in 47.3% of patients and good results in 24.6% patients. Of the 71 patients showing excellent results, 57.7% had Kellgren Lawrance grade 1 osteoarthritis. Poor response following PRP infiltration is shown by only 2 patients

**Conclusion:** Our study results support the application of autologous PRP as a safe and effective method in the treatment of the early stages of knee osteoarthritis. Significant clinical improvement was seen with 6 months of follow-up.

**Keywords:** Platelet Rich Plasma, PRP, Knee, Osteoarthritis

## INTRODUCTION

Hallmark of the pathological process is degeneration and damage of the articular cartilage. Secondary changes include subchondral sclerosis, hypertrophied joint margin, and osteoporosis of subchondral bones.<sup>1</sup> Commonest radiological findings are reduction of joint space and osteophyte formation. Pain is the most common presenting symptom, which gets aggravated by exertion and relieved by rest. The causes of pain in osteoarthritis of the knee are many, but low-grade inflammation and sensitization of nerve endings are important mechanisms.<sup>2</sup> The management of chondral disease is challenging due to its low regenerative potential and healing ability.

There are operative and non operative methods for treatment of osteoarthritis. Goals of osteoarthritis treatment are pain relief, enhanced joint mobility, prevention or correction of deformity and slow the progression of disease process. Operative treatments are arthroplasty, osteotomies etc. Non operative treatment methods include physiotherapy, oral

cartilage supplements, analgesics, intraarticular injections etc. The best method of treatment is a combination of pharmacological and non pharmacological methods.<sup>3</sup>

Intraarticular corticosteroid and viscosupplementation injections have tried for treatment of osteoarthritis. American academy of orthopedic surgeons guidelines recently demonstrated inconclusive evidence to recommend for or against corticosteroid, but given strong evidence against hyaluronic acid visco supplementation injections for patients with symptomatic osteoarthritis as it may cause joint destruction and flare up of osteoarthritis process.<sup>4</sup> This leads to emergence of newer injectables for functional improvement and symptomatic relief in early osteoarthritis. Recent studies proved that there are several growth factors that accelerate regeneration of meniscal tissue and cartilage, especially Platelet derived growth factor (PDGF) and Transforming growth factor beta (TGF-b). But the huge expense of genetically engineered growth factors limited their clinical use.<sup>5</sup>

When the clinical use of mitogenic growth factors for meniscus and cartilage are considered, Platelet rich plasma (PRP) provides one of the most important sources. PRP can be easily prepared from patient's own blood by a series of centrifugation steps. As PRP is an autologous source of growth factors, it will be an effective modality of treatment for osteoarthritis by promoting meniscal tissue regeneration by supraphysiological release of growth factors from platelet and endogenous fibrin scaffold at the site of treatment. Most studies prove that therapeutic PRP should have platelet concentration 4-6 times greater than the whole blood.<sup>6,7,8,9</sup>

Logic behind intra articular infiltration of PRP is that platelets are the first cells to arrive at the site of injury and have potential to release growth factors at the site.<sup>10</sup> Due to multiple growth factor content, PRP has effect on inflammation and metabolism, and these combined effects

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make PRP a potential injectable option for management of osteoarthritis.<sup>11</sup>

The objective of our study was to assess the utilization and efficacy of platelet-rich plasma (PRP), for the management of early knee osteoarthritis

## MATERIAL AND METHODS

This study was conducted in the department of orthopaedics, Sree Gokulam Medical College and Research Foundation, Venjaramoodu, Trivandrum between May 2018 to April 2019. Patients attending OPD are selected for the study. A total of 150 patients were included in the study. All adult patients (age >40 years) presenting with early osteoarthritis (Kellgren and Lawrence grade 1 and 2) of knee diagnosed on the basis of clinical symptoms like pain, knee joint effusion, medial joint line tenderness, morning stiffness and clinical and radiological signs of osteoarthritis are included in the study, while those who not having any of these symptoms and with advanced osteoarthritis were excluded. MRI of knee is taken in all selected patients to study the extend of cartilage damage. Data was collected using a structured proforma. Patients were recruited on presentation to the orthopedic opd according to the selection criteria. The purpose, procedure, risks and benefits of the study were explained to the patients and a formal written consent was taken. Visual Analogue Scale (VAS) score of the patient for the affected knee is documented. Patients underwent infiltration of 5 ml autologous PRP prepared by Tricell or Harvest PRP kits under aseptic precaution in OPD procedure room. Patients were followed up for at least six months after the procedure. On final follow-up patient satisfaction with the procedure was assessed through VAS scoring. Results were presented according to improvement of knee pain as presented on the visual analogue scale at follow up of 6 months.

### Procedure

With sterile technique, we obtained 30 ml of venous blood of patient and transferred it to the PRP kit and centrifuge machine. After the processing was completed, we extracted the PRP from the centrifuge into a syringe. Cleansing of the patient's skin around the injection site was done; towels or drapes were used to create an aseptic field. Administration of a local anesthesia was done. With sterile technique, we injected the PRP intraarticularly into the knee; and dressing or bandage was applied to protect the needle entry site.

### Preparation of PRP

30 milliliters of whole blood was collected from the arm into a Tricel or Harvest PRP kit. From the drawn venous blood, PRP is separated by two-step centrifugation as per the specifications of the manufacturer (Tricel or Harvest). The resulting buffered platelet concentrate contained approximately 6 to 8 times concentration of platelets compared to baseline whole blood. No activating agent was used. The total time from blood drawn to injection in the patients was about 30 minutes.

### Pre-Injection Guidelines

1. No corticosteroids for 2 to 3 weeks before the procedure.

2. Non-steroidal anti-inflammatory drugs (NSAIDs) were discontinued
3. No anticoagulation use 5 days before the procedure.
4. Increased fluid intake in the 24 hours preceding the procedure

### Injection technique

Initially, 2% lignocaine was infiltrated into the skin and subcutaneous tissue as a local field block. The 5 ml platelet concentrate was injected using a 18-G needle into the knee joint under aseptic precaution.

### Post-Procedure Protocol

Immediately after the injection, the patient was kept in sitting position without moving the knee for 15 minutes. Patients were started with static quadriceps, static hamstrings, ankle toe movements, and knee range of movement exercises.

### Evaluation of the Patients

When patients come to opd with symptoms of knee osteoarthritis, X-rays AP and lateral view of both the knees in standing position were taken and osteoarthritis was graded as per Kellgren and Lawrence grading, and was confirmed by taking an MRI. Before the procedure and at every follow up patient's pain perception was evaluated as per Visual Analogue Scale (VAS) (ANNEXURE 1) where the patient marked a dot on a line 100 mm long. Pain score was presumed to be at 100 mm mark at the start of treatment.

### Evaluation of results

Depending upon improvement in pain score as per Visual Analogue Scale, the results were graded as follows:

1. Excellent: 90-100% improvement
2. Good: 70-89% improvement
3. Fair: 40-69% improvement
4. Poor: <40% improvement

## RESULTS

The study included 150 patients with early knee osteoarthritis (Kellgren and Lawrence grading 1 and 2), who have attended Orthopedics OPD of Sree Gokulam medical college and research foundation, venjaramoodu, Trivandrum between May 2018 and April 2019.

Of the 150 patients we studied, 88 were males (58%) and 62 (42%) were females. Age of patients varied from minimum 40 years to maximum of 71 years with average age of 56 years. Common age group presented with early knee osteoarthritis is between 50–59 years comprising 56% of total study population (table-1).

In our study 64 patients (42%) were presented to our OPD with knee pain of less than one year duration. Average duration of pain was 1.36 years (table-2).

In our study of 150 patients with early osteoarthritis of knee, 88 patients (58.6%) presented with Kellgren lawrance grade 2 and remaining (62 patients, 41.3%) have grade 1 osteoarthritis (table-3).

Study outcome was assessed using Visual Analogue Scale (VAS) improvement of knee pain after the procedure. The results were evaluated at 1<sup>st</sup> month, 3<sup>rd</sup> month, 6<sup>th</sup> month follow up and compared with that of preprocedural values.

Age group	Number of patients		Total number of patients
	Male	Female	
40 - 49	21	11	32
50 - 59	48	36	84
>60	19	15	34
Total	88	62	150

**Table-1:** Age and sex distribution

Duration of pain	Number of patients	Percentage
<1 year	64	42%
1 – 2 year	45	30%
2 – 3 year	17	11.3%
3 – 4 year	16	10.6%
>4 year	8	5.3%

**Table-2:** Duration of knee pain

Kellgren lawrance grading	Number of patients	Percentage
Grade 1	62	41.3%
Grade 2	88	58.6%

**Table-3:** Kellgren and Lawrance grading

Result	Number of patients in Kellgren lawrance		Total
	Grade 1	Grade 2	
Excellent	30 (62.5%)	18 (37.5%)	48 (32%)
Good	25 (64.1%)	14 (35.8%)	39 (26%)
Fair	22 (52.3%)	20 (47.6%)	42 (28%)
Poor	14 (66.6%)	7 (33.3%)	21 (14%)

**Table-4:** Results in 1 month follow up

Result	Number of patients in Kellgren lawrance		Total
	Grade 1	Grade 2	
Excellent	42 (59.1%)	29 (40.8%)	71 (47.3%)
Good	32 (57.1%)	24 (42.8%)	56 (37.3%)
Fair	11 (57.8%)	8 (42.1%)	19 (12.6%)
Poor	2 (50%)	2 (50%)	4 (2.6%)

**Table-5:** Results in 3 month follow up

Result	Number of patients in Kellgren lawrance		Total
	Grade 1	Grade 2	
Excellent	41 (57.7%)	30 (42.2%)	71 (47.3%)
Good	34 (57.6%)	25 (42.3%)	59 (39.3%)
Fair	5 (62.5%)	3 (37.5%)	18 (5.3%)
Poor	1 (50%)	1 (50%)	2 (1.3%)

**Table-6:** Results in 6 month follow up

At 1 month follow up, the procedure gave excellent results in 48 (32%) patients and good results in 39 (26%) patients. PRP infiltration given better results with Kellgren lawrance grade 1 osteoarthritis at 1<sup>st</sup> month follow up (table-4).

At 3 month follow up, PRP infiltration gave excellent results in 47.3% patients with early osteoarthritis and good results in 37.3%. Of the 71 patients showing excellent result, 59.1% were Kellgren Lawrance grade 1 and 40.8% patients were

grade 2 osteoarthritis. Poor results are seen in 2.6% of patients following the procedure (table-5).

At 6 month follow up, results were excellent in 47.3% of patients and good results in 24.6% patients. Of the 71 patients showing excellent results, 57.7% had Kellgren Lawrance grade 1 osteoarthritis. Poor response following PRP infiltration is shown by only 2 patients (table-6).

## DISCUSSION

Osteoarthritis is a very common condition which lead to significant morbidity to person's life. As the life expectancy of patients increases, there is increase in number of patients with symptomatic osteoarthritis. Osteoarthritis is joint destruction due to imbalance in the equilibrium between the break down and repair of joint tissue. Studies showed a number of biochemical pathways that could have been targeted therapeutically through biological intervention to prevent worsening of degenerative changes.<sup>12</sup>

The factors influencing osteoarthritis include inflammatory cytokines, anti inflammatory cytokines, enzymes, transcription factors etc. Inflammatory cytokines influence the production of cytokines and enzymes through intracellular pathways of signal transduction and are believed to be a major factor in pathogenesis of osteoarthritis by altering tissue formation by promotion of catabolic processes.<sup>13</sup> The most important inflammatory cytokines associated with osteoarthritis include Interleukin-1 beta (IL-1b) and Tumor necrosis factor alpha (TNF-a). IL-1b and TNF-a are found at elevated levels in fluids and tissues affected by osteoarthritis. These elevated levels of IL-1b and TNF-a contribute to cartilage degeneration by influencing gene expression of chondrocytes. Thus, altering the structural proteins by inhibiting synthesis of type 2 collagen and aggrecan and by promoting synthesis of matrix metallo proteinases (MMPs). This leads to accelerated cartilage destruction. Elevated levels of TNF-a and IL-1b can also lead to disorders in chondrogenic progenitor cells and induce chondrocyte death. IL-1b has a stimulating effect on production of reactive oxygen species which generate free radicles that directly damage articular cartilage.<sup>14</sup>

IL-4 is an anti inflammatory cytokine that is associated with chondroprotective effect. It acts by inhibiting both degradation of proteoglycan in articular cartilage and secretion of matrix metalloproteinases, thus preventing aggrecan breakdown and severe cartilage erosion. This effect is less prominent during osteoarthritis due to less susceptibility of chondrocyte to IL-4. Also, IL-1b and TNF-a decreases action of anti inflammatory cytokines IL-10 which stimulate synthesis of type 2 collagen and aggrecan.<sup>15</sup>

Low level of matrix metalloproteinases (MMPs) expression leads to tissue remodeling and turnover of healthy cartilage. But during osteoarthritis, when elevated levels of IL-1b and TNF-a bind to chondrocytes, through NF-kB pathway upregulation of MMPs expression happens. Upregulation of MMP-13, a key enzyme in cartilage degeneration through its ability to cleave both type 2 collagen and aggrecan lead to cartilage destruction. Nuclear factor kappa beta (NF-

KB) contribute significantly to the process involved in cartilage generation by inducing elevated levels of harmful factors and hindering cartilage repair process through altered expression of inflammatory cytokines, enzymes and transcription factors. Once activated by IL-1b and TNF-a, NF-KB becomes a positive regulator for expression of proinflammatory cytokines IL-1b, TNF-a and IL-6, while also promoting activity of enzymes MMP-9, MMP-1 and MMP-13, thus leads to cartilage destruction.<sup>16</sup>

In recent years, there has been an increasing prevalence in the use of autologous blood products that might provide cellular and humoral mediators to favour tissue healing in a variety of applications including osteoarthritis of knee joint. The rationale is based on the activity of blood growth factors. Growth factors are a diverse group of polypeptides that have important roles in the regulation of growth and tissue development, determining behavior of all cells including chondrocytes.

Platelets are one of the most important source of growth factors. Platelets are key components involved in hemostasis and has the property of stimulating formation of new connective tissue and revascularization. Platelets are small, clear cells measuring between 2-3 micrometer in size. They are formed from fragmentation of precursor megakaryocytes. Platelets have a life span of 5-9 days. The normal platelet count in human being are between 1.5-4.5 lakh/cubic mm.<sup>17</sup> A sample of blood normally contains 93% red blood cells, 6% platelets and 1% leucocytes. In platelet rich plasma (PRP), the ratio of red blood cells to platelets is reversed, thereby increasing growth factor content that may aid in tissue healing and regeneration. The exact ratio of RBC: WBC: platelet in PRP varies according to the way PRP is prepared.<sup>18</sup>

Platelet form blood clot in three stages, namely activation, secretion and aggregation. Platelet circulating in the blood get activated when they come in contact with von Willebrand factor (VWF), collagen from exposed endothelium or by thrombin. When platelets are activated, they degranulate and release contents inside the alpha granules and dense granules. The alpha granules stimulate platelet adherence to the exposed endothelium, while the dense granules activate intrinsic coagulation pathway.

The main growth factors within the platelet include Platelet derived growth factor (PDGF), Transforming growth factor beta (TGF-b), insulin like growth factor -1 (IGF-1), vascular endothelial growth factor (VEGF) etc. PDGF activate macrophage, stimulate angiogenesis, stimulate fibroblast chemotaxis and enhance collagen synthesis. TGF-b enhances proliferative activity of fibroblast, stimulate collagen and fibronectin formation and induce osteoclast formation. IGF-1 stimulate protein synthesis, enhances bone formation by activating osteoblasts and fibroblast chemotaxis. Platelet derived endothelial growth factor (PDEGF) promote wound healing by stimulating proliferation of keratinocytes and dermal fibroblasts. VEGF stimulate angiogenesis, migration and mitosis of endothelial cells etc.<sup>19</sup>

With the growth factors released from granules, platelet

facilitate the three stages of healing namely inflammation, proliferation and remodeling by initiating clotting cascade and release of histamine and serotonin. This increases capillary permeability of the area thus allowing greater access to inflammatory cells to the site and encouraging migration of leucocytes. With this, fibroblast proliferation happens and they lay down ground substance. The purpose of PRP is to form a high concentration of the above mentioned growth factors and create an optimum environment to accelerate cartilage healing process.<sup>20</sup>

PRP is prepared from peripheral blood with the aim of maximally concentrating the platelet content. To inhibit the coagulation process, Acid dextrose dextrose (ACD) is added to the container. Then the mixture is placed in the centrifuge machine and centrifuged at specific rpm and time according to the PRP kit. After the centrifugation, blood is converted to 2 layers; an inferior layer containing erythrocyte and a superior layer consisting of plasma in which the platelet layer will be isolated. Broadly, platelet concentrates are of 4 types depending upon the leucocyte and fibrin content. They are pure PRP (p-PRP), leucocyte and PRP (L-PRP), pure platelet rich fibrin (P-PRF) and leucocyte and platelet rich fibrin (L-PRF). Platelet in the PRP degranulate and release 70% of stored growth factors in 10 minutes and a small amount of growth factor will be released throughout the life span of platelet. Platelet degranulation can be augmented by adding calcium chloride to PRP. This convert autologous prothrombin to thrombin and platelet get trapped within fibrin matrix and gradual release of growth factors by 7 days. The isolated PRP is extracted from the container and infiltrated into the knee joint under a sterile environment.<sup>21</sup>

A study conducted by Dai, Zhou and Zhang concluded that intra articular PRP infiltration have demonstrated superior clinical and functional outcomes at 6 month follow up when compared to hyaluronic acid infiltration.<sup>22</sup> Multiple studies conducted by Sudman, Anitua and Sprechero demonstrated that PRP preparation that include elevated leucocyte are known to have an antimicrobial effect as well.<sup>23,24,25,26</sup>

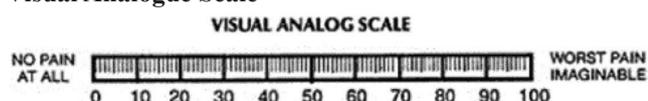
PRP derived growth factors are therapeutically compelling because of the anabolic effect and synergistic roles that can be applied to damaged cartilage tissue. PRP is one of few that contain several bioactive factors that are able to reestablish synovial fluid homeostasis, modulate inflammation and induce cell migration and recovery.<sup>27</sup>

Despite clinical and basic science research contributions that have helped to define PRP and its uses, there is lack of significant clinical trials and there are inconsistencies in reporting standards makes it difficult to translate these results to clinical practice. It is also important to point out that PRP treatment has a higher incidence of post injection pain following intraarticular infiltration. The mechanism of post injection pain is not clear.

Our study results support the application of autologous PRP as a safe and effective method in the treatment of the early stages of knee osteoarthritis. Significant clinical improvement was seen with 6 months of follow-up

## ANNEXURE 1

### Visual Analogue Scale



## CONCLUSION

Standardization of PRP production methods and administration are necessary in order to accurately measure and assess adverse effects as well as outcome. The methodology used to prepare PRP is another area that needs further research. There are different PRP formulations used for cartilage repair such as activated PRP, inactivated PRP and fibrin clots, and its standardization is not done yet. So it is crucial to validate PRP preparation methodologies in further clinical trials that can be used for evaluating efficacy of PRP treatment for cartilage repair in the future.

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