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Intra-articular platelet rich plasma in osteoarthritis knee

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Abstract

Background: Osteoarthritis is a slowly progressive disease of the diarthrodial joints. With articular cartilage degeneration, chondrocytes undergo mitosis and clustering. Degeneration of cartilage changes its biomechanical, biochemical, and structural properties. Numerous, non-invasive treatment options are available with emphasis on pain management, improvement in function and with a potential to modify the disease process and progress of cartilage degeneration. Platelets contain many growth factors, cytokines, and bioactive proteins which help regulate tissue healing and restoration. Autologous Platelet rich plasma contains a very high concentration of platelets above baseline levels and hence help in the improvement of disease.

Methods: We conducted a study on 70 knees diagnosed as having Kellgren-Lawrence (KL) Grade 2-4 Osteoarthritis knee. Autologous Platelet Rich plasma was prepared and was injected into the affected knee joint. The study group was followed up at 1 week, 4 weeks, 12 weeks. Clinical outcome analysis was done for the efficacy on the basis of WOMAC score and NRS Score. Statistical analysis of data was performed and P-value was calculated.

Results: Results obtained after statistical analysis suggested an overall improvement in WOMAC score in all grades of Osteoarthritis knee. Improvement in the patients having early stages was more in comparison to that seen in the patients in late stages.

Conclusion: Platelet Rich Plasma therapy in an effective treatment option to improve the clinical outcomes in patients with Osteoarthritis knee. It has an advantage of giving satisfactory outcomes. Also, it is low cost, minimally invasive and safe in application.

Keywords: PRP, osteoarthritis, intra-articular, WOMAC

Introduction

Osteoarthritis/Osteoarthrosis is used to define an idiopathic, slowly progressive disease of the diarthrodial (synovial) joints [1]. Osteoarthritis is a chronic, disabling condition that affects 10–15% of adults over 60 years of age [2]. Pathogenesis involves the focal degeneration of articular cartilage, subchondral bone thickening (sclerosis), marginal osteochondral outgrowths (osteophytes), and joint deformity [1]. As per general belief, degeneration of cartilage in OA is characterized by two phases: a biosynthetic phase, during which the chondrocytes attempt to repair the damaged extracellular matrix; and a degradative phase, in which the activity of enzymes produced by the chondrocytes digests the matrix, matrix synthesis is inhibited, and the consequent erosion of the cartilage is accelerated [3]. When articular cartilage degeneration starts, chondrocytes undergo mitosis and clustering. While the metabolic activity of these chondrocyte clusters is high, the net effect of this activity is to promote proteoglycan depletion in the matrix surrounding the chondrocytes [4]. As disease develops, collagen matrix becomes damaged, the negative charges of proteoglycans get exposed, and cartilage swells from ionic attraction to water molecules. Damaged cartilage does not bounce back after loading as it normally does due to loss of proteoglycans and hence becomes more prone to further injury. Chondrocytes at the basal level of cartilage undergo apoptosis [5]. In the subchondral bone changes takes place in trabecular thickness, number, and separation [6]. Growth factors and cytokines stimulate the bone cells. Osteoclasts and osteoblasts cells in the subchondral bony plate become activated [7, 8]. Bone formation produces a thickening and stiffness of the subchondral plate. Trauma to bone during joint loading may be the primary factor driving this

bone response.

Healing from injury (including microcracks) may produce joint stiffness. Bone death caused by bone trauma with shearing of microvasculature, leads to a cut off of vascular supply to some bone areas [9]. At the margins of the joint, near areas of cartilage loss, osteophytes are formed. Osteophytes are thought to arise through chondrogenic differentiation of progenitor cells, most commonly these osteophytes are formed within the periosteum [10]. Osteophytes are an important radiographic hallmark of OA [11].

Physical examination of knee joint in patients with OA reveals localized tenderness, bony or soft tissue swelling, bony crepitus, joint effusion and restriction of mobility [12]. Symptomatic OA of the knee which is described as having pain during most days of a month along with radiologic evidence of arthritis has a prevalence of 22% to 39% in India [13]. Numerous, non-invasive treatment approaches with emphasis on pain management, improvement in function and with a potential to modify the disease process defined for this disease include analgesics, steroids and non-steroidal anti-inflammatory drugs, glucosamine/chondroitin supplementation, physical therapy, and hyaluronic acid (HA) injections. But, most of these treatments have short-term success, and does not address the biological pathology and have shown only minor benefits and have many side effects [14, 15]. PRP is defined as the volume of the plasma fraction from autologous blood having platelet concentration above baseline (200000 platelets/ μ l). Clinical efficacy can be expected with a minimum increase of four- to six-fold from this baseline (1 million platelets/ μ l) [16]. PRP contains a very high concentration of platelets above baseline levels. Platelets and white blood cells (WBCs) are the sources of high concentration of cytokines. Cytokines are well documented to modify processes such as cell migration, angiogenesis, and collagen synthesis and wound healing. PRP delivers a high concentration of autologous growth factors which are contained in the alpha granules of platelets [17]. Application of PRP in musculoskeletal disorders are growing significantly. Although comparing PRP with other intra-articular and soft tissue injections has led to conflicting results, but it seems that PRP has useful effects on healing and functional improvement of injured tissues.

Materials and Methods

This prospective randomized clinical study was conducted in the department of orthopaedics in our institution during the period June, 2018 to April, 2019 after obtaining clearance from the Board of ethics. Patients attending the Orthopaedics Department (OPD and IPD) with complaint of knee pain were screened and those diagnosed as Knee Osteoarthritis were chosen for the study. The Patients were included in the study on the basis of Inclusion and Exclusion criterias and selected

patients received intra articular injection of Platelet Rich Plasma into the knee joint and served as the study group. Total of 70 knees diagnosed as having Kellgren-Lawrence (KL) Grade 2-4 Osteoarthritis were included and study group received intra-articular injection of autologous PRP into the knee joint after written and informed consent. Patients included were having age between 50 years to 80 years. Were with Primary disease with Kellgren Lawrence Grade 2 to 4. Patients with symptoms suggestive of Osteoarthritis knee for > 3months and no relief in symptoms after 6 weeks of non-invasive treatment were included. Patients with secondary Disease, uncontrolled Diabetes, infection at other sites in body, local skin disease and history of any coagulopathy were excluded from the study.

Study Procedure: A detailed history, complete physical examination and routine investigations were done for the study population. Baseline Western Ontario and McMaster Universities Index (WOMAC) score [18] was obtained and calculated. Following this, Intra-articular injection of autologous Platelet Rich Plasma in the affected knee joint was given. Patients were called for follow up at 1 week, 4 weeks, 12 weeks. Patients were advised graduated exercises. Outcome Analysis was done for the efficacy on the basis of WOMAC score. Statistical analysis of the data was done. P-value was calculated and was considered to be significant when less than 0.05.

Observations and Results

In this prospective randomized clinical study, total of 60 patients were screened and 40 patients were selected on the basis on inclusion and exclusion criteria. Out of these 40 patients, 10 patients were managed for single knee and 30 patients were managed for both knees. So, a total of 70 knees diagnosed as having Kellgren-Lawrence Grade 2-4 Osteoarthritis were included in the study and clinical intervention was done.

Results were obtained after statistical analysis. P value was calculated to assess the statistical significance of results.

Out of the 70 knees selected for the study 40.3% knees were of the male patients and 59.7% knees were of the female patients. Mean age of the study population was 61.18 ± 7.00 (50-79) years. Among study population, 45.7% subjects belonged to 51-60 years, 38.3% subjects belonged to 61-70 years and 16.0% subjects belonged to above 70 years.

The mean WOMAC score was compared between baseline, 1 week, 4 weeks, 12 weeks and 24 weeks using the repeated measures ANOVA test. There was a significant difference in mean WOMAC score between baseline, 1 week, 4 weeks and 12 weeks. The mean WOMAC score at Baseline was 79.48 ± 7.83 , 1 week was 71.69 ± 7.39 , 4 weeks was 64.26 ± 7.72 and 12 weeks was 61.27 ± 7.82 .

Table 1: Comparison of WOMAC scores

WOMAC score	Mean	Mean	Mean	Mean
Baseline	+/-	+/-	+/-	+/-
	SD	SD	SD	SD
	Overall	OA grade 2	OA grade 3	OA grade 4
	79.48	74.06	80.22	86.82
1 week	+/-	+/-	+/-	+/-
	7.83	6.9	6.85	4.43
	71.69	69.4	72.06	78.73
4 weeks	+/-	+/-	+/-	+/-
	7.39	6.43	6.88	7.01
	64.26	62.69	64.24	70.64
12 weeks	+/-	+/-	+/-	+/-
	7.72	7.42	7.45	8.08
	61.27	60.13	61.57	67.48
	+/-	+/-	+/-	+/-

	7.82	7.59	7.29	8.85
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Discussion

OA is a common joint disease in the world and is one of the leading causes of disability in the world, with more than 10% of the elderly population having symptomatic disease. In osteoarthritis of the knees, microscopic degenerative debris is a constant cause of chemical irritation and mechanical limitation during walking and knee movement, resulting in aggravation of pain [20]. By mediating chondro-protective action, PRP therapy can delay joint deterioration by interfering with the early catabolic and inflammatory events and by promoting anabolic responses subsequently reducing OA pain [21]. Joint changes such as synovitis, subchondral bone remodeling (thickening, bone collapse, bone cysts), degeneration of ligaments, menisci and hypertrophy of joint capsule are involved in the pathogenesis of osteoarthritis. PRP represents an autologous biological therapy option in which the patient's own plasma and platelet-derived growth factors are used for regenerative purposes to stimulate processes such as angiogenesis, mitogenesis, cell proliferation, and cell migration to chemo-attractants in the knee joint. This therapy has an advantage of giving long term effects with low cost, minimally invasive, feasible and safe application.

In our study, the mean age of the study population was 61.49 ± 7.06 (50-79) years. This was in accordance with the study by Goyal *et al.* [19]. Findings suggest that the incidence of osteoarthritis increases with age, and many people by the 6th decade develop radiographic evidence of OA. The peak performance of an individual is considered to be around age of 30 years and after that, physical decline starts gradually. Around the age of 50 years, the decline in activities become fast which can be an attributing factor for the development of symptomatic degenerative changes in older age groups. PRP was found to be effective in OA in all the age groups but effect was less in older age groups in comparison to that in younger population.

In this study, the mean WOMAC score decreased significantly from baseline to as early as 1 week. Effect of PRP, in the later stages of follow up effect gradually plateaued at 12 weeks. This coincides with the results of study done by Cerze and colleagues [20] and Sanchez and colleagues [21]. In certain other recent related systematic reviews, on comparing the effectiveness of PRP to other intra-articular injections, exercise or analgesia. PRP injections were found to produce statistically significant improvements in overall WOMAC scores for patients with knee osteoarthritis up to 12 months after intervention. This suggests that PRP has sustained effects with significant improvement over longer periods. The findings of our study are in keeping with the studies of Cerza and colleagues [20], Sanchez and colleagues [21]. The improvement in WOMAC scores in our study can be attributed to the method of preparation using the double spin centrifuge and proper technique of PRP instillation into the knee joint. Sometimes, improper technique may lead to the PRP injection into the structures around the knee joint which may lead to poor outcomes and excessive pain in the post procedure period. Long-term outcomes of this therapy beyond 12 weeks and the need of repeat doses have not been established from our study, but good clinical outcomes were seen upto a follow up period of 12 weeks in all grades [2-4] of OA knee and effect was seen to be maintained during follow ups. So, single dose of PRP injection is effective. But, we cannot conclude on the duration of the expected benefit of PRP injections beyond a period of 12 weeks. As per different Osteoarthritis grades, an improvement in all the grades was

seen which is supported by the studies of Jubert *et al.* [22] and Gobbi *et al.* [23]. As observed in our study, improvement was more in early stages of osteoarthritis in comparison to late stages. Several factors could explain the less improvement of scores in advanced stages: greater degree of knee OA with advancing age leading to more osteophyte formation, more changes in surrounding soft tissue structures and lesser amount of remaining cartilage (which probably helps in stimulating chondroprotective effect). With advancing age, the effectiveness of regenerative therapies can also be decreased due to less reparative potential of cells leading to less effectiveness in old age patients with advanced arthritis. Study supports the advantages of using PRP, that is, its efficacy in improvement of knee joint function and reduction in pain in all grades of OA knee. Better results are seen in OA grade 2 followed by OA grade 3 and 4 in that order.

PRP injection for OA knee can be considered as a promisable treatment option in all stages of OA knee. Function improvement in KL stage 4 patients in terms of WOMAC score is less in comparison to that in early stages whereas in terms of NRS score, pain relief in KL stage 4 knees was seen. Side effects related to injection of platelet-rich plasma are considered uncommon and, when present, usually manifest in a mild and self-limiting form. In our study minor insignificant complications like aggravation of pain around the knee joint, stiffness in knee, erythema or swelling in the knee joint were seen in 4 patients. All these side effects were seen to occur within first week of therapy and were found to subside with the limb elevation, local application of ice, compression or by the use of analgesics and anti-inflammatory medications. Similar findings were also seen in much recently published research involving PRP as an intervention in knee OA by Paterson *et al.* [24]. These side effects were found to occur more in the initial period of study and that too in patients with KL Grade 3 or 4. The cause of aggravation of pain, erythema or swelling may be due to a wrong injection technique leading to PRP instillation in the ligaments or surrounding structures of the joint. When PRP instillation is done in late stages, there are chances that osteophytes can obstruct the passage of needle into the joint (especially when injection is given using a lateral approach) leading to increased chance of complications.

Current evidences suggest that main complication of PRP in knee OA is pain and stiffness around the knee joint. This too responds to simple treatment with analgesics and may last for a few days. A caution should be taken while instilling PRP into the knee joint, especially in late stages of OA.

All injections in our study were delivered under all aseptic precautions, so no case of knee joint infection was seen. Moreover, sterility should be maintained in every step of procedure starting from the collection of blood to the PRP preparation and instillation. Any break in the chain of sterility may lead to very disastrous complications like deep infection, adhesion formation etc. In case of any doubt about the sterility of the technique of PRP preparation, it is always wise to send a part of prepared PRP for microbiological investigations before instillation.

The present study has several limitations. First, this was an open-label study, so no comparison with a control group was performed. Second, the follow-up period was only till 12 weeks, which is relatively short to look for the long term efficacy of the treatment.

So, PRP is an easy, safe and economic option for the treatment of knee osteoarthritis. This treatment option has a

high level of predictability and has a long lasting effect along with a disease modifying potential.

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