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Role of Autologous Platelet Rich Plasma Intraarticular Injection in Primary Early Osteoarthritis of the Knee Joint

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Abstract: Platelet-rich plasma (PRP) is considered as an innovative and promising tool to stimulate repair of the damaged cartilage. PRP is a concentration of several protein growth factors which stimulate cell proliferation, migration, differentiation, and matrix synthesis and can affect chondrocyte metabolism and improve cartilage healing. A total of 42 patients with symptomatic Kellgren-Lawrence grade 1 and 2 osteoarthritis (OA) of Knee Joint were enrolled in this study in 2015. Patients were treated with an autologous single PRP intra articular injection (IAI). Results were assessed using Visual analog scale (VAS) and Knee injury and Osteoarthritis Outcome Score (KOOS). Both variables were assessed pre injection and at 3 weeks, 1 month, 3 months, and 6 months after treatment. There was stastically significant improvement in both variables at 6 months follow up. A single PRP IAI is effective for relieving pain and improving activities of daily living in early stage knee OA.
Keywords: Platelet rich plasma, Osteoarthritis, Intra-articular injection and Knee.

INTRODUCTION

Osteoarthritis (OA) of Knee joint is a common painful chronic disease faced by ageing adults. This multifactorial disease is characterized pathologically by a destruction of the articular cartilage, osteophyte formation, synovial inflammation, subchondral changes, meniscal damage, ligamentous degeneration. OA results from a complex interplay of genetic, biomechanical, metabolic and biochemical factors[1]. The OA is multifactorial in etiology and not completely understood. Age, body weight, lower-limb alignment, joint instability, previous injuries, knee surgery, cartilage defects,joint infection are strongly correlated to the development of knee OA[2]. Recent literature also suggests female predilection for developing OA of knee joint[3].

During the past years, increased importance has been placed on the biochemical equilibrium required for the cartilage health. It has become apparent that the inflammatory intermediaries contribute significantly to the development and advancement of changes in the joint OA[4]. Recently, Platelet Rich Plasma (PRP) is considered as an novel and promising tool to stimulate repair of the damaged cartilage. PRP is concentrate of platelets including various growth factors, glycoproteins, metalloproteinases in a pool of plasma. PRP is a concentration of several protein growth factors which stimulate cell proliferation, migration, differentiation, and matrix synthesis and can affect chondrocyte metabolism and improve cartilage healing in vivo. PRP is a pool of growth factors along with other biochemical intermediares which are stored in the granules of platelets, which have been found to take part in the regulation of articular cartilage. All the components of PRP seems to act by decreasing inflammation in the joint by downregulation of proinflammatory mediators such as interleukins and cytokines. In this way PRP may help in the treatment of degenerative lesions of articular cartilage and OA[5].

The purpose of this study was to assess and evaluate the clinical effects and safety of a single intra articular injection (IAI) of autologous PRP in patients with primary osteoarthritis of the knee joint.

MATERIALS AND METHODS

The study was conducted at our institute in 2015. Forty two patients were enrolloed in the study after obtaining informed consent and obtaining approval by institute ethics committee.Patients presented with primary osteoarthritis of the knee joint in Orthopedics out patient department who met inclusion criteria and provided informed consent were treated by single IAI of PRP.

The diagnosis of knee OA was made by history and physical examination including signs andsymptoms of knee pain with stiffness, joint crepitus and functional limitations. The diagnosis was confirmed by radiographs demonstrating changes such as osteophytes and joint space narrowing, subchondral bone sclerosis and cysts, and graded according to Kellgren and Lawrence classification[6].

Table-1: Kellgren and Lawrence classification

Grade 0: No changes
Grade 1: Doubtful narrowing of the joint space and possible osteophytic lipping
Grade 2: Definite osteophytes and possible narrowing of the joint space
Grade 3: Moderate multiple osteophytes, definite narrowing of the joint space, and some sclerosis, and possible deformity of the bone ends
Grade 4: Large osteophytes, marked narrowing of the joint space, severe sclerosis, and definite deformity of the bone ends

Table-2: Study Inclusion Criteria

S No.	Inclusion criteria
1	Age group range from 40-70 years
2	Patient with mild to moderate osteoarthritis of knee (Kellgren- Lawrence scale grade 1 and 2)
3	Completed informed consent

Table-3: Study Exclusion Criteria

S No.	Exclusion criteria
1	Pregnancy or breastfeeding
2	Knee surgery within 3 months of treatment, infection of the knee joint within 6 months
3	Any patient with severe (Grade3,4) Osteoarthritis of the knee
4	Presence of systemic disorders such as diabetes, rheumatoid arthritis, hematological diseases (coagulopathy/bleeding disorders), severe cardiovascular and liver diseases, skin allergy , infections, malignancies and immunosuppression
5	Patients with hemoglobin values of less than 11gm % and platelet count less than 1,50,000/ml.
6	Patients on therapy with anticoagulants,use of intraarticular cortisone injection within 6 wks,patients with history of drug abuse.
7	Any neurovascular disease in the limb, Lack of informed consent

Radiographic examination was done which included standard weight bearing anteroposterior and lateral radiograph of affected knee joint. The detailed history of the patients was recorded and a Performa was filled. Clinical examination including Visual Analog Scale (VAS) and Knee Injury and Osteoarthritis Outcome Score (KOOS) were done.

PRP Preparation

Patients were sent to Institute's blood bank for preparation of PRP.The procedure entails collection of blood sample in three parts.

- One 3ml sample in Ethylenediaminetetraacetic acid (EDTA) Vacutainer for complete blood count of the patient.
- Two 8 ml (total of 16 ml) samples were collected aseptically in sterile Acid Citrate Dextrose (ACD) vacutainers.
- PRP was prepared using a single spin method. The Citrated blood was then centrifuged at 440 g for 10 minutes at room temperature to produce PRP under strict aseptic laboratory settings under laminar hood.

The patient was taken to the minor operating room for the PRP injection. The skin was sterilely prepared. PRP was injected using anterolateral approach with an 18- gauge needle under aseptic technique. Immediately after the injection, passive flexion and extension of the affected knee was performed three times to allow the PRP to spread throughout the joint, followed by 10 minutes of resting

in supine. Subsequently the patients were sent home with instructions to limit the use of the leg for at least 24 hours and to use cold therapy/ice on the affected area to relieve pain if any. During this period, the use of non-steroidal anti inflammatory medication was forbidden. During the treatment period, rest or mild activities (such as using an exercise bike or mild exercise in a pool) were permitted, and subsequently a gradual resumption of normal sport or recreational activities was allowed, as tolerated.

Outcome

All patients were assessed and evaluated using VAS and KOOS for clinical outcome measures at a pre injection visit and after 3 weeks, 1 month, 3 months and 6 months follow-up visits.Any Complications and adverse events were also recorded.

Statistical Analysis

Statistical analysis was performed using SPSS 20.0 (Statistical Package of Social Sciences, Chicago, IL, USA) software.

Data were expressed as the mean ± standard deviation. D'Agostino–Pearson normality test was used to test the normality of data distribution. Data were normally distributed, and pairedcomparisons were performed by two-tailed paired t-test.The significance level was set at *p*-value lower than 0.05.The results were expressed as mean ± SD.

RESULTS

Twenty two female patients (55%) and twenty male patients (45%) with mean age of 55 years (range: 40-70 years) participitated in this study. Out of 42 Patients, 40 were evaluated finally at 6 months ,whereas 2 patients were lost at final follow-up. Mean KOOS score at baseline was 58.5 ± 14.0, and mean VAS score before injection was 6.02±1.36. At 6 months follow-up, the mean KOOS score improved to 76.0 ± 13.0, and the mean VAS score was 3.5± 0.9.These improvements in KOOS and VAS score were statistically significant ($p < 0.001$). No adverse reaction or complications was noted after PRP injection.

DISCUSSION

The main finding of this study is the stastically significant improvement of VAS and KOOS score in patients with knee OA. Patel *et al*. documented adverse events such as dizziness, nausea, sweating at the time of injection. All adverse events subsided within few minutes while the patients were under observation[7]. Minor adverse events such as mild pain and effusion related to the PRP injections were observed in the study by Filardo *et al*.[8].

Meheux *et al*. performed a systematic review of 6 randomized, controlled trials and infered that PRP injection resulted in significant improvements for up to 1 year post-injection period[9].

The etiopathogenesis of OA is complex and involves many mechanical and biochemical processes. Aging is the most important single risk factor of OA, and any unfavourable biomechanical environment results in mechanical demand that predispose to articular cartilage damage[10-12] However, OA is not related to only mechanical stress, but many cellular and biochemical processes are also involved in its pathogenesis[13].

PRP acts at different levels within the joint. It decreases cartilage catabolism,improves anabolism and increases collagen 2 and prostaglandin synthesis[14]. Insulin-like growth factor 1 (IGF-1) in PRP may decrease the expression of apoptotic programmed cell death 5 (PDCD5)[15]. PRP seems to influence synovial cells by increasing hyaluronic acid production and decrease im matrix metalloproteinases mediated by interleukin 1 [16]. PRP also downregulates proinflammatory mediators by regulation of cyclooxygenase-2 (COX-2),nuclear factor kappa B and IL-1b[17]. This can explain pain reduction which is main and disabiling symptom.

Many PRP formulation are available for clinical uses and products can vary which may influences the efficacy of treatment and the results of clinical trials. Ehrenfest *et al*. [18] proposed a classification based on platelet, fibrin, and leukocyte concentration: pure PRP (P-PRP), leukocyte- and platelet-rich plasma, pure platelet-rich fibrin, and leukocyte- and platelet-rich fibrin. In particular, the content and different concentration of leukocytes in PRP products may affect the anti-inflammatory effects of PRP. The role of leucocytes in PRP is a controversial issue in literature, and it has not been proven that taking leucocytes from a PRP sample could either benefit or result better outcomes for the patient.

First clinical trial for intra articular use of autologous PRP in Knee OA was done by Sanchez *et al*. which established the safety of PRP[19].

Kon *et al*. observed improvement in variables such as International Knee Documentation committee (IKDC) and VAS scores at 1 year follow up in 91 patients treated by 3 freezed thawed PRP injections at 3 week intervals[20].

Li *et al*. documented better results in the PRP group compared to Hyaluronic acid (HA) group at 6 months follow up[21].

In study by Say *et al*. better results were obtained in the KOOS score and visual pain scale in PRP group compared to HA group at 6 months follow up. Also the application for the PRP was more economical than that of the HA[22]. Majority of the studies have included early OA for PRP therapy and

consistently showed benefits in terms of symptomatic improvement[23].

The present study is not without limitations. First, this was an open-label study and no comparison with a control group was performed. Second, the follow-up period was relatively short. Subsequent double blinded trials with longer follow up period and with a control group would be desirable. This study further strenghthens the fact that PRP injection is an effective and safe treatment for low grade knee OA in terms of improving function and reducing pain at six months follow-up.

CONCLUSION

A single intra-articular injection of PRP is an effective and safe treatment modality for relieving pain and improving function as well as activity of daily living and quality of life in patients with early stage knee OA.

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