Platelet Rich Plasma as a Boon for Osteoarthritic Knees- A Prospective Observational Study

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ABSTRACT
Introduction: Knee pain is a leading cause of disability and the most prevalent form in the world. It is associated with tissue inflammation, physical disability and imbalanced homeostasis in cartilage. As the number of people with age greater than 35 years increases, so does the prevalence of knee pain and the need for cost effective treatment and care. A treatment strategy is needed which takes into account the underlying physiology of degenerative joint disease, but it should also consider the different age ranges and their needs in different population.

Aim: To assess the clinical and functional benefits associated with the use of intra-articular Platelet Rich Plasma (PRP) in treatment of patients with knee pain of primary Osteoarthritis (OA).

INTRODUCTION
Platelet-rich plasma is an autologous concentration of a higher number of platelets in a small volume of plasma compared to whole blood, prepared by centrifugation of whole blood. Platelets contain various amount of cytokines and growth factors which have the capacity of stimulating cellular growth, vascularisation, proliferation, tissue regeneration, and collagen synthesis. PRP delivers high concentrations of cytokines and growth factors to damaged tissues and is considered to have a regeneration effect on tendon and cartilage tissue [1,2]. Chronic knee pain puts a person to inconvenience in social, familial and business environments. Knee pain can occur in numerous ways and due to various diseases. Between the ages of 30 and 65 years, the general incidence and prevalence of knee OA has been reported to increase by as much as 10 times that of younger age groups, affecting nearly 33.6% of people >65 years or an incidence of 1 in 10 [3,4]. Since PRP contains growth factors and plasma proteins, it can regulate anti inflammatory signals and equilibrate angiogenesis [4,5]. Based on this, its use in order to reduce the progression of knee pain has been suggested in a study [6]. In OA knee, PRP injections delay the need for joint replacement surgery by promoting cartilage repair thus relieving osteoarthritic symptoms [7]. PRP is prepared from the patient’s own blood, so there is no risk of developing a tumour or donor blood transfusion infections like HIV, HBsAg, HCV etc., [8]. Adverse effects can occur as with any injection like small risk of infection or local injury to nerves or blood vessels, scar tissue formation and calcification at the injection site [9]. The conservative treatment options for osteoarthritic knee pain are: Non Steroidal Anti Inflammatory Drugs (NSAIDs) including non selective Cyclooxygenase (COX) inhibitors and selective COX-2 inhibitors (Coxibs), steroids, chondroitin sulfate, diancerein, glucosamine sulfate etc. Intra-articular therapies with injectable steroids, hyaluronic acid, viscous gel etc., also aid in temporary pain relief.

The aim of the present study was to assess the clinical and functional benefits associated with the use of intra-articular PRP in treatment of patients with knee pain due to primary OA.

MATERIALS AND METHODS
This was a prospective observational study done from January 1st 2014 to December 31st 2015. All patients presenting to orthopaedics outpatient department of Health Care Global (HCG) hospital, Bengaluru, Karnataka, India, with Kellgren and Lawrence Grade 1 and 2 OA knees were considered. All patients fulfilling the inclusion and exclusion criteria and consenting to participate in the study were enrolled. At the end of two years, 50 patients were enrolled and completed all 3 follow up WOMAC questionnaires by physical presence or telephone contact. PRP was prepared usinguffy coat method, where 50 mL Whole Blood (WB) was mixed with anticoagulant citrate dextrose and centrifuged at a ‘hard spin’ of 4000 rpm for 15 minutes. A supernatant buffy coat is formed and contains leucocytes rich at upper and PRP in middle layer. This layer mainly comprises of the necessary PRP [10,11]. The difficulty lies in separating this thin buffy coat from the underlying RBC layer. To obtain PRP by buffy coat method WB was mixed with anticoagulant and stored at 20°C to 24°C before centrifugation [Table/Fig-1] and then centrifuged at a ‘high’ speed of 4000 rpm. Three layers were formed because of its density. The bottom layer consists of RBCs, the middle layer consists of PRP and the topmost layer consists of leucocyte rich with platelet poor plasma. Supernatant plasma was removed from the top of the container and this buffy coat layer was transferred to another sterile tube. Now centrifuged at a low speed of 1000 rpm (soft spin) to separate WBCs and obtain PRP [12].

Inclusion criteria had patients aged >40 years, both male and female, painful arthritic knees of Kellgren and Lawrence Grade 1 and 2, platelet count >150,000/cumm [13] and patients willing for intra-articular autologous PRP injection and attend to a follow up of minimum 3 visits post procedure at 1, 3 and 9 months respectively. Patients with cancer or metastatic disease, an active local or systemic infection, pregnant or is breastfeeding [14], uncontrolled systemic conditions, patients undergoing corticosteroid therapy, and patients using anticoagulant therapy were excluded from the study.

Result: Statistically significant improvements in WOMAC scores were noted in all the evaluated measures in all patients.

Conclusion: A minimum of two intra-articular injections of PRP is an effective treatment for mild to moderate osteoarthritis of knees.

Keywords: Arthroplasty, Knee, Osteoarthritis
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which healed within a week by analgesics alone. WOMAC scores compared individually for pain, stiffness and physical function at 1st, 3rd and 9 months post PRP injection versus pre-injection [Table/Fig-4] showed statistical significance with p-value less than 0.001 for almost all except for pain at 1st month (p=0.2408) as shown in the [Table/Fig-5].

STATISTICAL ANALYSIS
Statistical analysis was done using unpaired t-test for the WOMAC values obtained pre and post PRP injection.

RESULTS
A total of 50 patients with mild to moderate OA knees were involved in the study and completed a minimum of 9 months post PRP injection follow up. Gender wise 28 females and 22 males were involved making a percentage of 56% and 44% respectively. Two patients developed superficial tenderness at injection site which healed within a week by analgesics alone. WOMAC scores compared individually for pain, stiffness and physical function at 1st, 3rd and 9 months post PRP injection versus pre-injection [Table/Fig-4] showed statistical significance with p-value less than 0.001 for almost all except for pain at 1st month (p=0.2408) as shown in the [Table/Fig-5].
In our study, PRP showed beneficial effects in arthritic knees by decreased pain and stiffness and improving the physical function. Since the past decade, PRP has evolved as a non-operative treatment modality for cartilage injuries [15]. Even though there are significant variations in its makeup, the initial PRP prepared by centrifugation consistently contains highly concentrated platelets and a number of plasma proteins. Platelets are produced by their precursor megakaryocytes as anucleated cells [16]. Different types of growth factors, adhesion molecules, coagulation factors, cytokines, chemokines and integrins are stored in platelets [17]. The platelets in PRP after activation release different growth factors at concentrations significantly higher than the baseline blood levels, which includes transforming growth factor-β, Platelet-Derived Growth Factor (PDGF), Insulin-like Growth Factor (IGF), basic fibroblast growth factors, Vascular Endothelial Growth Factor (VEGF), epidermal growth factors, etc. [18]. Many of these are anabolic cytokines like transforming growth factor-β, IGF, basic fibroblast growth factor and PDGF, are chondroprotective and chondro-promoting [19]. These stimulate chondrocyte and multipotent Mesenchymal Stem Cell (MSC) proliferation, promote chondrocyte synthesis of aggrecan and Collagen type II (Co III), drive MSC chondrogenic differentiation, prevent chondrocyte and MSC apoptosis, and diminish the catabolic effects of inflammatory cytokines, such as IL-1β, and Matrixmetallo Proteinases (MMPs). PRP platelets are also a source of inflammatory mediators and modulators. Platelets after incubation with polyacrylamide beads, may release numerous anti-inflammatory cytokines, including IL-1 receptor antagonist (IL-1ra), soluble Tumour Necrosis Factor (TNF) Receptor (stNF-R) I and II, IL-4, IL-10, IL-13, and interferon γ [20]. The significant difference between the concentrations of pro-inflammatory factors and anti-inflammatory cytokines in PRP suggests that PRP may suppress inflammation in OA knee pains, thereby protecting cartilage and reducing pain. PRP contains various plasma proteins, which form critical components in connective tissues healing mechanism [21]. Compared to serum, plasma contains fibrinogen and other clotting factors, which can be activated to form a provisional fibrin scaffold for cells to migrate, adhere and proliferate [22]. As articular cartilage is avascular and thus unable to initiate the same healing process as other tissues, PRP scaffold mimics the initial stage of wound healing and tissue repair. Dohan Ehrenfest DM et al., suggested the following classification for PRP: leukocyte poor PRP; platelet and leukocyte rich plasma; platelet rich and leukocyte poor fibrin; and platelet and leukocyte rich fibrin [23]. One study has showed the efficacy of PRP to improve functional outcomes for mild knee osteoarthritis [24]. Various RCTs have demonstrated the superiority of PRP over traditional approaches and have also demonstrated superiority of autologous PRP intra-articular injections over hyaluronic acid injections in reducing pain and recovering articular function [25,26], especially for younger patients and milder OA knees [27,28] with one study showing benefit of PRP even for Grade 3 knee OA [29]. Others have shown inconsistent superiority of PRP over viscosupplementation [30]. In an RCT with 1-year follow up, PRP was not superior to viscosupplementation for knee OA, with diminishing benefit beyond 9 months [31]. A study showed no difference for pain and functional outcome after having a single or a double injection of PRP, but both provided superior outcomes compared with control using saline [32]. Another study demonstrated superiority of PRP compared with viscosupplementation only when multiple PRP injections were used [28]. PRP was shown to be superior to steroid injection for knee OA [33]. Adverse effects have been minor, with leukocyte-rich PRP associated with increased pain and swelling relative to leukocyte-poor PRP [34].

**CONCLUSION**

PRP acts as one of the best non drug modalities of treatment and may delay the need for total knee arthroplasty. Thus, combining PRP (of which a minimum of two injections was appropriate), Hyaluronic Acid (HA) and stem cells would be an ideal combination for treatment of knee pain. Although, this is a promising method of treatment for knee pain, its long-term outcome is unknown and can’t be used in advanced osteoarthritis.

**REFERENCES**


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