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A comparative study of functional outcome of osteoarthritis knee post intraarticular injection of PRP and corticosteroid with minimum six months of follow-up

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Abstract
Aim: to compare current application of platelet rich plasma (PRP) with corticosteroid as intraarticular injection in the osteoarthritis knee patients. We focused on comparing functional outcome of the knee joint following both the modalities and drawing a conclusion after evaluating merits and demerits of both the intraarticular injections.
Introduction: Osteoarthritis (OA) is a chronic joint disease that usually occurs in older people and leads to pain and disabilities. OA treatment ranges from drug therapy to surgery. Drug and rehabilitation therapy are preferred over surgery, and, especially, there is a tendency toward compounds causing regenerative changes in the knee joint. In the present study, the effects of platelet-rich plasma (PRP) injection and corticosteroid injection were examined on the level of pain and function of the knee joint in patients with OA.
Methodology: All patients were included in the study after full filling the inclusion criteria and informed consent. Total 100 patients were included in the study of which all patients having even number in the end of OPD number were given PRP intraarticular injections whereas OPD numbers ending with odd number were given steroid intraarticular injections. Following admission all patients were evaluated and staged with grade 0 to 4 according to Kellgren-Lawrene grading scale and grade 1 to 4 according to Ahlback score. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to evaluate the Patients pre-and post-intraarticular injections. Accordingly, patients in the PRP therapy group received 7 mL PRP solution and those in the corticosteroid group received 80 mg methyl-prednisolone mixed with 2ml of plain lignocaine. Using the WOMAC, levels of pain and knee function were evaluated and recorded for each patient immediately prior to the first injection as well as at 6 weeks (immediately prior to the second injection), 3 months (6 weeks after the second injection), and 6 months later. Data collected for both the groups were analysed and compared with each other.
Conclusion: Results of the present study suggested a significant decrease in the overall WOMAC score of patients who undergo either PRP or corticosteroid intraarticular injections. This positive change in the overall WOMAC score led to an improvement in the quality of life of patients with knee OA shortly after the first injection. PRP injection is more effective than corticosteroid injection in the treatment of osteoarthritis knee. Our study has thrown up an interesting choice of treatment modality using Platelet Rich Plasma in the treatment of Knee Osteoarthritis and it has proved efficacious in the observation period of six months.

Keywords: Osteoarthritis knee, platelet-rich plasma, corticosteroid, methyl-prednisolone

Introduction

Osteoarthritis (OA) represents a failure of the diarthrodial, synovial lined joint. Among the elderly, knee Osteoarthritis is the leading cause of chronic disability. Because of the increased lifespan and obesity, the prevalence of osteoarthritis is on the rise in Indian population.
Osteoarthritis is age related, affecting more than 80% of people over the age of 55. OA in weight-bearing joints is strongly linked to body mass index. As life expectancy increases, and the rate of obesity reaches epidemic proportions, OA has become increasingly common. The pathogenesis involves an imbalance between normal cartilage derivative and repair mechanisms, which results in net cartilage loss, hypertrophy of bone, and osseous outgrowths called osteophytes. OA has a predilection for finger joints, knees, hips, shoulders, and the spine.

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Occurrence in an atypical joint, such as an elbow, can usually be traced to prior trauma, a congenital joint abnormality, underlying systemic disease, or a chronic crystalline arthropathy. The heterogeneity of OA arises from the many factors that can contribute to cartilage damage.

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.

Osteoarthritis is a chronic disorder of synovial lined joints where there is progressive softening and disintegration of articular cartilage accompanied by new growth of cartilage and bone at the joint margins, cyst formation and sclerosis at subchondral regions of bone, mild synovitis and capsular fibrosis.

Osteoarthritis differs from simple wear and tear in that it is asymmetrically distributed, often associated with abnormal loading rather than frictional wear. It is not an inflammatory disorder although at times there are local signs of inflammation. In its most common form osteoarthritis is unaccompanied by any systemic illness.

How is PRP made?
Not all PRP is the same, and preparation methods lack a standardized protocol [1]. After a blood sample is collected from the patient, that sample is run through a centrifuge, which separates the samples cellular products based on different specific gravity [2]. One primary difference in PRP systems involves this centrifugation, which can involve either one or two spins through the system. Systems utilizing one spin, such as autologous conditioned plasma (ACP) (Arthrex, Naples, Florida) and Cascade PRP (MTF Biologics, Edison, New Jersey), separate the sample into a plasma layer containing platelets and a separate layer containing red and white blood cells (Fig. 1).
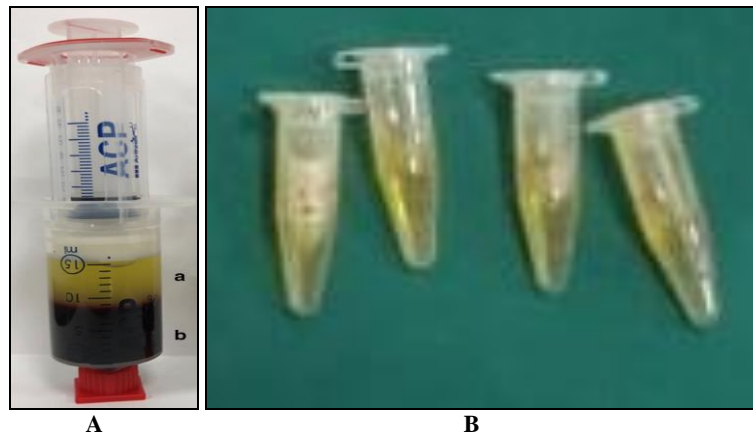

Fig 1: The resultant product of a single spin centrifugation, with an upper plasma layer (a) and a lower layer (b) containing both leukocytes and erythrocytes B: after separating the PRP from rest.

These one-spin systems typically result in platelet concentrations that are 1 to 3 times greater than whole blood; furthermore, the one-spin systems are efficient because they typically have short preparation times (under 10 min), which can remove the need for an anti-coagulant to be added to the preparation to prevent clotting. PRP systems that utilize two spins, like the Biomet GPS (Zimmer Biomet, Warsaw, Indiana) and Magellan PRP (Isto Biologics, Hopkinton, Massachusetts), focus on separating the blood sample into three layers: a layer with red blood cells, a buffy coat layer containing platelets and white blood cells, and a platelet depleted plasma layer. The focus of the two-spin systems is to concentrate the buffy coat layer, which contains higher platelet concentrations ($> 5\times$ whole blood) than the one-spin systems. Due to the nature of the two-spin cycle, the preparation times for these products are longer, typically 30 min or greater, often requiring the use of an anti-coagulant to prevent the sample from clotting during the preparation process.

Growth factors in PRP
Growth factors have been extensively studied for OA and cartilage repair because of their ability to enhance matrix synthesis. The efficacy of growth factors in cartilage repair is related to the recruitment of chondrogenic cells, stimulation of proliferation, and enhancement of cartilage matrix synthesis [3]. Growth factor therapy could be an attractive method for stimulation of the repair of damaged cartilage matrix. The platelet alpha-granules contain a range of important growth factors; therefore, they provide an obvious and readily accessible source of autogenous growth factors. The important growth factors contained in platelets and their actions are summarized in Table 1. Platelet-rich plasma (PRP) is defined as an autologous concentration of human platelets in a small volume of plasma [4]. PRP is also a concentration of several fundamental protein growth factors proved to be actively secreted by platelets to initiate mesenchymal tissue healing. These growth factors stimulate cell proliferation, migration, differentiation, and matrix synthesis and can affect chondrocyte metabolism, chondrogenesis and improve cartilage healing *in vivo* [5, 6]. PRP also contains plasmatic proteins, such as fibrin, fibronectin, and vitronectin, which act as mesenchymal cell adhesion molecules. It is believed that PRP can augment or stimulate healing with the same biologic healing process that normally occurs in the human body after injury.

Table 1: Growth factors present in platelets and its function [7].

Growth Factor	Function
Transforming growth Factor Y beta	Stimulates undifferentiated mesenchymal cell proliferation; regulates endothelial, fibroblastic, and osteoblastic mitogenesis; regulates collagen synthesis and collagenase secretion; regulates the mitogenic effects of other growth factors; stimulates endothelial chemotaxis and angiogenesis; inhibits macrophage and lymphocyte proliferation.

Basic fibroblast growth factor	Promotes growth and differentiation of chondrocytes and osteoblasts; mitogenic for mesenchymal stem cells, chondrocytes, and osteoblasts.
Platelet derived growth factor	Mitogenic for mesenchymal stem cells and osteoblasts; stimulates chemotaxis and mitogenesis in fibroblast/glial/smooth muscle cells; regulates collagenase secretion and collagen synthesis; stimulates macrophage and neutrophil chemotaxis.
Epidermal growth factor	Stimulates endothelial chemotaxis/angiogenesis; regulates collagenase secretion; stimulates epithelial/mesenchymal mitogenesis.
Vascular endothelial growth factor	Increases angiogenesis and vessel permeability; stimulates mitogenesis for endothelial cells.
Connective tissue growth factor	Promotes angiogenesis, cartilage regeneration, fibrosis, and platelet adhesion.

Corticosteroid mechanism of action
Corticosteroids have both anti-inflammatory and immunosuppressive effect, but their mechanism of action is complex. Corticosteroids act directly on nuclear steroid receptors and interrupt the inflammatory and immune cascade at several levels. By this means, they reduce vascular permeability and inhibit accumulation of inflammatory cells, phagocytosis, production of neutrophil superoxide, metalloprotease, and metalloprotease activator, and prevent the synthesis and secretion of several inflammatory mediators such as prostaglandin and leukotrienes [8, 9]. The clinical anti-inflammatory reflections of these actions are decreases in erythema, swelling, heat, and tenderness of the inflamed joints and an increase in relative viscosity with an increase in hyaluronic acid (HA) concentration [8, 10].

Methodology
This study was conducted at the orthopaedic department at the Aarupadai Veedu Medical College and Hospital, Puducherry. Patients diagnosed with Osteoarthritis knee were included in this study and all the patients were included in this study after full filling the inclusion criteria and informed consent.

Inclusion criteria
Patients diagnosed with osteoarthritis at the OPD of Orthopaedics department of AVMC&H and were comparable with respect to
- Age,
- Sex,
- Height,
- Weight,
- Body mass index
- Pre-injection WOMAC score.

Exclusion criteria
- Immunosuppressed patients
- Patients with secondary osteoarthritis
- Patients with connective tissue disorders
- Patients with inflammatory disorder of joints
- Patients who have received steroid injections within past 6 months
- Patients with haemoglobin less than 10 mg %
- Patients with tumours, metabolic diseases of bone
- Patients with coexisting backache

Total 100 patients were included in the study of which all patients having even number in the end of OPD number were given PRP intraarticular injections whereas OPD numbers ending with odd number were given steroid intraarticular injections.
Following admission all patients were evaluated and staged with grade 0 to 4 according to Kellgren-Lawrene grading scale and grade 1 to 4 according to Ahlback score.

Kellgren Lawrence grading of osteoarthritis
Grade 0: No radiographic features of OA are present
Grade 1: Doubtful narrowing of joint space and possible osteophytic Lipping
Grade 2: Definite osteophytes, definite narrowing of joint space
Grade 3: Moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour
Grade 4: Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour

Ahlback radiological criteria
Grade 1: Joint Space Narrowing (Less Than 3 Mm)
Grade 2: Joint Space Obliteration
Grade 3: Minor Bone Attrition (0-5 Mm)
Grade 4: Moderate Bone Attrition (5-10 Mm)
Grade 5: Severe Bone Attrition (More Than 10 Mm)

The blood bank of Aarupadai Veedu medical college and hospital had gracefully consented to prepare and provide Autologous Platelet Rich Plasma. About 15 ml of venous blood was collected from the patient. The collected blood was centrifuged in a refrigerated centrifuge and Platelet Rich Plasma was separated after removing red blood cells and buffy coat. The whole process of separating Platelet Rich Plasma was standardized and done under strict aseptic precautions. We in this study did not use leucocyte filter and the final Platelet Rich Plasma contained minute traces of leucocytes.
Accordingly, patients in the PRP therapy group received 7 mL PRP solution and those in the corticosteroid group received 80 mg methyl-prednisolone mixed with 2ml of plain lignocaine. Using the WOMAC, levels of pain and knee function were evaluated and recorded for each patient immediately prior to the first injection as well as at 6 weeks (immediately prior to the second injection), 3 months (6 weeks after the second injection), and 6 months later. Data collected for both the groups were analysed and compared with each other.

Injection protocol
The Injection procedure was performed in Emergency operation theatre. The Patient was placed supine on the operation table. Parts painted and draped. Under sterile aseptic precautions 7 ml of Platelet Rich Plasma mixed with 2 ml of calcium gluconate was injected into the supra patellar pouch of knee or into the joint cavity from medial approach sterile bandaging given. The Patient is advised bed rest for 2 days. The Patient is advised to avoid NSAIDS for 2 days before and after injection. Paracetamol in doses of 500mg is allowed in cases of febrile illness or discomfort due to pain.
In the corticosteroid group, 2ml of lignocaine mixed with 80mg of methyl-prednisolone is injected in to the suprapatellar pouch of the patients. The Patients are advised to carry on with their regular routine work from Day 2.
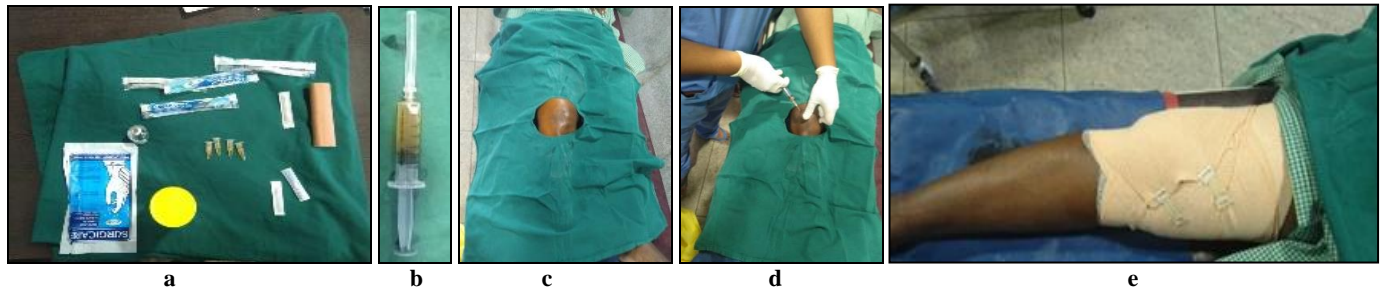
Illustrated cases

Fig 2: Things used for PRP or corticosteroid intraarticular injections, B: PRP injection, C: aseptic precautions (painting with betadine solution and draping with sterile linen), D: supra-patellar injection given from medial side of knee joint, E: jones compression bandage applied after intraarticular injection

Outcome analysis

The PRP group and the corticosteroid group are advised to follow up at 6 weeks, 3 months and 6 months. Outcome analysis for the efficacy was done for reduction in pain, reduction in stiffness and improvement in physical function using WOMAC scale.

The Patients were also assessed for reduction in pain using Visual analogue scale both at pre-injection and at 6 months post injection.

The Pain, the Patient perceive is graded on a visual scale and the score calculated
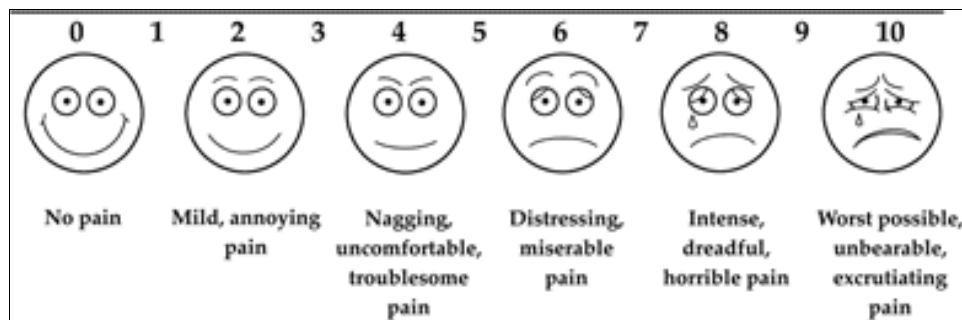

Fig 3: Visual Analog scale for pain

The WOMAC (Western Ontario and McMaster Universities) Index of Osteoarthritis

Overview

The WOMAC (Western Ontario and McMaster Universities) index is used to assess patients with osteoarthritis of the hip or knee using 24 parameters. It can be used to monitor the course of the disease or to determine the effectiveness of Therapy

Scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

Circle one number for each activity

Pain
1. Walking 0 1 2 3 4
2. Stair Climbing 0 1 2 3 4
3. Nocturnal 0 1 2 3 4
4. Rest 0 1 2 3 4
5. Weight bearing 0 1 2 3 4

Stiffness
1. Morning stiffness 0 1 2 3 4
2. Stiffness occurring later in the day 0 1 2 3 4 59

Physical Function
1. Descending stairs 0 1 2 3 4
2. Ascending stairs 0 1 2 3 4
3. Rising from sitting 0 1 2 3 4
4. Standing 0 1 2 3 4
5. Bending to floor 0 1 2 3 4

6. Walking on flat surface 0 1 2 3 4
7. Getting in / out of car 0 1 2 3 4
8. Going shopping 0 1 2 3 4
9. Putting on socks 0 1 2 3 4
10. Lying in bed 0 1 2 3 4
11. Taking off socks 0 1 2 3 4
12. Rising from bed 0 1 2 3 4
13. Getting in/out of bath 0 1 2 3 4
14. Sitting 0 1 2 3 4
15. Getting on/off toilet 0 1 2 3 4
16. Heavy domestic duties 0 1 2 3 4
17. Light domestic duties 0 1 2 3 4.

Total Score: _____ / 96 = _____%

Results

The Efficacy of Platelet Rich Plasma and corticosteroid in reducing pain, stiffness and physical function were assessed and scored on WOMAC index for both the groups. The Results were analysed using unpaired t-test and chi-square test.

Age distribution revealed mean age in PRP group to be 49.92 and the mean age in corticosteroid group was 54.16. The p-value derived using unpaired t-test is 0.1120, rendering age factor insignificant.

Gender distributions were comparable on both groups with 80% being male 20% being female. The p-valve using chi square test is 0.0833. The Gender factor was insignificant.

The mean height in PRP group was 159.66 and the mean height in corticosteroid group was 159.68. The p-valve using unpaired t

test turned insignificant (0.9895).

The mean weight, in PRP group was 68.62 and corticosteroid group was 67.66 with p-valve of 0.4777(insignificant).

The mean BMI was 26.97 in PRP group and 26.64 in corticosteroid group. The p-valve is 0.5507(insignificant).

Thus, the study ensured that all patients were comparable on baseline characters.

The Global WOMAC showed in PRP group a mean of 74.2 at pre-injection period which decreased to 62.46 at 6 weeks follow up and 47.68 at 3 months and declining to 33.40 at 6 months. The study showed a significant decrease in global WOMAC score, which was also consistent throughout the study period.

The Individual variables such as pain, stiffness and physical function were assessed. Mean score for pain showed a decrease from 16.58 to 11.32 at 6 weeks post-injection. At the end of 6 months follow up, the mean was 5.34. The mean score for pain in corticosteroid group showed a marginal decreased from 16.30 to 13.74 at 6 weeks but returned to 15.46 at 6 months follow up. The p-value using unpaired t-test showed significant improvement. Secondary variable stiffness showed significance difference at 3 months follow up and 6 months follow up.

The mean of Physical function decreased from a pre-injection score of 52.12 to 24.62 at 6 months follow up in PRP group.

Corticosteroid group showed a marginal dip in mean scores from 48.30 to 45.80 and to 44.38 at 3 months. The scores levelled at 46.20 at the end of 6 months

Visual analogue score showed a decrease in mean of 7.22 to 3.06 which denoted a change of patient 's perception of pain from intense, dreadful, horrible pain to mild annoying pain in PRP group.

Corticosteroid group showed a marginal dip from 6.86 to 4. 98 on mean, showing insignificant change in pain.

Discussion
The most important finding of the present study was that multiple PRP injections resulted in better clinical results, particularly in patients with early OA when compared with corticosteroid group. However, there was no difference in the results between treatment methods in the patients with advanced OA. One of the important results of this study was that a single dose of PRP or corticosteroid did not have a superior effect on the patients with early or advanced OA.

Conclusion
The Epidemic of Modernization coupled with effective health care delivery has led to an expanded lifespan of human beings. The focus of health care providers is undergoing a drift towards non-communicable and degenerative disorders.

Osteoarthritis represents a failure of diarthrodial joint, characterized by degenerative changes in articular cartilage of joint. The management of Osteoarthritis has undergone a sea change during the last century. Osteoarthritis has been managed by conservative methods like lifestyle changes, physiotherapy and surgical methods like joint replacement arthroplasty, depending upon the stage of the disorder.

A constant search for molecules that could aid in cartilage regeneration, thus interfering in disease process has thrown up surprises. One such ideology is, garnering the beneficial effect of growth factors in platelets to regenerate cartilage in a synovial joint.

Our study relied on injecting a highly concentrated mix of platelets or corticosteroid into joint cavity and observing the patients for reduction in symptoms of pain, stiffness and improvement in physical function. our study has revealed a consistent reduction in pain and stiffness and a clear improvement in lifestyle of the patients who received PRP injections when compared with corticosteroid for 6 months of follow-up.

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