"FUNCTIONAL OUTCOME OF SINGLE VERSUS MULTIPLE INTRA-ARTICULAR PLATELET RICH PLASMA (PRP) INJECTIONS FOR EARLY OSTEOARTHRITIS KNEE - A COMPARATIVE STUDY"

By

Dr. PARAMANANTHAM MADHAVAN

DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTER, KOLAR, KARNATAKA

In partial fulfillment of the requirements for the degree of

MASTER OF SURGERY
IN
ORTHOPAEDICS

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APRIL 2022

SRI DEVARAJ URS MEDICAL COLLEGE,

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I hereby declare that this dissertation entitled "**FUNCTIONAL OUTCOME OF SINGLE VERSUS MULTIPLE INTRA-ARTICULAR PLATELET RICH PLASMA (PRP) INJECTIONS FOR EARLY OSTEOARTHRITIS KNEE- A COMPARATIVE STUDY"** is a bonafied and genuine research work carried out by me under the guidance of **Dr. HARIPRASAD S**, Associate Professor, Department of Orthopaedics, Sri Devaraj Urs Medical College, Kolar, and under the co-guidance of **Dr. SUBHASHISH DAS,** Professor, Department of Pathology, Sri Devaraj Urs Medical College, Kolar, in partial fulfilment of University regulation for the award "**M.S.DEGREE IN ORTHOPAEDICS**", the examination to be held in April/May 2022 by SDUAHER. This has not been submitted by me previously for the award of any degree or diploma from the university or any other university.

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Date: **Dr.PARAMANANTHAM MADHAVAN**

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ABBREVATIONS

Abbreviation	Explanation
ACL	Anterior Cruciate Ligament
ADAMTS	A Disintegrin And Metalloproteinase with Thrombospondin-like motifs
BMI	Body Mass Index
CMC	Carpometacarpal Joint
COX-2	Cyclooxygenase-2
CPDA	Citrate Phosphate Dextrose Adenine
CB	Cannabinoid Receptors
DIP	Distal Interphalangeal Joint
ECM	Extracellular Matrix of Cartilage
GF	Growth Factor
GI	Gastro Intestinal
HGF	Hepatocyte Growth Factor
HA	Hyaluronic Acid
HMW-HA	High Molecular Weight -Hyaluronic Acid
IA	Intraarticular
IAHA	Intra-Articular Hyaluronic Acid
IASI	Intra-Articular Steroid Injection
IFN	Interferon
IL	Interleukin
IKDC	International Knee Documentation Committee
KOOS	Knee Injury and Osteoarthritis Outcome Score
KL	Kellgren and Lawrence
LMW-HA	Low Molecular Weight Hyaluronan
OARSI	Osteoarthritis Research Society International
MCP	Metacarpophalangeal Joint
MM	Medial Meniscus
MRI	Magnetic Resonance Imaging
MMP	Matrix Metalloproteinase

NSAID	Non-Steroidal Anti-Inflammatory Drug
NF-JB	Nuclear Factor Kappa B
OA	Osteoarthritis
PCL	Posterior Cruciate Ligament
PIP	Proximal Interphalangeal Joints
PDGF	Platelet-Derived Growth Factor
PRP	Platelet Rich Plasma
PGFs	Platelet-Rich Growth Factors
PRF	Platelet-Rich Fibrin Matrix
PG	Prostaglandin
PRC	Platelet-Rich Concentrate
PA-PRP	Photo-Activated Platelet Rich Plasma
PeRP	Platelet Enhanced Plasma
PDCD5	Programmed Cell Death 5
S-PRP	Single - Platelet Rich Plasma Injection
M-PRP	Multiple- Platelet Rich Plasma Injection
RA	Rheumatoid Arthritis
RCT	Randomized Control Trial
rhFGF-18	Recombinant Human Fibroblast Growth Factor18
TGF	Transforming Growth Factor
TNF	Tumour Necrosis Factor
THA	Total Hip Arthroplasty
TKA	Total Knee Arthroplasty
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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ABSTRACT

"FUNCTIONAL OUTCOME OF SINGLE VERSUS MULTIPLE INTRA-ARTICULAR PLATELET RICH PLASMA (PRP) INJECTIONS FOR EARLY OSTEOARTHRITIS KNEE- A COMPARATIVE STUDY"

BACKGROUND:

Osteoarthritis is a major cause of pain and disability and is detrimental to quality of life. Many non-invasive treatment options have been recommended to relieve symptoms and extend the quality of life with Osteoarthritis. Platelet-Rich Plasma (PRP) is evolving into a promising solution for various orthopaedic conditions like tendinopathies, non-union and arthritis of knee.

AIM AND OBJECTIVE:

To determine whether single Intra-articular Platelet-rich plasma injection when compared with multiple Intra-articular Platelet-rich plasma injections given in the early stages of osteoarthritis of the knee has better functional outcome when measured using the Western Ontario and McMaster Universities Osteoarthritis Index and for reduction in pain which is measured by Visual Analogue Scale at 6^{th} week, 3^{rd} month and 6^{th} month.

METHODOLOGY:

The comparative study was conducted among patients diagnosed with early osteoarthritis presented to department of Orthopaedics, R. L. Jalappa Hospital & Research Centre attached to Sri Devaraj Urs Medical College Affiliated to Sri Devaraj Urs Academy of Higher Education and Research Tamaka, Kolar during the period, between January 2020 and June 2021. Patients were divided into Group I & Group II where Group 1 (34 samples) received Single Intra-articular Platelet-Rich Plasma injection (S-PRP) and patients in group II (30 samples) received Multiple (2)

Intra-articular Platelet-Rich Plasma injections (M-PRP) on presentation and on 3rd month. Visual Analogue Scale (VAS) to measure pain and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC Score) to assess functional status was used at first visit before intervention, on 6th week, 3rd month and 6th month after intervention. The collected data were entered in Microsoft (MS) Excel and analysed using IBM. SPSS statistics software 23.0 Version.

RESULTS:

The average age of the participants in the current study was 55.26 years in the S-PRP group and 51.13 years in the M-PRP group, with standard deviations of 4.8 and 7.4 years, respectively. Among the study participants, about 66 percent were females and the remaining were males. In all groups, about two-thirds of the participants felt right knee pain. Only 14% of people had problems with both knees. At the end of 6th month, the mean pain scale in S-PRP group is 4 and in M-PRP group is 5.77, this difference in mean is statistically significant ($P < 0.001$). Thus, multiple PRP injection have greater response in reduction of pain when compared to single PRP injection according to VAS pain scale score. The mean score by using the WOMAC Score in the S-PRP group is 45.26 and M-PRP group is 45.33 at the 6th week of follow-up. This difference of means in both groups is not statistically significant ($p = 0.920$) by using the independent T-test. Thus, according to the WOMAC Score, there is no statistically significant difference in the treatment response with PRP injection between S-PRP and M-PRP groups. The lowering trend was detected after S-PRP and Multiple-PRP injections at pre-injection, 6th week, 3rd month and 6th month respectively, as determined by WOMAC score. The Paired T test revealed that these differences were statistically significant. The decrease in WOMAC score is due to the fact that both therapies improved the subject's functional

status by reducing pain. The significance of the correlation test between Pain and WOMAC score at pre-injection, 6^{th} week, 3^{rd} month and 6^{th} month can be demonstrated.

CONCLUSION:

Intra-articular Platelet-rich plasma injection is a valuable and trustworthy treatment for improvement functional status and reduction in pain for Grade 1 and 2 Osteoarthritis up to 6 months post injection, and a minimum of two injections appears to be suitable.

KEYWORDS: Platelet-rich plasma, Osteoarthritis, Visual Analogue scale, Western Ontario and McMaster Universities Osteoarthritis Index, Functional Status

INTRODUCTION

Osteoarthritis (OA) is a multifactorial degenerative illness characterised by articular cartilage loss, bone enlargement at the borders, subchondral sclerosis and a variety of biochemical as well as morphological changes in the synovial membrane as well as joint capsule.[1]

Osteoarthritis is the second widespread rheumatologic illness and the most common joint illness in India, with an occurrence of 22% to 39%. Women are more likely than men to have OA, although the prevalence rises drastically with age. Nearly half of all women above 65 years of age have symptoms and 70% of those above 65 years show radiographic evidence. Knee osteoarthritis is a general cause of mobility loss, especially in women. The 10th greatest cause of nonfatal burden was projected to be OA.[2,3]

However, genetic predisposition play an important role in the hands and hips than in knee OA.[4–8] Furthermore, certain racial and gender disparities were reported.[9] OA is also associated with elderly age, obesity and joint malalignment, it was primarily portrayed as primarily an aging-related and mechanically hammered condition. However, more recent research has recognized and labelled an overabundance of additional factors contributing to knee OA pathogenesis.[10]

Osteoarthritis of the knee is a major issue that ageing adults face and to alleviate the pain and morbidity associated with OA pain, physicians and orthopaedician's around the world have tried a variety of non-surgical treatment modalities ranging from oral chondro-protectives, intra-articular steroids and visco-supplements. Platelet-rich plasma is becoming a viable treatment option for a variety of orthopaedic disorders, including tendinopathies, non-union and knee arthritis. The effectiveness of PRP in treating sports injuries in a number of high-profile athletes has helped to the hype

around PRP therapy, resulting in an increase in PRP use for treating OA knees over the last seven years. The recent literature suggests that PRP of precise specifications could be useful for pain treatment in early OA knees. Various clinical trials have consistently shown that PRP is superior to Hyaluronic Acid (HA). Nonetheless, lack of knowledge in using PRP in OA, more targeted clinical and in vitro research is needed.[11]

Platelet-rich plasma is an autologous blood component with a high concentration of platelets that is used to treat bone, tendon and ligament injuries in orthopaedic and sports medicine practises.[12,13] In addition, PRP injections can be used to treat cartilage damage and OA.[14,15] Regardless of hopeful preclinical outcomes and widespread clinical curiosity in orthopaedic as well as sports medicine, there are still many unsolved concerns about PRP's therapeutic applicability and efficacy. There is ambiguity regarding the number and frequency of injections required for optimal efficiency, as well as the best treatment for various stages of gonarthrosis (From cartilage injury to advanced OA).[16]

The goal of the current study was to describe the clinical effects of PRP for early stages of OA and to explore the ideal number of PRP injections required for early stages of OA. It was expected that PRP treatment would reduce knee scores by freeing Growth factors and bioactive compounds that would potentially alter the deteriorated knee.

AIM AND OBJECTIVES

To determine whether Single intra articular Platelet-Rich Plasma injection(S-PRP) when compared with Multiple intra articular Platelet-Rich Plasma injections(M-PRP) given in the early stages of OA knee has better functional outcome when measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC Score) and pain by Visual Analogue Scale (VAS) at 6^{th} week, 3^{rd} month and 6^{th} month.

OBJECTIVES

1. To estimate the pain using Visual Analogue Scale and functional status using Western Ontario and McMaster Universities Osteoarthritis Index for the patients presenting with early stages of OA knee, before intervention.
2. To estimate the pain using Visual Analogue Scale and functional status using Western Ontario and McMaster Universities Osteoarthritis Index after single IA-PRP injection at 6^{th} week, 3^{rd} month and 6^{th} month for the patients presenting with early stages of OA knee.
3. To estimate the pain using Visual Analogue Scale and functional status using Western Ontario and McMaster Universities Osteoarthritis Index after Multiple (2) IA-PRP injection at 6^{th} week, 3^{rd} month and 6^{th} month for the patients presenting with early stages of OA knee.
4. To determine whether single IA-PRP injection when compared with multiple IA-PRP injections given in the early stages of OA knee has better functional outcome when measured using the Western Ontario and McMaster Universities Osteoarthritis Index and for reduction in pain which is measured by Visual Analogue Scale at 6^{th} week, 3^{rd} month and 6^{th} month.

RESEARCH QUESTION

Whether single IA-PRP injection when compared with multiple IA-PRP injections given in the early stages of osteoarthritis of the knee has better functional outcome when measured using the Western Ontario and McMaster Universities Osteoarthritis Index and for reduction in pain which is measured by Visual Analogue Scale at 6^{th} week, 3^{rd} month and 6^{th} month?

NULL HYPOTHESIS

Single IA-PRP injection is not superior to multiple IA-PRP injections when given in the early stages of OA knee for the better functional outcome which is measured using the Western Ontario and McMaster Universities Osteoarthritis Index and for reduction in pain which is measured by Visual Analogue Scale at 6^{th} week, 3^{rd} month and 6^{th} month.

ALTERNATE HYPOTHESIS

Single IA-PRP injection is superior to multiple IA-PRP injections when given in the early stages of osteoarthritis of the knee for the better functional outcome which is measured using the Western Ontario and McMaster Universities Osteoarthritis Index and for reduction in pain which is measured by Visual Analogue Scale at 6^{th} week, 3^{rd} month and 6^{th} month.

REVIEW OF LITERATURE

Introduction

Osteoarthritis is a prevalent and disabling ailment that is a significant and growing health burden with significant consequences for those affected, health-care systems and wider socioeconomic costs.[17,18] With the combined impacts of global population ageing and obesity, as well as an increase in the frequency of joint injuries, this already burdensome syndrome is growing more frequent, with an estimation of 250 million individuals are already affected worldwide.[19–21]

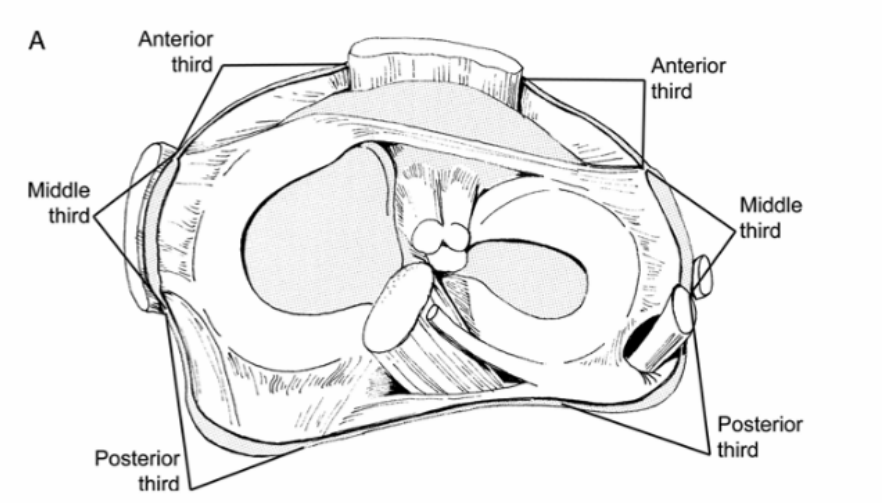
According to the Disease & Injury Incidence and Prevalence Collaborators "Global Burden of Diseases, Injuries and Risk Factors Study 2015", knee OA accounts for roughly 85 percent of the universal problem of OA, with a prevalence of 10% in men and 13% in women aged 60 and up.[22,23] Osteoarthritis is very challenging to manage.

Total joint replacement surgery is the gold-standard end-stage therapy, as there is no other viable therapeutic alternative to prevent OA from developing or advancing. Discomfort management and lifestyle adjustments are the only known therapy options for low-grade OA, which is a chronic illness characterised by pain and decreased joint mobility and function. According to certain research, therapeutic interventions such as intra-articular corticosteroid injections, hyaluronic acid injections, platelet-rich plasma, or mesenchymal stem cells may help to slow down the progression of the illness.

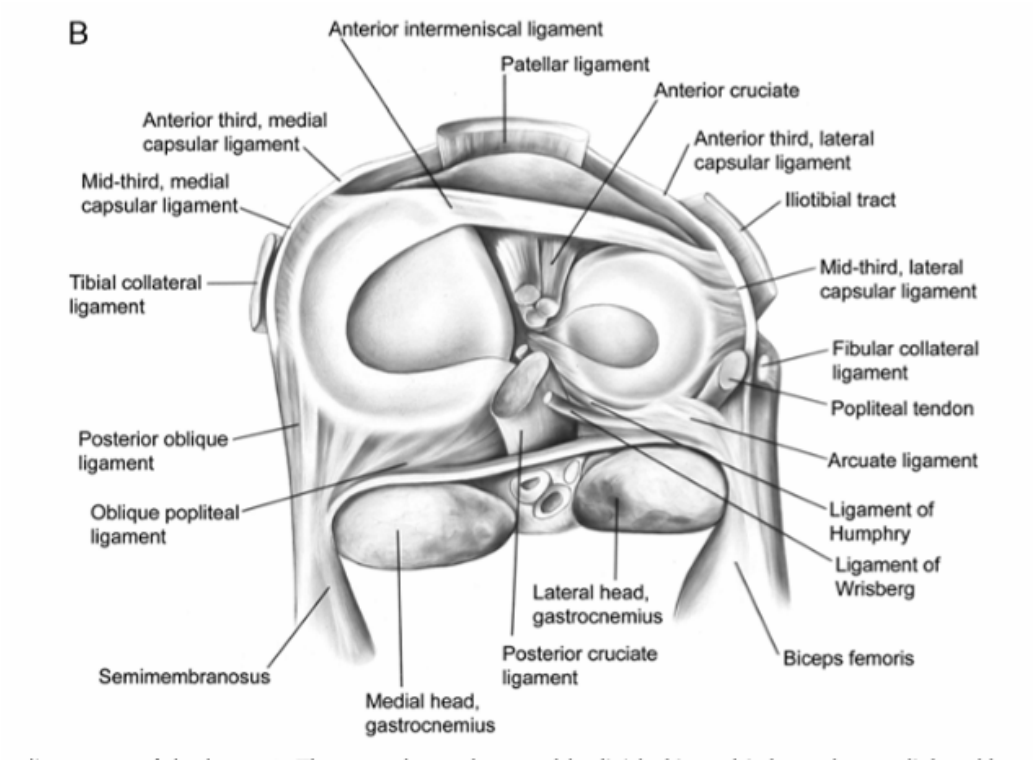
Relevant Anatomy

The knee joint is one of the modified hinge joint, also a sort of synovial joint that comprise 3 functional compartments: the patellofemoral articulation, that includes the patella or "kneecap" as well as the patellar groove which is on the anterior of the femur through which it glides; and the medial and lateral tibiofemoral articulations, that connect the femur to the tibia. Synovial fluid bathes the joint, which is confined inside the synovial membrane known as the joint capsule. Patella is one among the body's largest sesamoid bone.[24]

Figure 1: Capsular Ligaments of Knee Joint

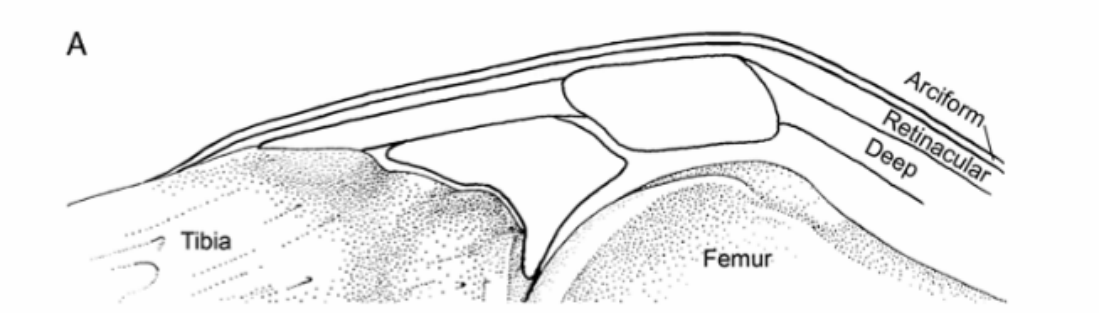


(A) On the medial and lateral sides, the capsule can be crudely separated into thirds. The extensor mechanism, or patellofemoral articulation, comprises the first third, whereas the tibiofemoral articulation comprises the second third.[24]

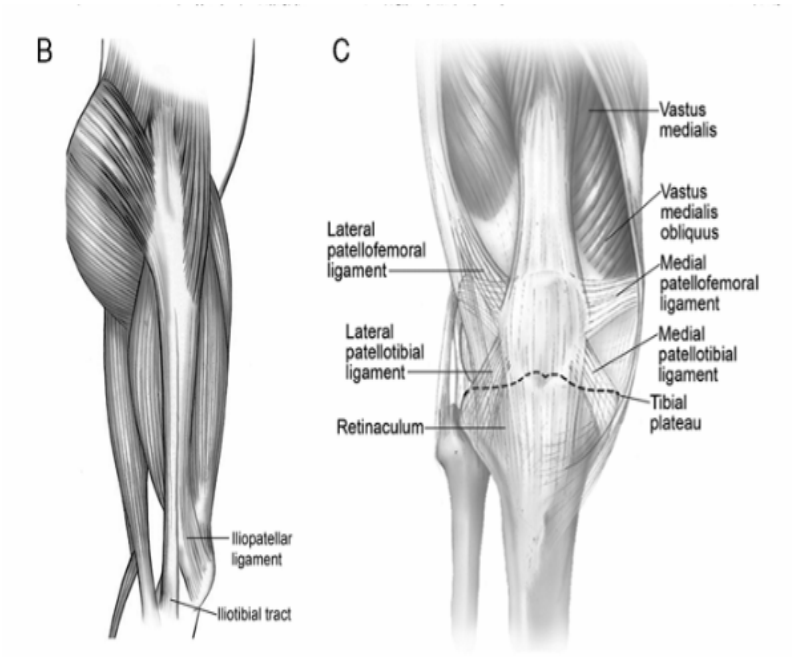


(B) The major structures involved in menisco-ligamentous stability.

Figure 2: Extensor mechanism anatomy



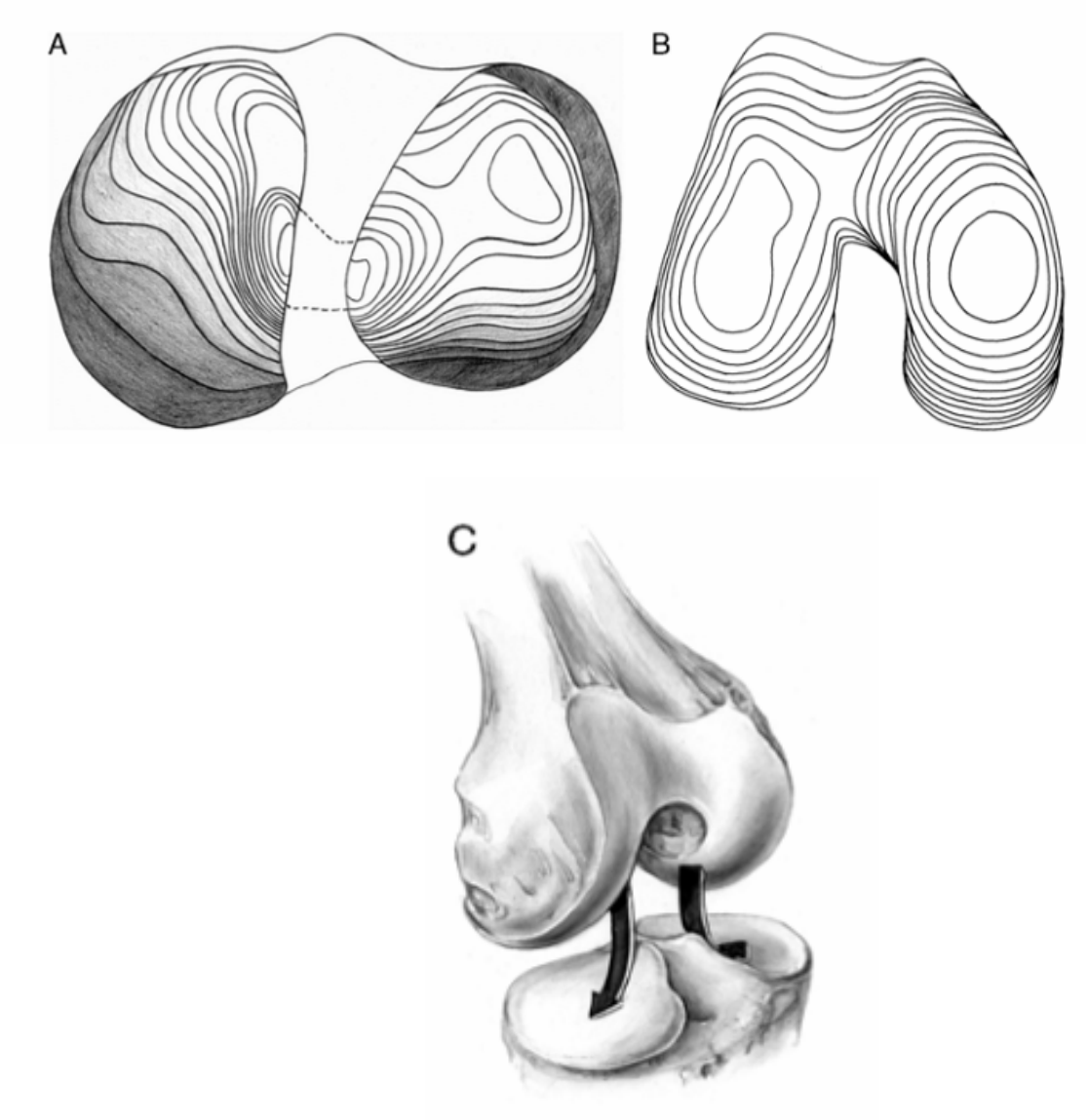
(A) This aponeurosis' connective tissue is divided into three coats: superficial arciform layer, intermediate retinacular layer and also deep layer.



(B) The tensor fascia lata along with gluteus maximus muscles provide dynamic input to the iliotibial tract. The ilio-patellar ligament, which is fragment of the extensor mechanism, and the iliotibial tract, which is fragment of the tibiofemoral joint, are functionally separated.

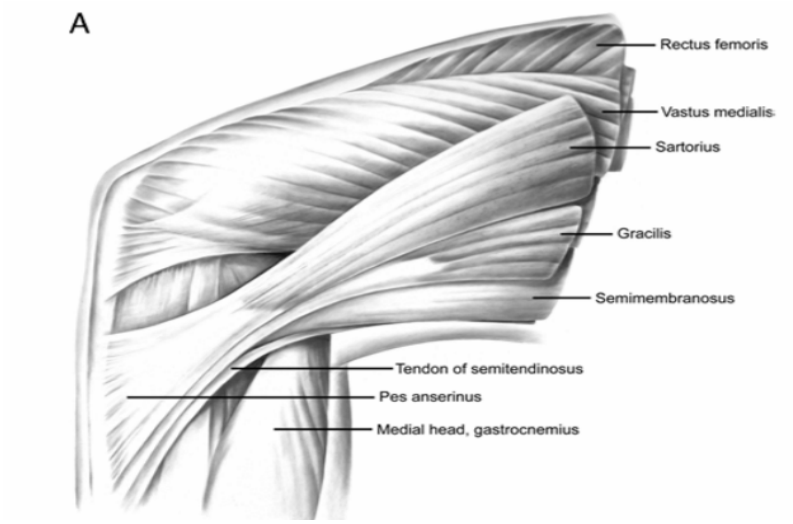
(C) Ligaments of the retinal layer. Some patellar stabilisation operations are currently focusing on the medial patellofemoral and lateral patella-tibial ligaments.

Figure 3: Bony topography

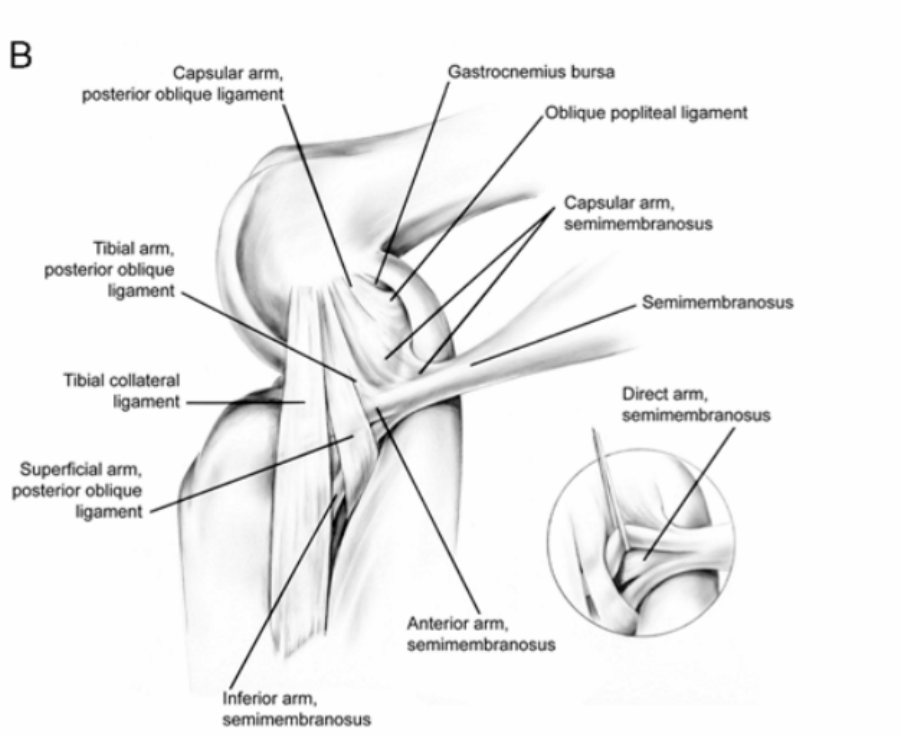


(A) Tibial plateau (B) Femoral condyle gives certain steadiness to the tibiofemoral articulation which guides the screw-home mechanism. (C) Weight shouldering happens on the tibial eminences and on the central plateaus.

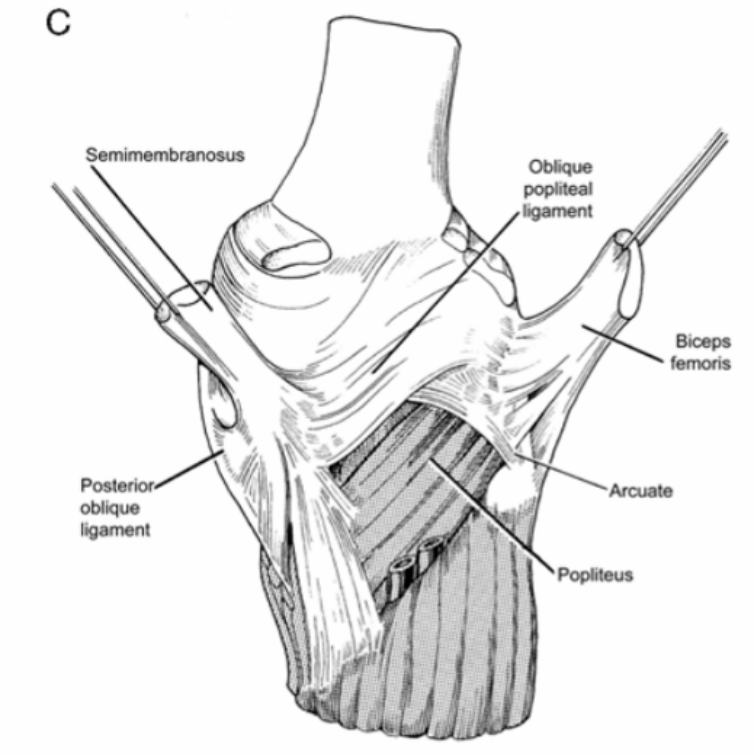
Figure 4: Anatomy of medial capsule and related structures



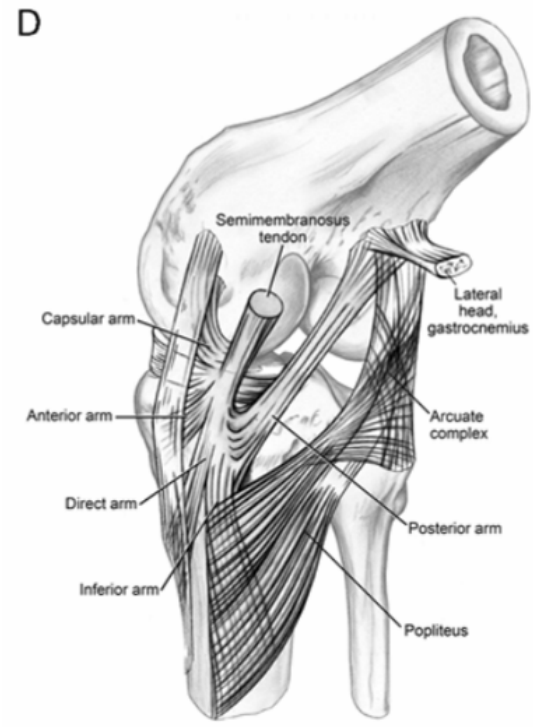
(A) Superficial anatomy



(B) Capsular structures deep to the sartorial fascia

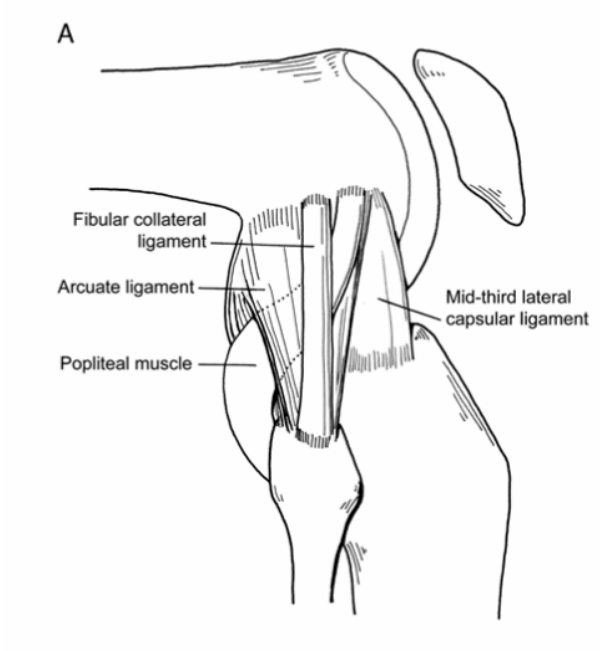


(C) The semimembranosus and the posteromedial capsular structures are related to the posterior capsule.

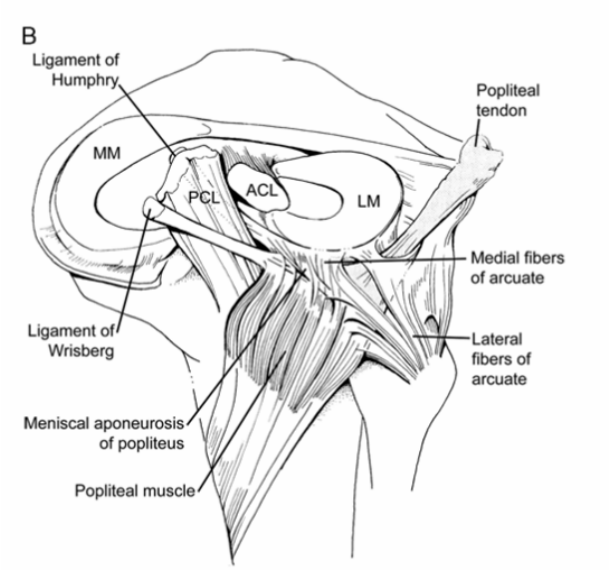


(D) The 5 arms of insertion of the semimembranosus.

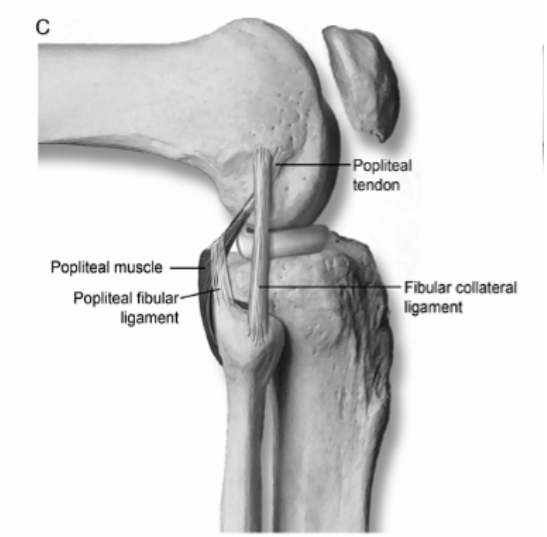
Figure 5: Lateral capsular structures



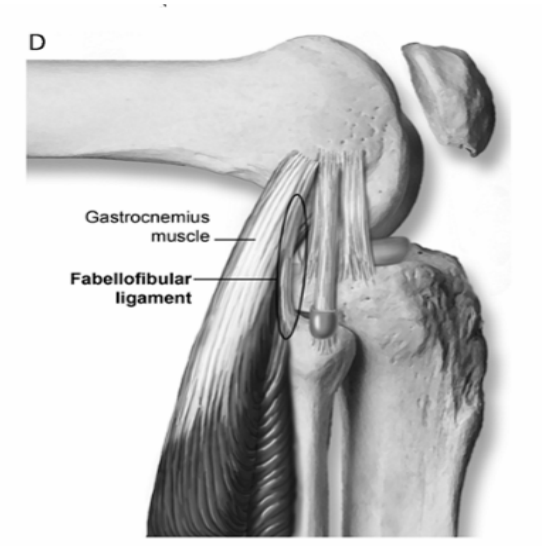
(A) The chief mid-third lateral capsular ligaments



(B) Wrisberg and Humphry's relationship between the popliteus, arcuate ligament, lateral meniscus, along with lateral meniscofemoral ligaments.



(C) The fabellofibular ligament arises from the bony or cartilaginous fabella's lateral aspect and inserts lateral to the fibular styloid's tip, just lateral and possibly distal to the insertion of the popliteal fibular ligament.



(D) The popliteal fibular ligament originates at the popliteal musculotendinous junction and travels distally to connect with the medial aspect of the fibular styloid.

Burden of disease

The knee is the furthermost customary site of osteoarthritis in clinical practise, followed by the hand and hip. Knee osteoarthritis accounts for about 85 percent of all osteoarthritis cases worldwide. When comparing the years lived with disability worldwide between 1990 and 2005 and 2005–15, osteoarthritis along with diabetes were accountable for the principal upsurges in years lived with disability globally, comparatively to the other top 20 reasons of disability; attributable to the global elderly and also for obesity epidemic. In 2015, osteoarthritis was the fourth major cause of years lived with disability worldwide, accounting for 39% of all years lived with disability. By 2020, it is anticipated to be the fourth leading reason of years lived with disability worldwide.[25]

Signs and symptoms

The utmost conventional symptom is discomfort, which results in a loss of capacity and, in some cases, stiffness. Prolonged activity aggravates the pain, which is alleviated by relaxation. The most common time for stiffness is in the morning and it usually lasts less than thirty minutes after starting daily activities, but it might return after periods of inactivity. When the damaged joint, notably the shoulder and knee joint, is moved, osteoarthritis can generate a cracking noise (called "crepitus"). Joint locking and instability are also common complaints. Because of the discomfort and stiffness, these symptoms would have an impact on their regular activities. Some patients claim that chilly temperatures, extreme humidity, or a drop in barometric pressure cause them more discomfort, although studies have yielded inconsistent results.

Although some joint in the body can be disturbed by osteoarthritis, it most usually affects the hands, foot, backbone and large weight-bearing joints like the hips and knees. Movement configuration are often impaired when osteoarthritis advances. The most prevalent cause of a knee joint effusion is osteoarthritis.

Hard bone enlargements termed Heberden's nodes in Distal Interphalangeal Joints (DIP) or Bouchard's nodes in Proximal Interphalangeal Joints (PIP) can occur in smaller joints, such as the fingers and while they are not always painful, they do limit finger movement significantly. Toe osteoarthritis may be a role in the formation of bunions, which appear red or swollen.[26]

Novel understandings on pathogenesis

Osteoarthritis is a disease that affects the complete joint, counting the hyaline articular cartilage, subchondral bone, ligaments, capsule, synovium and periarticular muscles. Mechanical, inflammatory and metabolic variables all have a role in the pathophysiology of osteoarthritis, which leads to structural damage and failure of the synovial joint. The disease is not a passive degenerative disease or so-called wear-and-tear disease, but rather an active dynamic modification resulting from an imbalance between the repair and obliteration of joint structures.[27,28]

The location of cartilage varies as osteoarthritis progresses, and the cartilage loses its integrity.[29] The material characteristics of cartilage are altered as a result of the compositional alterations, making it more susceptible to physical stresses.

At first, the erosions are only visible on the surface; later, deeper cartilage fissures appear, followed by the enlargement of the calcified cartilage zone. Hypertrophic chondrocytes boost their synthetic activity in an attempt to repair, but they also produce matrix breakdown products and proinflammatory mediators, which disrupt

chondrocyte function and encourage proliferative and pro-inflammatory responses in the neighbouring synovium. Synoviocytes that are proliferating emit pro-inflammatory chemicals, as well as tissue hypertrophy and enhanced vascularity.

Bone turnover is increased in the subchondral bone and vascular invasion occurs from the subchondral bone through the tidemark and into the cartilage. The development of subchondral bone marrow lesions is linked to this bone remodelling and healing. Osteophytes, which form at the joint edges when endochondral ossification is reactivated, are influenced by inflammatory biological factors, as well as loading and aberrant joint kinematics.[30] Figure 6 summarises the pathogenic process in detail.

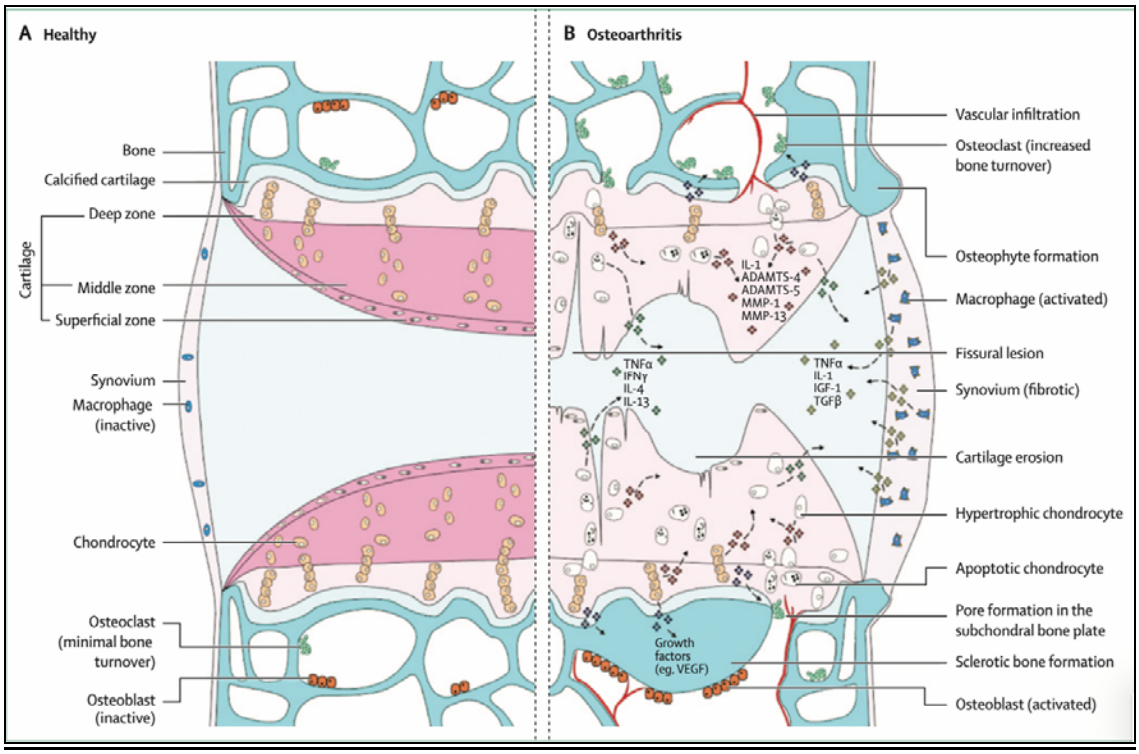


Figure 6: Signalling pathways along with structural changes in the advancement of osteoarthritis

ADAMTS - A Disintegrin And Metalloproteinase with Thrombospondin-like motifs. IL - Interleukin. MMP - Matrix Metalloproteinase. TNF- Tumour Necrosis Factor. IFN- Interferon. IGF- Insulin-like Growth Factor. TGF- Transforming Growth Factor. VEGF- Vascular Endothelial Growth Factor.[31]

Osteoarthritis is commonly regarded as a heterogeneous disease with a variety of underlying processes that lead to comparable joint damage consequences.[32] Osteoarthritis might be thought of as a syndrome rather than a single disease in this context. Each of the typical osteoarthritis risk factors may activate a separate mechanistic route leading to osteoarthritis, so mediators that promote OA in elder persons may differ from those that promote OA after a joint injury in a younger adult or in obese people. A number of stratums have been planned to define different mechanistic categories based on specific pathological pro cesses, such as an augmented inflammatory component, mechanical overload, metabolic alterations and cell senescence. These mechanistic traits are likely to overlap and require more research. [33–36]

Classification of Osteoarthritis

Although the pathophysiology of OA is unknown, it is assumed to include a complex interaction of mechanical, metabolic, cellular, genetic and immunologic events. Several efforts have been composed in the past to define diagnostic criteria for OA that include patient-reported joint pain and consistent radiography evidence. Primary (idiopathic) and secondary OA are the two main types of OA. Secondary OA is commonly caused by reasonably well-understood posttraumatic, dysplastic, viral, inflammatory or biochemical aetiologies. Although the cause of primary OA is unknown, genetics, age-related physiological changes, ethnicity and biomechanical variables are all thought to play a role.

Kellgren-Lawrence Classification of Osteoarthritis

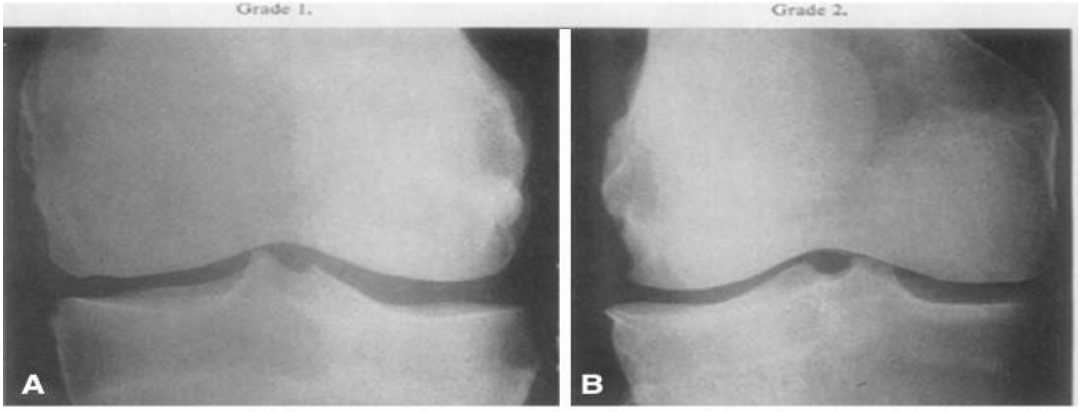
Plain radiography endures a backbone in the diagnosis of Osteoarthritis. The first formal efforts at launching a radiographic cataloguing scheme for OA were defined by Kellgren and Lawrence (KL) in 1957. After perusing rheumatism in coal miners North West England, Kellgren examined both the inter as well as intra-observer consistency of radiographic variations of rheumatism detected in the hand. They concluded that there was extensive difference among diverse spectators, KL undertook to launch a classification scheme with an related set of standardized radiographs for Osteoarthritis of diarthrodial joints. [37]

They insinuated 5 grades sorting scheme and scrutinized plain radiographs of 8 joints incorporating the distal interphalangeal, metacarpophalangeal, first carpometacarpal joint, wrist, cervical and lumbar spine, hips along with knees to estimate both inter and intra-observer consistency of each. They observed that the tibiofemoral joint of the knee had the maximum interobserver correlation coefficient ($r = 0.83$) as well as the second highest intra-observer correlation coefficient ($r = 0.83$) among the diarthrodial joints they inspected.[38] These initial outcomes would forecast the forthcoming relevance of their classification scheme to the knee precisely. Currently, the Kellgren and Lawrence classification is the utmost employed clinical tool in diagnosis of osteoarthritis.

The Kellgren-Lawrence classification was initially labelled using Anterior-posterior knee radiographs. Each radiograph was allocated a score from 0 to 4, which they interrelated to growing brutality of osteoarthritis, with Grade 0 suggesting no occurrence of osteoarthritis and Grade 4 suggesting severe osteoarthritis Additionally, KL endowed thorough radiographic explanations of osteoarthritis.

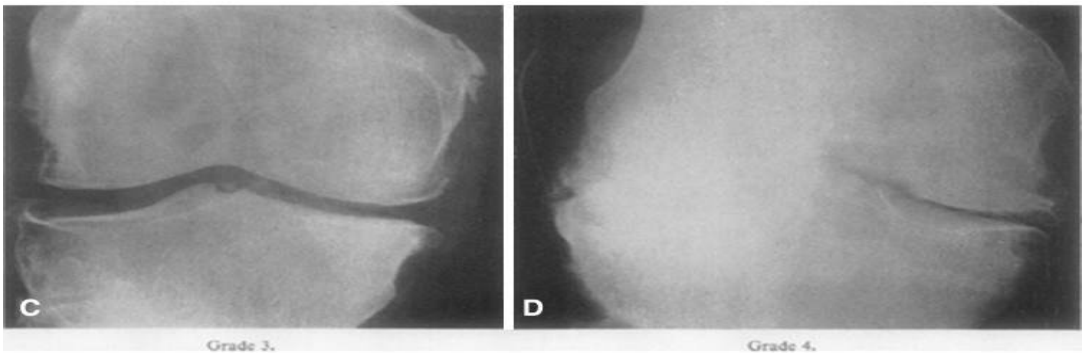
Figure 7: Kellgren Lawrence Osteoarthritis Classification Criteria

(A) Grade 1: Illustrative knee X-ray of Kellgren and Lawrence classification Grade 1, which establishes uncertain tapering of the joint space with likely osteophyte formation. [38]



(B) Grade 2: Illustrative knee X-ray of Kellgren and Lawrence classification Grade 2, which reveals probable reduction of the joint space with certain osteophyte development

(C) Grade 3: Illustrative knee X-ray of Kellgren and Lawrence classification Grade 3, which establishes certain tapering of joint space, modest osteophyte development, a few sclerosis and likely deformity of bony ends



(D) Grade 4: Illustrative knee X-ray of Kellgren and Lawrence classification Grade 4, that establishes huge osteophyte development, rigorous reduction of the joint space with noticeable sclerosis and certain irregularity of bone ends.

Treatment modalities for OA

Non-pharmacologic

Weight loss and physical activity have been shown to improve symptoms and functional status in OA patients in recent studies.[39] Osteoarthritis Healthy Weight for Life, an 18-week programme based in Australia, engaged 1383 people with a mean age of 64 and a BMI of 34 kg/m2 (82 percent were obese). Almost every participant (94%) lost at least 2.5 percent of their starting weight and one-third lost more than 10%. The researchers discovered a dose-response association between KOOS (Knee Injury and Osteoarthritis Outcome Score) alteration and percentage weight reduction, indicating that at least 7.7% of baseline weight loss was required to obtain a minimal clinically meaningful difference in WOMAC performance (derived from the KOOS).[40]

Following bariatric surgery, a study printed in the Journal of the American Medical Association found improvements in numerous OA-relevant indicators in a group of 2200 patients. In this cohort, the median pre-surgery BMI was 46 kg/m2; 70% had a 3-year follow-up, with a median weight loss of 30% of baseline, as well as significant improvements in knee and hip pain and function as quantified by WOMAC. Although the proportion of patients who improved their pain between one and three years postoperatively declined, the majority of these patients showed clinically meaningful improvements in body pain, physical function and walking ability.[41]

An update to the Cochrane Database of systematic reviews on aquatic exercise for knee and hip OA found modest improvements in pain, disability and quality of life after completing this extremely safe treatment for a mean of 12 weeks (standardised mean difference about 0.3 for all outcomes).[42]

Based on the findings of the FIDELITY study (a double-blind, sham surgery-controlled trial of arthroscopic partial meniscectomy for degenerative medial meniscal tears), which encountered no advantage for surgery compared to conservative treatment, researchers looked at benefit for mechanical symptoms specifically. They found no significant differences in mechanical signs by treatment group in this post-hoc study, indicating that the existence of such indications is not an sign for surgical reparation and supporting their claim that "Degenerative meniscal tears represent an early sign of knee osteoarthritis, rather than a clinically significant article in and of themselves."[43]

Pharmacologic: Oral NSAIDs

NSAID treatment for OA has been studied in a number of researches over the last year. In December 2016, the very large, multicentre PRECISION trial was published in the New England Journal of Medicine. This trial comprised around 24,000 patients with OA or Rheumatoid Arthritis (RA) who were receiving celecoxib, naproxen or ibuprofen (8000 per group) for about two years and were simultaneously on a proton pump inhibitor. For main (first myocardial infarction, stroke or cardiovascular death) or secondary (coronary revascularization, hospitalisation for unstable angina or transient ischemic attack) outcomes or efficacy, there was no important variance between the three drugs. Gastro Intestinal (GI) events were lower in the celecoxib group than in the ibuprofen or naproxen groups, while renal events and hospitalizations for hypertension were lower in the celecoxib group than in the ibuprofen or naproxen groups.[44]

A network meta-analysis of randomised controlled trials of any NSAID (1980–2015, including coxibs), acetaminophen and placebo with over 100 individuals per group,

published in the Lancet, looked at the effectiveness of different NSAIDs. They ended up finding: 1) That all NSAID preparations, irrespective of dose, improved pain compared to placebo; 2) Very little support for the effectiveness of paracetamol; and 3) The largest effect size for diclofenac and etoricoxib (0.6), confirming that diclofenac 150 mg per day is by far the most effective presently offered NSAID for pain and function in OA.[45]

One weakness of this study, according to an accompanying editorial, is that the drugs were given on a daily basis at a predetermined dose rather than as needed, which would be more reflective of ordinary use.[46] Furthermore, this meta-analysis did not take into account safety outcomes, such as cardiovascular risk, which has been observed to be similar between coxibs and diclofenac, resulting in diclofenac's use being curtailed in recent years.[47] A six-week randomised trial comparing celecoxib, naproxen and placebo in Asian patients with knee OA (n=367) found no difference in VAS pain, a little improvement in general assessments for active therapy vs placebo and slightly more GI side events in the naproxen group.[48] Finally, a group from Belgium and Luxembourg conducted a cross-sectional research on over 800 patients, finding that while over 34% of the patients were classed as having a high GI risk according to recognised risk factors, only 37% were taking a GI protective medication.[49] As always, physicians should weigh the risks and benefits of these treatments and oral NSAIDs should be administered at the lowest effective dose for the shortest amount of time possible.

Pharmacologic: Topical NSAIDs

Because of their safety profile, topical NSAIDs are an appealing alternative for OA therapy. In excess of 10,000 people took part in 39 studies in the Cochrane Review of

topical NSAIDs for musculoskeletal pain. All of the research considered in this review were about OA and were of moderate to high quality. Topical diclofenac and ketoprofen were more successful than carrier alone in tests lasting 6–12 weeks, with a number needed to treat of 7 for ketoprofen and 10 for diclofenac.[50]

Another trial in 633 people with knee OA compared a novel topical NSAID, s-flurbiprofen plaster, to regular flurbiprofen commercially available in Japan and found that the investigational treatment provided a slight but considerable benefit; both were found to be safe.[51]

Pharmacologic: other

Other pharmacologic drugs and combinations were shown to have no or limited benefit in numerous studies. Despite adequate increases in blood vitamin D in the treatment group, a randomised controlled study of vitamin D for symptomatic knee OA (n=474) with a 3-year follow up found no difference in radiographic medial joint gap width between vitamin D and placebo. "In OA, Vitamin D supplementation has no specific role" the authors found.[52]

In two research studies, glucosamine in a new mixture (including mud bath therapy) formulation (N-acetyl glucosamine and chondroitin sulfate) provided limited benefit. [53–56] Artemisia annua (ginghao) and bromelain were the subjects of three other short studies that looked at innovative herbal and plant extracts (pineapple extract).[57]

Intra-articular corticosteroid

Two groups conducted literature studies on intra-articular steroids injection (IASI) and discovered significant but short-term benefits. First, McCabe et al. looked at all

randomised controlled trials of any IA steroid preparation for painful hip OA and found five studies with 346 individuals, 134 of whom got hip IASI. All injections were image-guided (ultrasound or fluoroscopy), the majority of patients had severe illness and were Total Hip Arthroplasty (THA) candidates and all patients experienced pain relief 3–4 weeks after IASI. At the 8-week follow-up, two studies revealed a clinically noteworthy decrease in pain, resulting in a number needed to treat of 2.4 to obtain one OMERACT-OARSI response (based on 50 IASI and 40 controls).[58]

By acquiring data from the agreeing authors of all qualified trials (n=30), researchers from the Osteoarthritis Trial Bank accomplished an individual patient data meta-analysis of published randomised controlled trials of IASI in hip or knee OA. Data from 620 patients was given by only 7 corresponding authors. Nearly 4 studies compared IASI to placebo, 2 studies to IAHA, 2 studies with tidal irrigation, and 1 study with botulinum toxin; 2 trials were of hip OA and 5 studies were of knee OA. The researchers discovered that IASI had noteworthy short-term (4 weeks) and mid-term (1–3 months) benefits, but no influence on long-term (12 month) results, with no difference in inflammatory indicators.[59]

Intra-Articular Hyaluronic Acid

In the year of this review, many investigations of intra-articular hyaluronic acid (IAHA) preparations were published. Zhang et al. investigated the relevance of joint aspiration prior to IAHA administration by randomly assigning 92 symptomatic knee OA patients to maximal aspiration or no aspiration prior to weekly IAHA for 5 weeks, with a 25-week follow-up. The authors noticed that while the aspiration group's Visual Analogue Scale pain with walking and WOMAC function improved better,

there was no difference in overall "overall effectiveness" as judged by the patient or the investigator.[60]

Two studies looked into Intra-articular Hyaluronic acid in big populations using claims databases. Altman, et al. looked at the effect of Intra-articular Hyaluronic acid on the time to Total Knee Arthroplasty (TKA) in people who got it (n8000) or didn't get it (n14,000) before TKA. They discovered that those not taken Intra-articular Hyaluronic acid had a median time to TKA of 326 days, compared to 908 days for those who did; the time to TKA augmented with further IAHA courses.[61]

Another study looked at payment information in the 12 months leading up to TKA for 250,000 patients who had TKA between 2005 and 2012. They discovered that 15% of these patients received at least one IAHA therapy and that these therapies accounted for 16% of total knee Osteoarthritis expenditures, subsequent only to MRI at 18% and greater than any other treatment group.[62]

For symptomatic knee Osteoarthritis, 2 studies compared IAHA with IASI. A randomised controlled trial in ninety nine people related a single dose of IAHA to a single injection of 40 mg triamcinolone in combination with 1% lidocaine (total volume of drug injected was 6 mL for both groups); improvement is same as in pain, function, and range of motion were seen in both groups at 6 months, but the IASI group had better short-term (1–2 weeks) VAS pain scale and WOMAC function.[63]

In a single-center single-blind randomised trial, another group evaluated two injections of either IAHA (n=75) or IASI (n=75) for symptomatic knee OA one week apart. Both groups improved on the WOMAC total score, with a therapeutic effect peaking at 6 weeks, however the IAHA group improved more through 26 weeks (no difference at 52 weeks).[64] In terms of VAS pain scale, all groups improved similarly over the first six weeks; however, IAHA improved more at weeks 12 and 260 and

there was no difference at 52 weeks. Other trials were either unblinded or compared one form of IAHA to another, which are not explored further here. [65–69]

Other intra-articular treatments

Two preliminary studies of innovative IA treatments, Recombinant Human Fibroblast Growth Factor18 (rhFGF-18) and mesenchymal stem cells, found no significant safety issues.[70,71] Several investigations of various IA platelet rich plasma regimens and preparations for OA have been conducted. PRP injection vs oral acetaminophen, saline or IASI for symptomatic knee OA showed modest improvements in pain and function at week 12 in three small studies.[72–74] 111 patients with symptomatic hip OA were randomly assigned to one of three groups: PRP alone, HA alone or a combination of PRP and HA. All patients had three ultrasound-guided IA injections spaced one week apart (PRP: 5mL; HA: 2mL; PRP+HA: 7mL), with follow-up at 2rd, 6th and 12 months. In this trial, the PRP alone group exhibited more efficacy than the HA or mixed groups, especially at 2rd and 6th months, with the combination group having more adverse effects ("transient pain reaction").[75]

History of Platelet-Rich Plasma

PRP is sometimes referred to as platelet-rich growth factors (PGFs), platelet-rich fibrin matrix(PRF) and platelet concentrate.

PRP was first described and conceptualised in the field of haematology.[76] In the 1970s, haematologists coined the term PRP to characterise plasma with a higher platelet count than peripheral blood, which was first used as a transfusion product to treat people with thrombocytopenia.[77]

PRP was first used in maxillofacial surgery as PRF ten years later. PRP's anti-inflammatory effects boosted cell proliferation and fibrin had the potential for adhesion and homeostatic capabilities.[78]

PRP has since mostly been employed in the musculoskeletal field for sports injuries. It has received substantial media attention as a result of its use in professional athletes and it has been widely employed in this industry.[79] Cardiac surgery, paediatric surgery, urology, plastic surgery and ophthalmology are among the medical specialties that use PRP.[80]

The use of PRP in dermatology in tissue regeneration, wound remedial, scar correction, skin revitalizing benefits and alopecia, has lately gained popularity.[81–86]

Mechanism by which PRP works for knee OA Osteoarthritis

The normal joint metabolism is altered by osteoarthritis, supporting increased catabolism and diminished anabolism. Platelet alpha-granules comprise and discharge a variety of growth factors, such as hepatocyte growth, vascular endothelial growth factor, platelet-derived growth factor and Transforming growth factor-b (TGF-b), all of which may affect the altering joint mileu in Osteoarhtritis. PRP affects joint homeostasis on multiple levels. [87,88]

In cartilage it reduces catabolism, and improves anabolism which in turn promotes chondral remodelling. High content of collagen II and prostaglandin (PG) synthesis have been found in the research done by Akeda et al. and Pereira et al. Raising chondrocyte proliferation and production of matrix molecules have also been found in the study. [89–94]

Increased hyaluronic acid (HA) production influences synoviocytes, resulting in a more favourable and balanced state of angiogenesis and a decreased interleukin-1 (IL-1)-mediated increase in certain matrix metalloproteinases (MMPs). [95,96]

Insulin-like growth factor 1 (IGF-1) in PRP may downregulate the expression of programmed cell death 5(PDCD5), which influences the apoptotic pathway of osteoarthritic chondrocytes (PDCD5).[97] Mifune et al., found lower levels of apoptosis in in vivo investigations, and the authors speculated that the complex interplay of PRP within the joint would positively affect chondrocyte apoptosis.[98]

The well-documented pain decrease, which is the most obvious and disabling sign of knee OA, can be explained by an overall downmodulation of joint inflammation. This could be due to the inflammatory cascade's main actors, nuclear factor kappa B (NF-jB) and cyclooxygenase-2 (COX-2), being regulated.[99,100] Other factors could include Hepatocyte Growth Factor(HGF), a major cytokine found in PRP alpha-granules, reducing NF-jB transactivation activity, or an anti-inflammatory effect by inhibiting monocyte-like cell chemotaxis. PRP inhibited the inflammatory cascade generated by IL-1ß and tumour necrosis factor-alpha (TNF-a), according to Wu et al., by inhibiting IL-1ß, COX-2, and MMP-2 gene expression.[101]

Increased mRNA levels of cannabinoid receptors CB1 and CB2 (receptors implicated in analgesic and anti-inflammatory actions) were observed by Lee et al., which could explain PRP's analgesic impact.[102]

Preparation of platelet-rich plasma

PRP refers to the plasma portion of autologous blood that has a higher platelet content than normal. PRP is defined as platelet counts of 4–5 times the baseline (1.5–4.5 105/lL). PRP is also recognized as autogenous platelet gel, platelet enhanced plasma (PeRP), and platelet-rich concentrate (PRC).

PRP preparation can be done in a multiplicity of ways, and there are at least 25–30 ready-to-use kits on the market. Initial research used PRP generated in the laboratory

using various ways and commercial kits have evolved as a result of these investigations. PRP can be made in one of two ways: "single-spinning" or "Double-spinning.". Anitua et al. dubbed the product EndoRet after preparing PRP using a single-spin technique and an open approach that included micro-pipetting (plasma rich in growth factors).[103]

Patel et al., in his study, managed the patients with open technique to manufacture PRP, which included a single-spin, micro-pipetting and extra WBC filtration and their output was leucocyte-poor.[104] Kon et al. employed a double-spin method to generate PRP, which was then cryopreserved and used at three-weekly intervals.[105]

In terms of platelet count and leucocyte concentration, centrifugal forces and time, as well as the number of spins (double versus single), affect the PRP result. Because of the heterogeneity in yield, it was necessary to classify PRP so that research could be compared and two classification methods emerged. One is Mishra et al Sports's Medicine Platelet-Rich Plasma classification system, which divides PRP into 4 categories based on the activation method (activated or not activated) and the leucocyte count (increased or absent), with each type having two further subtypes A and B based on platelet concentration.[106] The PAW cataloguing by DeLong et al. is another international classification system that considers the absolute platelet count (P1-low to P4-high), the mechanism of platelet activation and the presence or absence of leucocytes.[107]

Platelet activation

Different activators can be used to activate platelets. Traditional activators of platelets include bovine or autologous thrombin, however there are concerns about its tolerance and side effects. In the vast majority of clinical investigations, calcium chloride is the most commonly employed activator. Other activators that can be used include

collagen type-1 and batroxobin. According to Rodeo et al., activated platelets release 70% of their growth factors (GFs) within the first 10 minutes and the majority of them over the next hour.[108] These growth factors are absorbed by the fibrin gel that forms and the numerous growth factors are then released in a controlled manner. The most essential element controlling subsequent release is the amount of fibrin in the gel. The ultimate fibrin content is influenced by platelet concentration, fibrinogen concentration and the enzymes involved in the procoagulant cascade. The duration of GF release at the injection site is controlled by the criteria listed above.

Better outcomes may be obtained through studies targeted at improving the regulated delivery of GFs from PRP at the target spot. The use of chitosan (scaffolds) and gelatin hydrogel as PRP carriers are two innovative techniques under discussion.[109,110] Saito et al., showed that gelatin hydrogel microspheres impregnated with PRP injections significantly inhibited OA progression both morphologically and histologically in a rabbit OA model. [111]

What specific type of PRP is ideal for Knee OA?

There are some answers and many questions to be answered based on the existing material.

Different PRP preparations — Magalon et al., investigated five different commercial PRP preparations in a single donor model and discovered considerable biological difference in the PRP product among preparations, which they hypothesised to be the cause of the variability of PRP study outcomes. [112]

Intra-individual differences were discovered by Mazzocca et al. in the same individual and the PRP yield by the same procedure varied with time in samples obtained at different times.[113]

When it comes to the argument between fresh PRP and freeze-thawed PRP, fresh PRP looks to be superior. Platelet's shape and functional qualities can be influenced by the degranulation of alpha-granules during storage in freezing temperatures.[114] In our preliminary research, we stated our reservations about the cryopreservation of PRP. In terms of patient compliance, however, freeze thawing PRP is superior because it can be prepared in one sitting. Roffi et al., investigated the effects of freezing/thawing on the release of PRP molecules and their impact on chondrocyte and synoviocyte metabolism.[115] Although the freeze-thawed PRP secreted less protein, the gene expression in cultured chondroctyes and synoviocytes was identical to that of fresh PRP. They came to the conclusion that PRP cryopreservation is a safe approach that adequately retains PRP quality as well as its potential to trigger proliferation and the formation of ECM components in chondrocytes and synoviocytes. PRP with fewer leucocytes appears to be better for knee OA than PRP with more leucocytes.

Clinical studies

Cerza et al. compared four PRP injections at one-week intervals with an Randomized control trial (RCT) on 120 patients and found that the PRP group had better WOMAC ratings at 24 weeks. They discovered no link between the grade of OA and its severity.[116]

They found that intra-articular PRP had good results International Knee Documentation Committee (IKDC scores) in early degenerative cartilage lesions. Younger patients, those with a low body mass index (BMI) and those with less cartilage deterioration had better results, according to the researchers. They also tracked the same patients for two years and found that the PRP group showed more sustained improvement than the HA group, with a small worsening after the first

year.[117] In early OA, however, they reported a similar effect in both the HA and PRP groups in their latest RCT.[118]

Sanchez et al. compared three PRP injections at one-week intervals (79 participants) with High Molecular Weight -Hyaluronic Acid injection (HMW-HA) in an RCT of 176 individuals with Ahlbacks grade 1–3 OA (74 patients). The percentage of patients with a 50% reduction in the WOMAC pain sub-score was the primary end measure. Other WOMAC sub-scores, the Lequesne index and Osteoarthritis Research Society International (OARSI) responders were used as secondary outcome measures. At 24 weeks, they discovered that the PRP group had greater results in terms of the primary endpoint. There were no differences in secondary outcome measures or the amount of acetaminophen consumed.[119]

Similarly better results were found in the PRP group in comparison to HA groups at six months interval by Li et al. and Say et al. in their prospective studies. [120,121]

Patel et al. were the first to compare normal saline (physiological control) to PRP and found that PRP was superior to placebo in terms of WOMAC scores, which lasted for six months. They detected benefits as early as 18 days and a small decrease of benefits by six months, based on which they predicted that the clinical effect could be due to an anti-inflammatory role, as chondral remodelling would have taken considerably longer time and would have delivered much more persistent results.[122]

Another option is to employ PRP on a yearly basis or when the patient requests it after the benefit has worn off. PRP was employed by Gobbi et al., at an annual interval and the clinical efficacy was established. More research is needed to see how long pain-free status can be maintained with numerous yearly injections.[123]

Hart et al. employed an unusual strategy in their study, comparing PRP (50 patients) to 1 percent mesocaine (50 patients) in knee articular injury grades 2 (fibrillation) and

grade 3 (fibrillation) (fissuring and fragmentation). Within a year, the PRP group had nine injections. The first six injections (loading dose) were given at weekly intervals, then there was a three-month hiatus, then three injections were given at three-month intervals (maintenance dose). They noticed that PRP groups improved more after 12 months in terms of IKDC, Tegner, Lysholm and Cincinnati scores. Magnetic resonance imaging, on the other hand, revealed no substantial effect on cartilage (MRI). As a result, no apparent benefit of a PRP-loaded operation could be demonstrated.[124]

Hassan et al. studied 20 individuals with mild to moderate OA who received 5 mL PRP at monthly intervals for six months (six injections) and saw significant improvements in knee stiffness, IKDC scores and VAS scale as compared to baseline. Patients with a young age, a low BMI and a short disease duration showed the greatest improvement. [125]

Sánchez et al., and colleagues have presented a unique method of PRP delivery in severe OA by injecting PRP into the subchondral area of the femoral condyle, tibial condyle and patella. They also used PRP intra-articular injections to treat synovial and cartilage pathologies in OA patients.[126]

Another intriguing method of administering PRP in OA is the use of photo-activated PRP (PA-PRP). Paterson et al. looked at the safety profile and feasibility of using PA-PRP in OA knees in a randomised controlled pilot research (23 participants). In comparison to the HA group, better results were seen. However, more research is needed to compare PA-PRP to PRP to see if photo-activation has any extra benefits above traditional PRP.[127]

There have been a few studies states that the PRP efficacy over HA in hip OA.[128,129] In talar osteochondral lesions, Mei-Dan et al., found that the PRP group had better results at 28 weeks.[130]

More patients are able to obtain the therapy now that commercial PRP kits are available on market. However, clinicians should not get carried away with the preliminary findings and should keep track of the patient's progress in order to contribute to the current research. To classify the PRP type, it's also a good idea to look at the yield and the end result.

MATERIALS AND METHODS

STUDY DESIGN:

The comparative study was conducted among patients with history of chronic knee pain, who diagnosed with early osteoarthritis

STUDY AREA:

The study was conducted among patients with early stages of osteoarthritis presented to department of Orthopaedics, R. L. Jalappa Hospital & Research Centre attached to Sri Devaraj Urs Medical College Affiliated to Sri Devaraj Urs Academy of Higher Education and Research Tamaka, Kolar.

STUDY PERIOD AND DURATION:

Period between January 2020 and June 2021 (1 year 6 months)

STUDY POPULATION:

All patients admitted to R. L. Jalappa Hospital & diagnosed with early stages of osteoarthritis presented to department of Orthopaedics during the period, between January 2020 and June 2021.

SAMPLE SIZE CALCULATION

$$n = \frac{2s_p^2 [Z_{1-\alpha/2} + Z_{1-\beta}]^2}{\mu^2_d}$$

$$S_p^2 = \frac{S_1^2 + S_2^2}{2S_1^2}$$

Where

S_1^2 - standard deviation in the first group

S_2^2 - standard deviation in the second group

μ^2d - mean difference between the samples

α - Significance level

1-β - Power

S_1^2 – 10.8

S_2^2 – 6.3

μ^2d – 9.4

α - 1%

Power - 90%

Sample difference was based on difference on Visual analogue score reported between single IA-PRP versus Multiple IA-PRP injection for early OA patients at 6 months mentioned in the RCT conducted by Gormeli et al in their study at Turkey by 2015.[16]

Required sample size was calculated as 27 per group.

With expected drop out of 10% in follow up, the estimated sample size was 30 per group. So, the minimum sample in each group was 30 and hence totally 60 samples.

INCLUSION CRITERIA:

- Clinically signs of Osteoarthritis
- Chronic knee pain more than 4 months
- Radiological documented grade I-II knee osteoarthritis (Kellgren – Lawrence)
- Patient age between 40 -60 years

EXCLUSION CRITERIA:

- Previous lower extremity surgery
- Diabetes Mellitus
- Rheumatic disease
- Severe cardiovascular disease
- Haematological diseases
- Infections
- Patient with haemoglobin value less than 11g/dL
- Platelet values less than 150,000/mm^3

SAMPLING METHOD:

All patients attending department of Orthopaedics, R. L. Jalappa Hospital & Research Centre attached to Sri Devaraj Urs Medical College Affiliated to Sri Devaraj Urs Academy of Higher Education and Research Tamaka, Kolar and diagnosed with early stages of osteoarthritis during the period, between January 2020 and June 2021.

RANDOMIZATION

The samples of 64 patients those who satisfied the inclusion and the exclusion criteria were randomised into two groups (30 samples in each group) by online random generator software.

All the subjects were interrogated and inspected and subjects were uninformed of their group allocation and to warrant that the criteria were fulfilled.

This trial was a single-blind study in which the participants did not informed of the intervention they obtained. The principal investigator and the treating staffs were not blinded.

Subjects were evaluated through Proforma and informed consent was obtained. Pre-intervention knee pain and functional status was assessed by VAS and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC Score). Repeated immediately after 6 weeks of intervention.

DATA COLLECTION PROCEDURE

The selected patients, after taking their consent correctly was subjected to a thorough history taking and physical examination. Patients was graded fitting to the Kellgren–Lawrence classification grade I-II for tibiofemoral joint degeneration. They were then subjected to initial investigations (Haemogram, HIV, HbsAg, RFT,) trailed by specific Investigation (X-ray knee standing –AP View/ 30 Degree Flexion Lateral View).

INTERVENTION

About 150 ml of whole blood will be collected in a double blood bag containing 63 ml of Citrate Phosphate Dextrose Adenine (CPDA) and was stored at room temperature 20-24degree Celsius till parting which was done within 1 hour of collection. Primarily blood was centrifuged by a light spin at 2630 Revolutions Per Minute (RPM) for 3 minutes and 1500RPM for another 15 minutes to sediment the RBCs and WBCs. Subsequently, blood bag was taken out and supernatant PRP was transported in the transfer bag under laminar airflow. Then the primary bag will be sealed with tube sealer. After I hour of resting platelets was re-suspended within the plasma. A minimum of 15ml of PRP was collected and succumbed for diagnostic evaluation with regard to the platelet count, sterility and relevant serological investigations before being injected into the joint.

Patients was divided into Group I and Group II where Group 1 received single intra-articular PRP injection and patients in group II received 2 intra-articular PRP injections on presentation and on 3rd month.

The skin was sterilely dressed, and each injection was given by an unblinded physician using the superolateral approach with a 22-G needle a 10 ml of PRP was administrated in right /left or both knees. The knee was immobilized for 10 min after the injection and sterile compression dressing was applied.

STUDY TOOLS

1. Visual Analogue scaleas mentioned in Annexure

2. Western Ontario and McMaster Universities Osteoarthritis Index as mentioned in Annexure

STUDY VARIABLES

- Age
- Gender
- Knee affected
- Grade of OA
- Co-morbidities
- Visual Analogue scaleat first visit before intervention, at 6^{th} week, 3^{rd} month and 6^{th} month after intervention.
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC SCORE) at first visit before intervention, at 6^{th} week, 3^{rd} month and 6^{th} month after intervention.

ETHICAL CONSIDERATION

Ethical approval was taken from the Institutional Ethics Committee. All ethical morality was followed in the study. The gathered data was casted-off only for the projected purpose of the study; the confidentiality and clandestineness of participants were preserved all over the process as assured by the researchers. The researchers did not collect any forms of secretive identification such as address and social security numbers all over the research work. The outcomes obtained from the data collection were dealt in with privacy and the researchers will dispose of entire data collected after dissertation publication.

DATA ANALYSIS

- The collected data were entered in MS excel and analysed using IBM.SPSS statistics software 23.0 Version.
- The data was described in descriptive statistics as frequency analysis, percentage analysis was used for discrete variables. Mean, Median and Standard deviation was used for continuous variables.
- The data was described in inferential statistics in which discrete variables in the two groups was compared for statistically significant difference using Chi Square test or Fisher's exact test. Continuous variables in the two groups were compared for statistically significant difference using Independent T test.
- Paired T test was applied to compare the efficacy of single IA-PRP injection versus multiple IA-PRP injections before and after intervention.
- In all the above statistical tools the probability value 0.05 was considered as significant level.

RESULTS

In the current study, about 64 individuals (34 in single-dose PRP arm (S-PRP) and 30 in multiple-dose PRP arm (M-PRP)) were included and analysed for the results.

SOCIODEMOGRAPHIC Profile:

The mean age of the study participants was 53.33 with standard deviation of 6.493. The mean age of the study participants was 55.26 years in the S-PRP group and 51.13 years in the M-PRP group with a standard deviation of 4.8 and 7.4 years respectively.

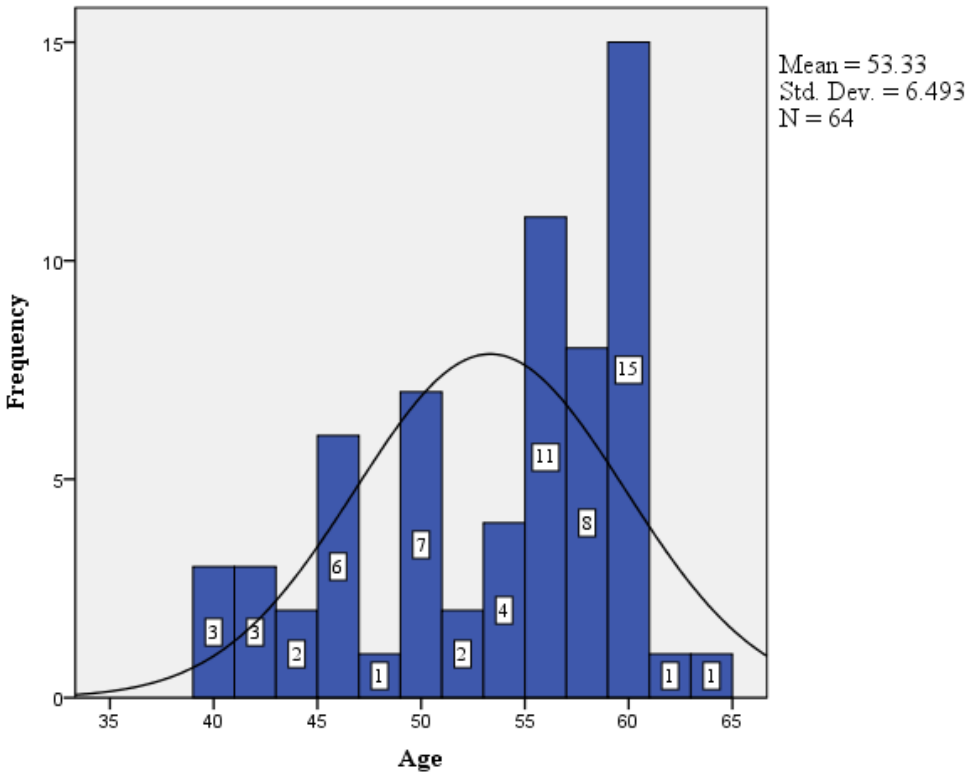


Figure 8: Age distribution of the study participants (n=64)

Table 1: Age distribution of the study participants (n=64 (S-PRP – 34 and M-PRP – 30))

Group		**Age**
Single PRP injection	Mean	55.26
	Median	56.00
	Mode	60
	Std. Deviation	4.889
	Minimum	43
	Maximum	62
	Interquartile range	53.50 - 59.25
Multiple PRP injection	Mean	51.13
	Median	50.00
	Mode	60
	Std. Deviation	7.417
	Minimum	40
	Maximum	64
	Interquartile range	44.75 - 58.25

Among the study participants, about 66 percent were females and the remaining were males as shown in the below diagram.

Figure 9: Gender distribution of the study participants (n=64)

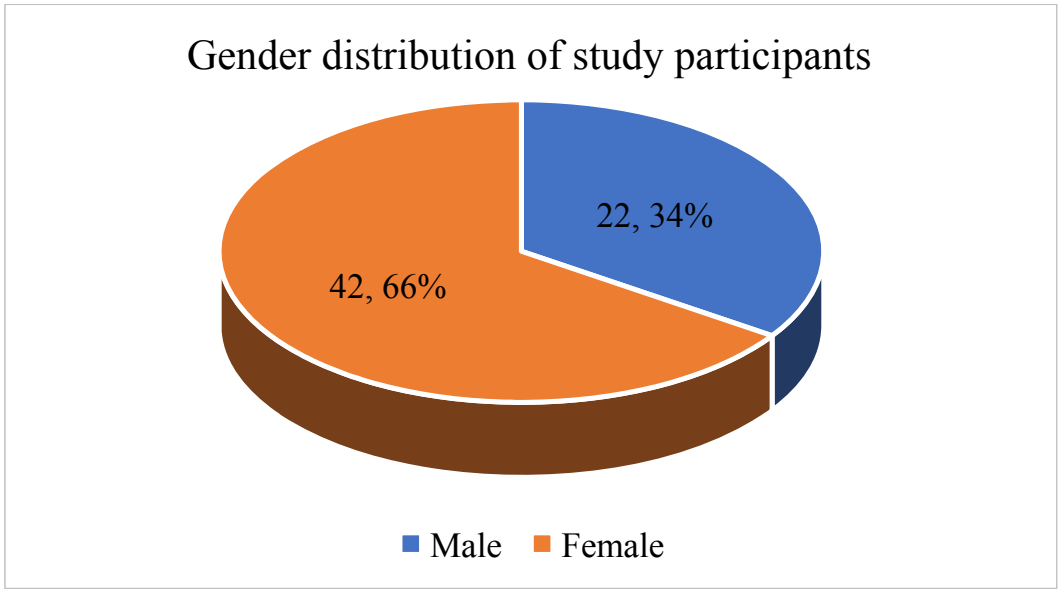
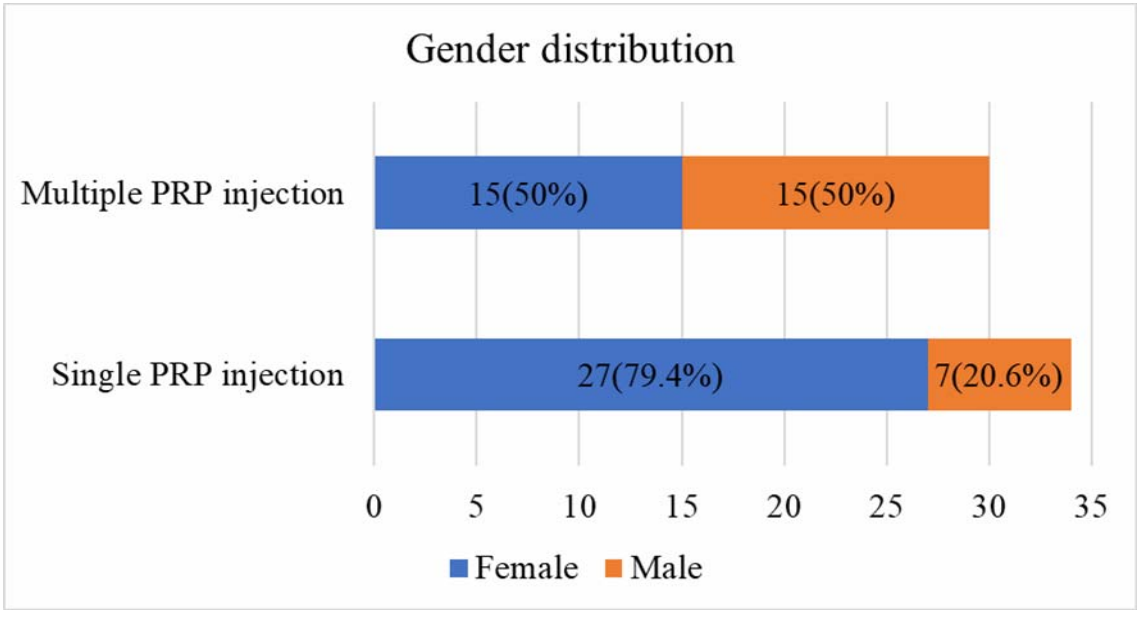


Figure 10: Gender distribution of the study participants based on the intervention (n=64 (S-PRP – 34 and M-PRP – 30))



Among the study participants, in the M-PRP arm, both gender was equally distributed but in the S-PRP arm, about 79.4 percent were females as shown in the above diagram.

Baseline characters of the study participants:

The mean BMI of the study participants was 27.67 with the standard deviation of 1.662. The mean BMI of the study participants was 27.94 in the S-PRP group and 27.37 in the M-PRP group as shown in the below diagram and table.

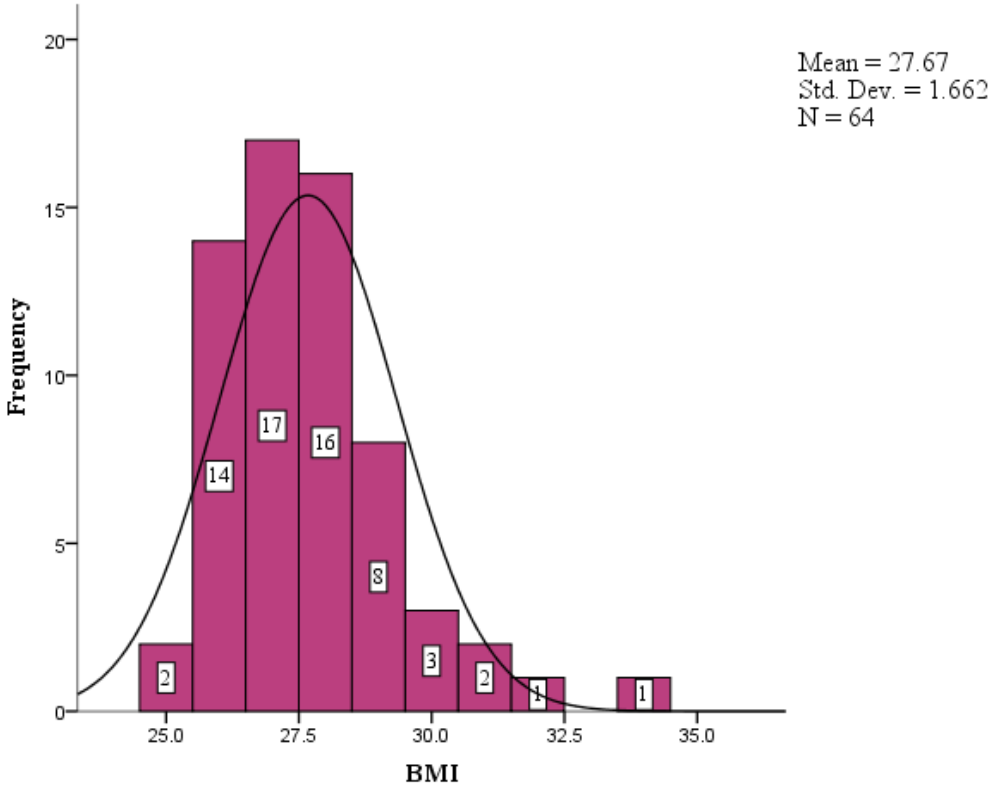
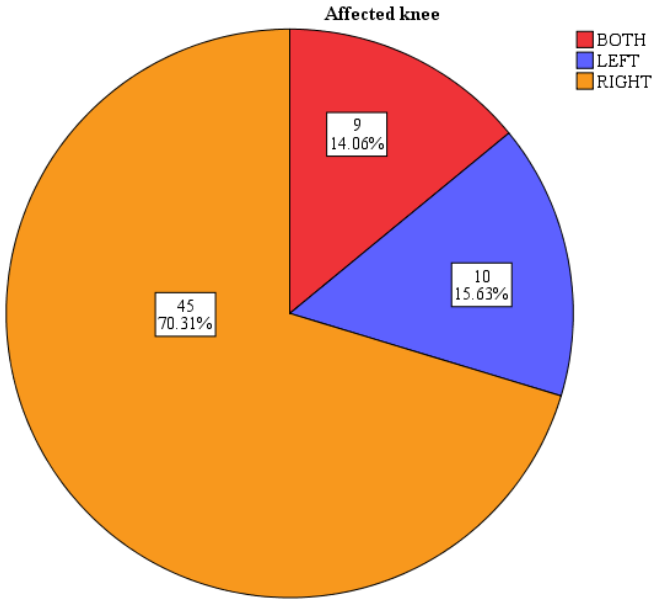


Figure 11: Distribution of study participants according to their BMI scores (n=64)

Table 2:Distribution of study participants according to their BMI scores (n=64 (S-PRP – 34 and M-PRP – 30))

Group		BMI
Single PRP injection	Mean	27.94
	Median	28.00
	Mode	28
	Std. Deviation	1.740
	Minimum	26
	Maximum	34
	Interquartile range	27.00 - 28.25
Multiple PRP injection	Mean	27.37
	Median	27.00
	Mode	26
	Std. Deviation	1.542
	Minimum	25
	Maximum	31
	Interquartile range	26.00 - 28.25

Figure 12: Distribution of study participants according to the affected knee (n=64)



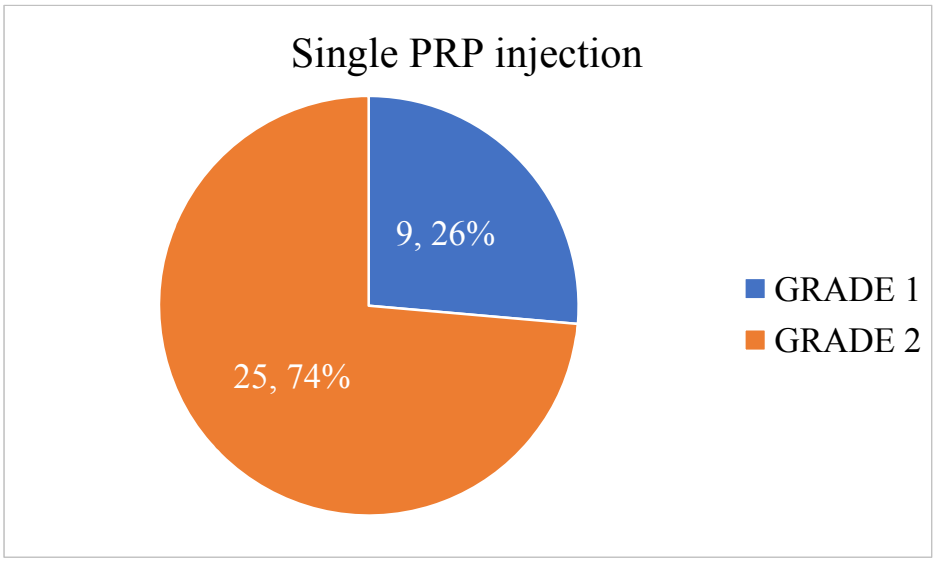
Among the study participants, about 70.31 percent had complaints in right knee and about 15.63 percent had complaints in left knee. 14.06 % had complaints in both knee.

Table 3: Distribution of study participants according to the affected knee (n=64 (S-PRP – 34 and M-PRP – 30))

Affected knee - Group		Frequency	Percent
Single PRP injection	Both	4	11.8
	Left	7	20.6
	Right	23	67.6
Multiple PRP injection	Both	5	16.7
	Left	3	10.0
	Right	22	73.3

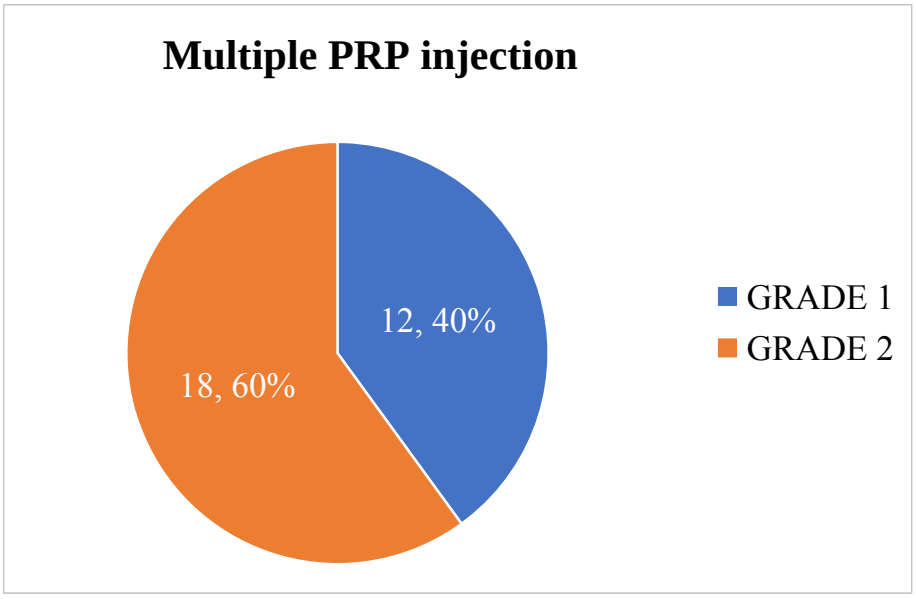
Among the S-PRP group, about 67.6 percent had complaints in the right knee which is similar to the M-PRP group which is 73.3 percent as shown in the below diagram and table.

Figure 13: Distribution of S-PRP group participants according to osteoarthritis grades (n=34)



Among the S-PRP group, about 73.5 percent of the individuals were classified to have grade 2 osteoarthritis and 26 percent of the individuals with grade 1

Figure 14: Distribution of M-PRP group participants according to osteoarthritis grades (n= 30)



Among the Multiple -PRP group, about 60 percent of the individuals were classified to have grade 2 osteoarthritis.

Comorbidities:

When comes to obesity, according to BMI categories, almost all participants were overweight. About 10.94 percent of the study participants were classified as obese class 1.

Figure 15: Distribution of study participants according to the BMI category (n=64)

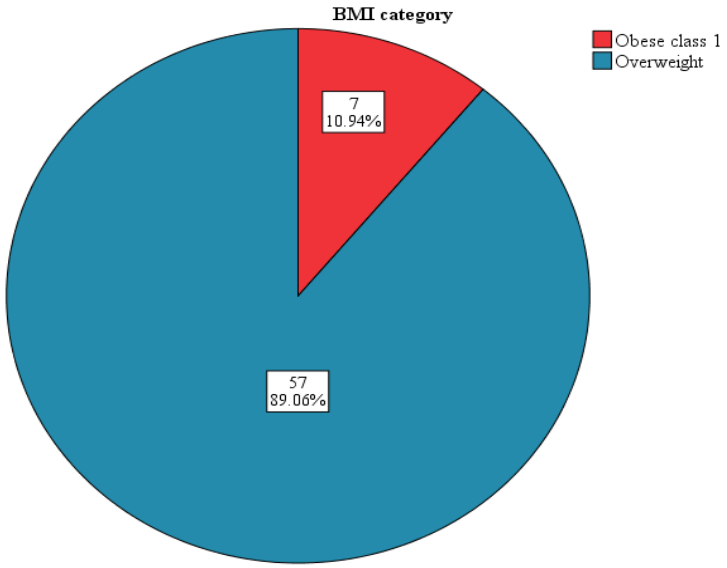


Table 4: Distribution of study participants according to the BMI category (n=64 (S-PRP – 34 and M-PRP – 30))

BMI category - Group		Frequency	Percent
Single PRP injection	Obese class 1	5	14.7
	Overweight	29	85.3
Multiple PRP injection	Obese class 1	2	6.7
	Overweight	28	93.3

Among the S-PRP group, about 14.7 percent were classified as obese class 1 and, in the M-PRP group about 6.7 percent were under obese class 1 as shown in the table.

When comes to diabetes, about 28.13 percent of the study participants have diabetes as shown in the below diagram

Figure 16: Distribution of study participants according to their diabetic status (n=64)

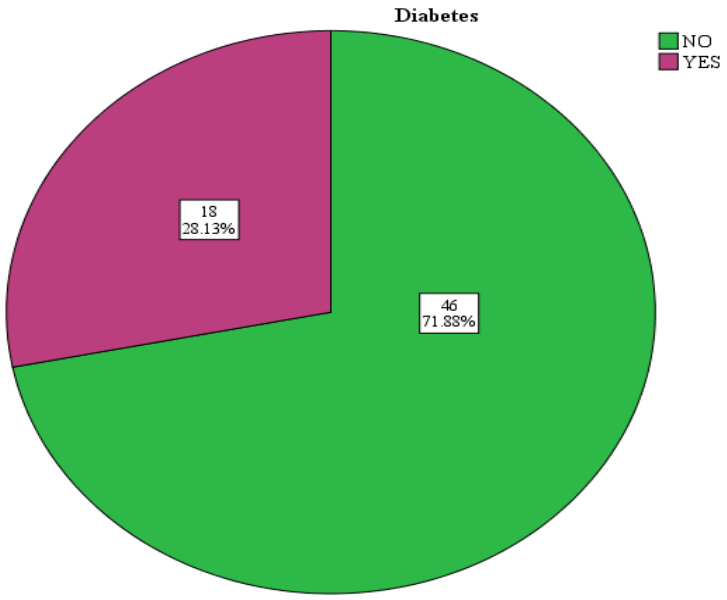


Table 5: Distribution of study participants according to their diabetic status (n=64 (S-PRP – 34 and M-PRP – 30))

Group		Frequency	Percent
Single PRP injection	No	26	76.5
	Yes	8	23.5
	Total	34	100.0
Multiple PRP injection	No	20	66.7
	Yes	10	33.3
	Total	30	100.0

When comes to diabetes, about 23.5 percent have diabetes in the S-PRP group and about 33.3 percent have diabetes in the M-PRP group as shown in the table.

When comes to hypertension, about 20.31 percent of the study participants have hypertension.

Figure 17: Distribution of study participants according to the presence of hypertension (n=64)

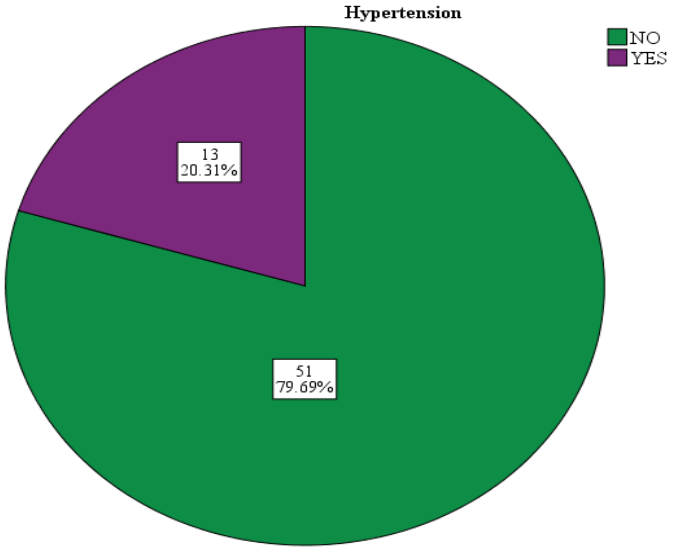
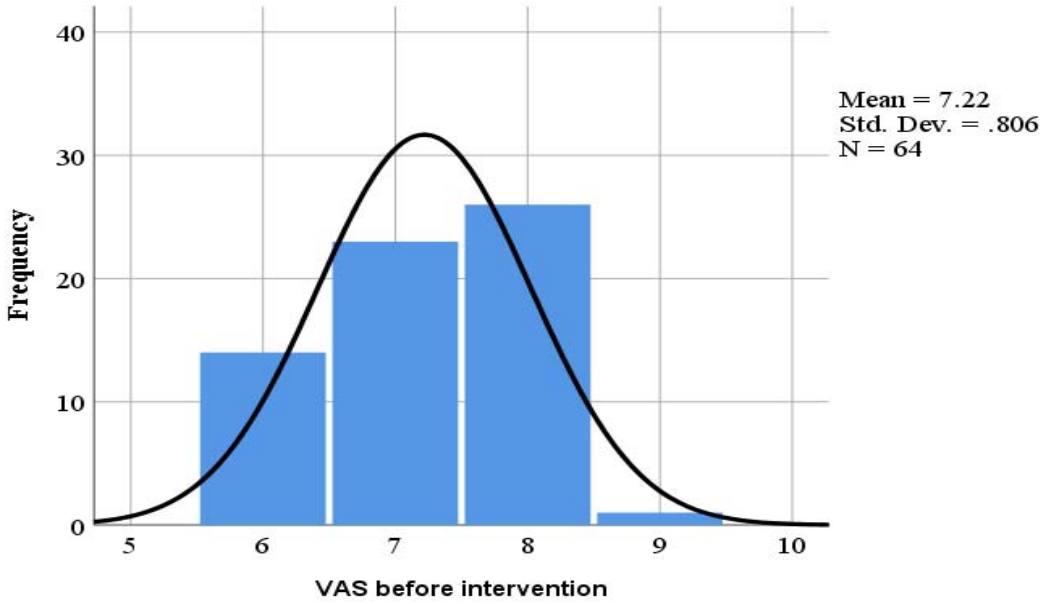


Table 6: Distribution of study participants according to the presence of hypertension (n=64 (S-PRP – 34 and M-PRP – 30))

Hypertension - Group		Frequency	Percent
Single PRP injection	No	27	79.4
	Yes	7	20.6
	Total	34	100.0
Multiple PRP injection	No	24	80.0
	Yes	6	20.0
	Total	30	100.0

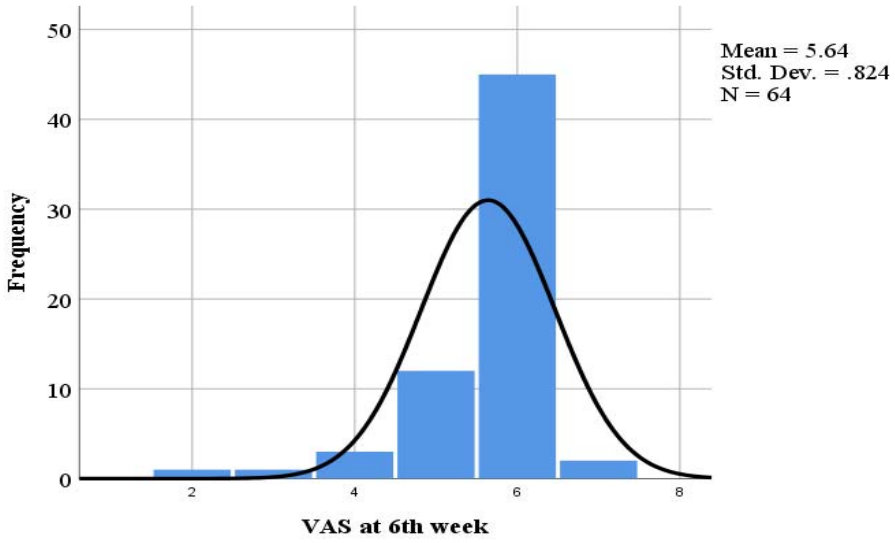
When comes to hypertension, in the S-PRP group about 20.6 percent have been diagnosed with hypertension and in the M-PRP group, about 20 percent have hypertension as shown in the table

Figure 18: Histogram showing VAS scale before intervention



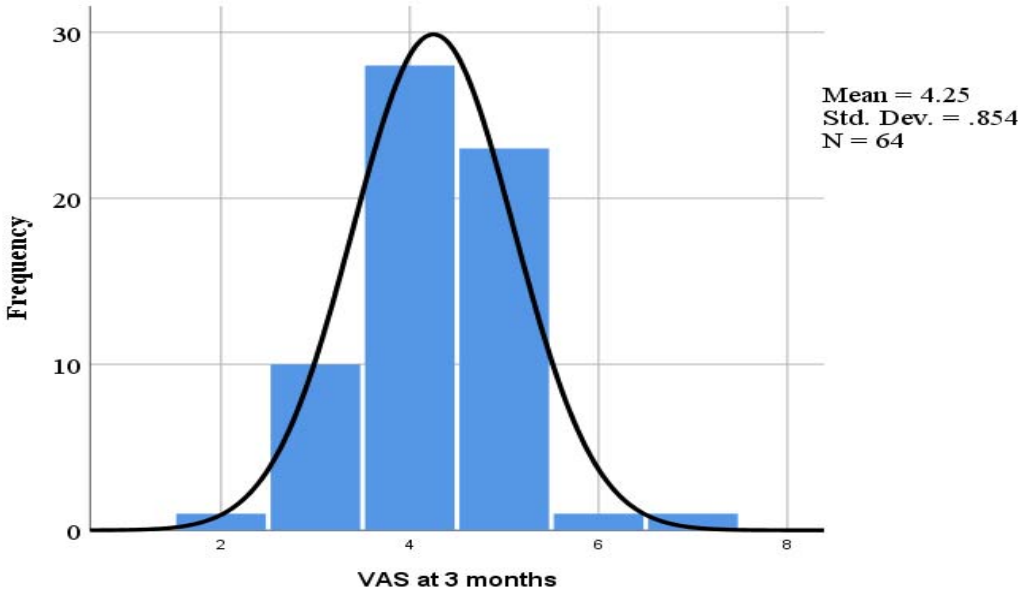
The mean VAS scale among the study participants before intervention was 7.22

Figure 19:Histogram showing VAS scale at 6 weeks after intervention



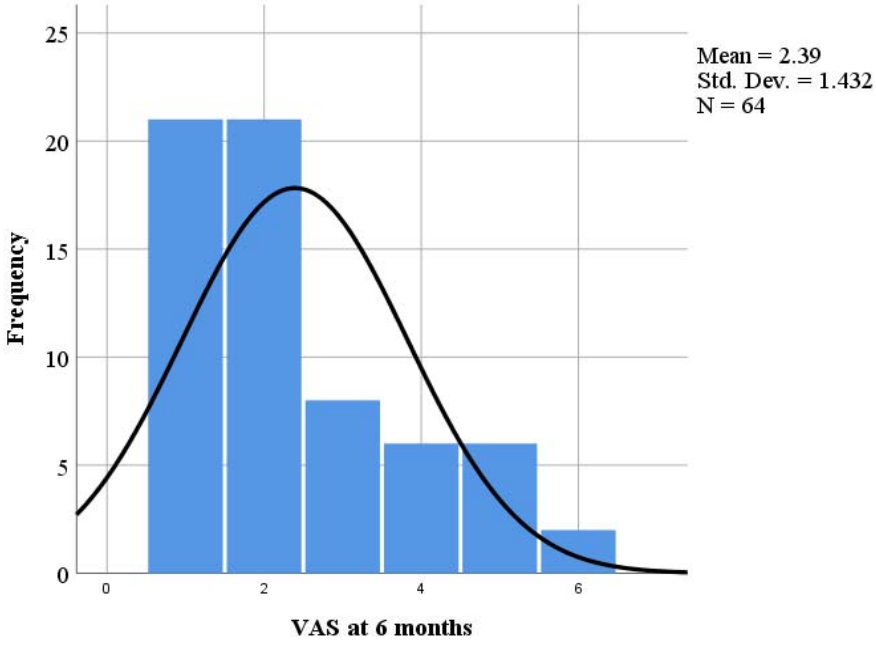
The mean VAS scale among the study participants six weeks after intervention was 5.64

Figure 20: Histogram showing VAS scale at 3 months after intervention



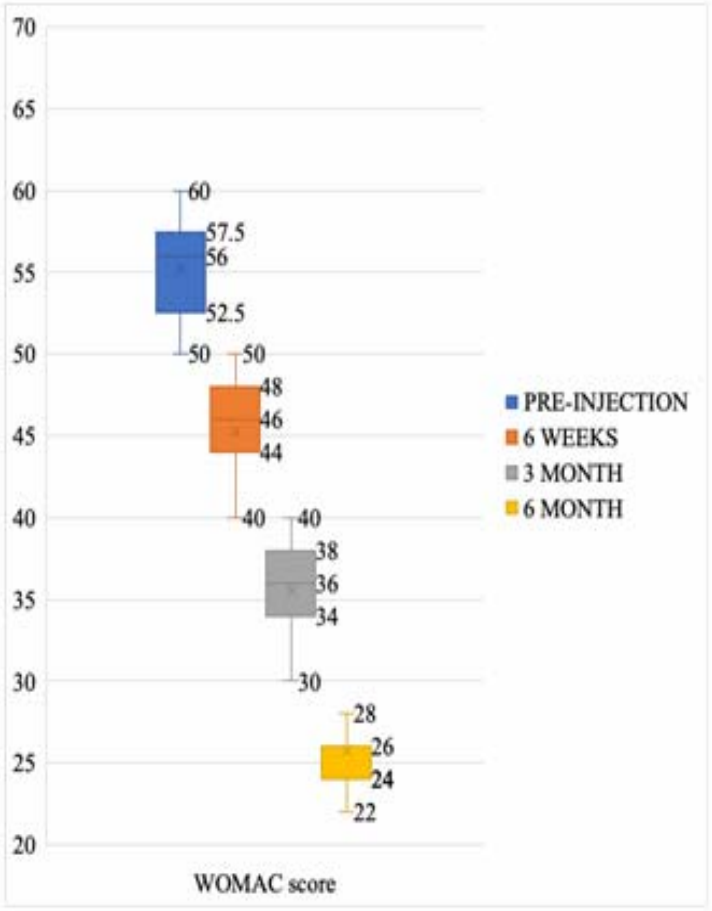
The mean VAS scale among the study participants 3 months after intervention was 4.25

Figure 21:Histogram showing VAS scale at 6 months after intervention



The mean VAS scale among the study participants 6 months after intervention was 2.39

Figure 22: Box-Whisker plot showing WOMAC score before and after intervention

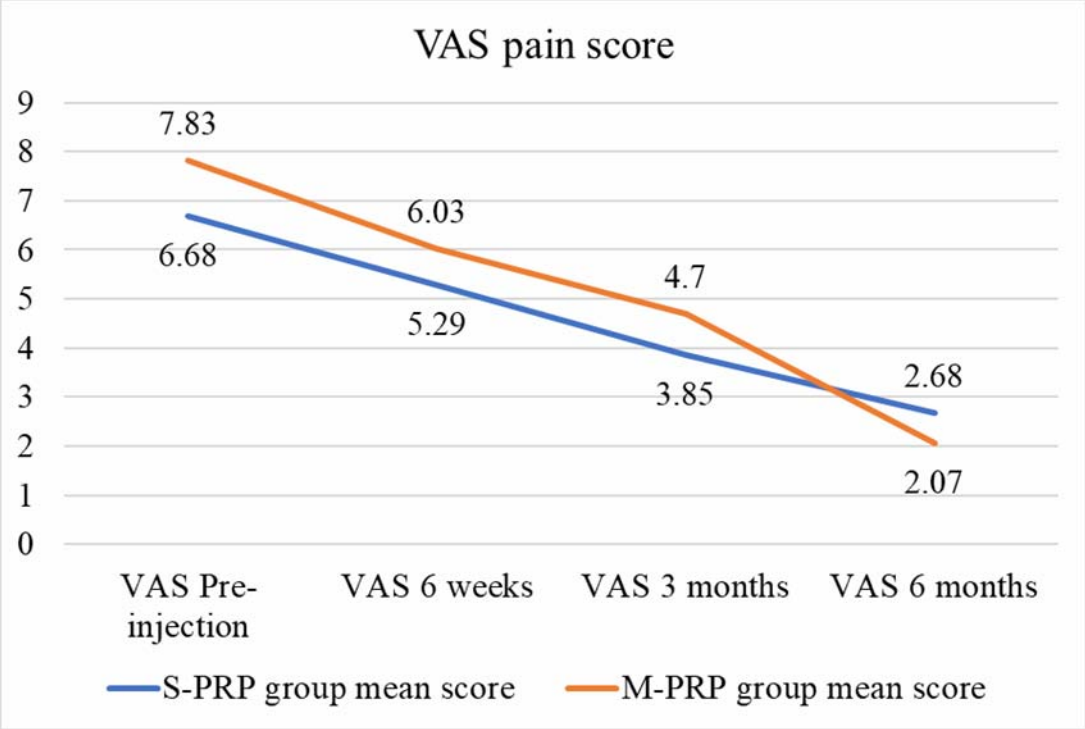


The mean WOMAC score among the study participants 6 weeks after intervention was 46, at 3 months after intervention was 36, at 6 months after intervention was 26.

Table 7:The pain scale distribution of study participants according to VAS scale (n=64 (S-PRP – 34 and M-PRP – 30))

Group		VAS Pre-injection	VAS 6 weeks	VAS 3 months	VAS 6 months
Single PRP injection	Mean	6.68	5.29	3.85	2.68
	Median	7.00	5.50	4.00	2.00
	Mode	7	6	4	2
	Std. Deviation	.638	1.001	.857	1.552
	Minimum	6	2	2	1
	Maximum	8	7	7	6
	Interquartile range	6.00 - 7.00	5.00 - 6.00	3.00 - 4.00	1.00 - 4.00
Multiple PRP injection	Mean	7.83	6.03	4.70	2.07
	Median	8.00	6.00	5.00	2.00
	Mode	8	6	5	1
	Std. Deviation	.461	.183	.596	1.230
	Minimum	7	6	3	1
	Maximum	9	7	6	5
	Interquartile range	8.00 - 8.00	6.00 - 6.00	4.00 - 5.00	1.00 - 2.25

Figure 23: Declining trend of pain scale in VAS pain scale among the study participants ((n=64 (S-PRP – 34 and M-PRP – 30))

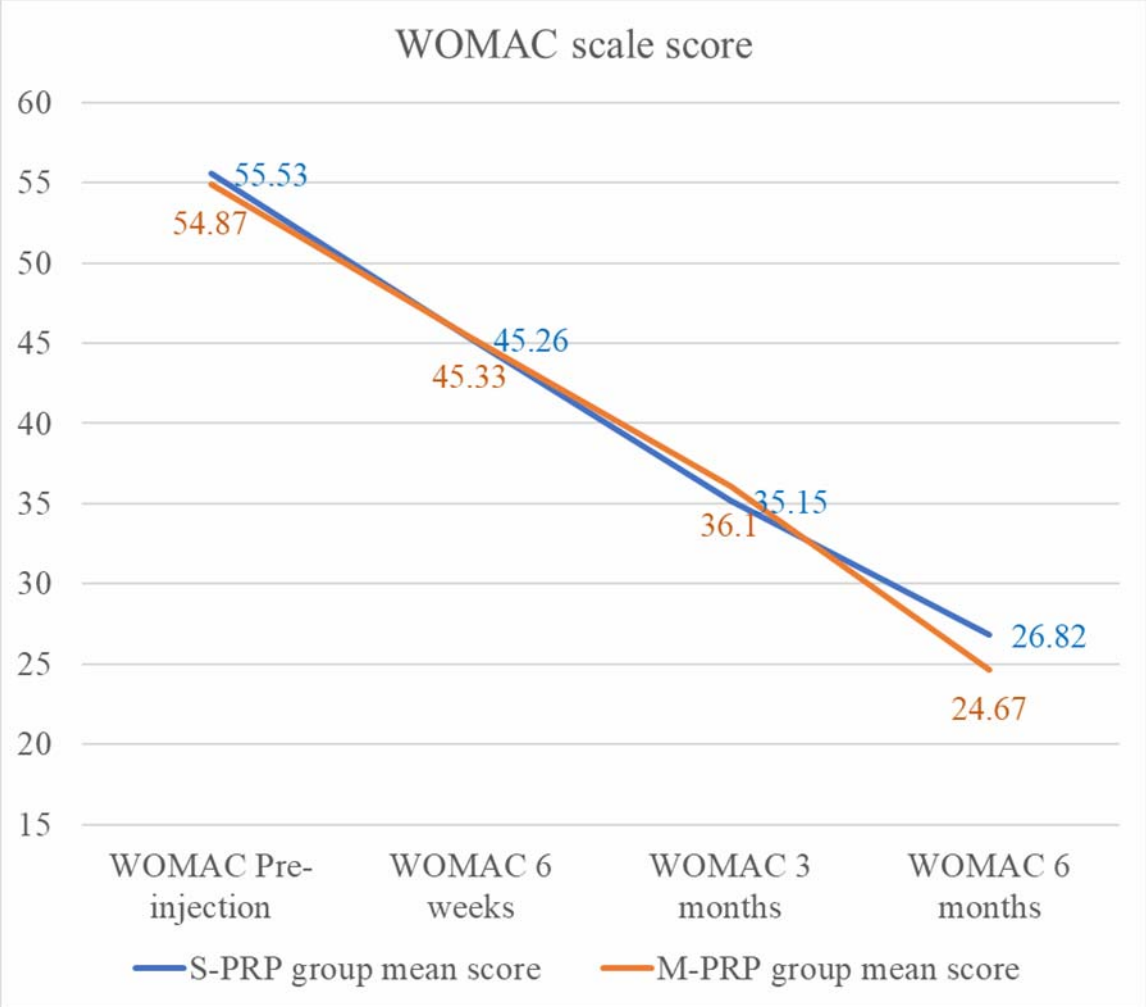


When comes to the VAS scale, the mean value of pain scale was 6.68 at the time of pre-injection which is reduced to the mean of 2.68 in the end of 6 months in the S-PRP group. In the M-PRP group, the mean value of pain scale was 7.83 at the time of pre-injection which is reduced to 2.07.

Table 8: The distribution of study participants according to the WOMAC score (n=64 (S-PRP – 34 and M-PRP – 30))

Group		WOMAC Pre-injection	WOMAC 6 weeks	WOMAC 3 months	WOMAC 6 months
Single PRP injection	Mean	55.53	45.26	35.15	26.82
	Median	56.00	46.00	35.00	24.00
	Mode	56	48	34	24
	Std. Deviation	2.259	2.885	2.512	8.919
	Minimum	52	40	30	18
	Maximum	60	50	40	66
	Interquartile range	54.00 - 56.50	42.75 - 48.00	34.00 - 38.00	23.50 - 28.00
Multiple PRP injection	Mean	54.87	45.33	36.10	24.67
	Median	55.00	46.00	36.00	24.00
	Mode	52	46[a]	38	24
	Std. Deviation	2.662	2.482	2.264	2.695
	Minimum	50	40	32	16
	Maximum	60	50	40	28
	Interquartile range	52.00 - 58.00	44.00 - 48.00	34.00 - 38.00	24.00 - 26.00

Figure 24: Declining trend of WOMAC scale scores among the study participants (n=64 (S-PRP – 34 and M-PRP – 30))



When comes to the WOMAC pain scale, the mean score of study participants at the time of pre-injection in the S-PRP group is 55.53 which is reduced to 26.8 at the end of the 6th month, in M-PRP group the mean score of the study participants were 54.87 and it is reduced to 24.6 after 6 months. The distribution of study participants according to the WOMAC score is shown in the below table and diagram.

Complication:

When comes to complications, about 9.38 percent have pain, about 4.69 percent have pain and swelling.

Figure 25: Distribution of study participants according to complications after treatment (n=64)

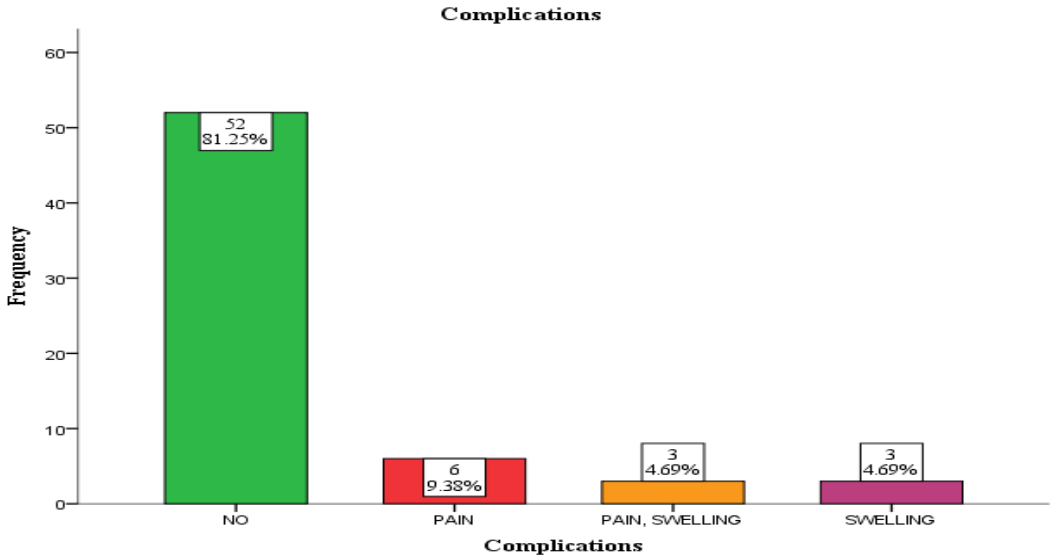


Table 9: Distribution of study participants according to complications after treatment (n=64 (S-PRP – 34 and M-PRP – 30)

Complications - Group		Frequency	Percent
Single PRP injection	No	29	85.3
	Pain	4	11.7
	Swelling	2	5.8
	Total	34	100.0
Multiple PRP injection	No	23	76.7
	Pain	5	16.7
	Swelling	4	13.4
	Total	30	100.0

When comes to complications, about 11.7 percent have pain in the S-PRP group whereas in the M-PRP group about 16.7 percent complaints of pain after treatment as shown in the table.

Association between S-PRP and M-PRP groups according to VAS scale

The mean value of pain scale by using the VAS scale in the S-PRP group is 6.68 and M-PRP group is 7.83 at the pre-injection time. This difference of means in both groups is statistically significant ($p < 0.001$) by using the independent T-test.

Table 10:Association between S-PRP and M-PRP groups according to VAS scale (n=64 (S-PRP – 34 and M-PRP – 30))

	Group	N	Mean	Mean Difference	P-Value
VAS Pre-injection	Single PRP injection	34	6.68	- 1.157	< 0.001
	Multiple PRP injection	30	7.83		

Since, the difference in pre-injection mean VAS scale is between the above two groups is statistically significant, further association was done with pain scale difference in each group between pre-injection time and follow up time.

Table 11: Comparison of mean Visual Analogue Scale before and after intervention by Paired T test

Time of assessment		Mean	Std. Dev	Mean difference	P value
Pair 1	Before injection	7.22	0.806	1.58	<0.0001
	At 6th week	5.64	0.824		
Pair 2	At 6th week	5.64	0.824	1.39	<0.0001
	At 3rd month	4.25	0.854		
Pair 3	At 3rd month	4.25	0.854	1.86	<0.0001
	At 6th month	2.39	1.432		
Pair 4	Before injection	7.22	0.806	2.97	<0.0001
	At 3rd month	4.25	0.854		
Pair 5	Before injection	7.22	0.806	4.83	<0.0001
	At 6th month	2.39	1.432		

The decreasing trend of pain which was measured by VAS scale observed after intervention by S-PRP and Multiple-PRP injection at pre-injection, 6^{th} week, 3^{rd} month and 6^{th} month respectively. These differences were statistically significant by Paired T test.

Table 12: Comparison of mean Visual Analogue Scale among S-PRP group before and after intervention by Paired T test

Time of assessment		Mean	Std. Dev	Mean difference	P value
Pair 1	Before injection	6.68	0.638	1.382	<0.0001
	At 6th week	5.29	1.001		
Pair 2	At 6th week	5.29	1.001	1.176	<0.0001
	At 3rd month	3.85	0.857		
Pair 3	At 3rd month	3.85	0.857	1.441	<0.0001
	At 6th month	2.68	1.552		
Pair 4	Before injection	6.68	0.638	2.618	<0.0001
	At 3rd month	3.85	0.857		
Pair 5	Before injection	6.68	0.638	4.000	<0.0001
	At 6th month	2.68	1.552		

The decreasing trend of pain which was measured by VAS scale observed after intervention by S-PRP injection at pre-injection, 6^{th} week, 3^{rd} month and 6^{th} month respectively. These differences were statistically significant by Paired T test.

Table 13: Comparison of mean Visual Analogue Scale among Multiple-PRP group before and after intervention by Paired T test

Time of assessment		Mean	Std. Dev	Mean difference	P value
Pair 1	Before injection	7.83	0.461	1.800	<0.0001
	At 6th week	6.03	0.183		
Pair 2	At 6th week	6.03	0.183	1.333	<0.0001
	At 3rd month	4.70	0.596		
Pair 3	At 3rd month	4.70	0.596	2.633	<0.0001
	At 6th month	2.07	1.230		
Pair 4	Before injection	7.83	0.461	3.130	<0.0001
	At 3rd month	4.70	0.596		
Pair 5	Before injection	7.83	0.461	5.767	<0.0001
	At 6th month	2.07	1.230		

The decreasing trend of pain which was measured by VAS scale observed after intervention by Multiple-PRP injection at pre-injection, 6^{th} week, 3^{rd} month and 6^{th} month respectively. These differences were statistically significant by Paired T test.

Table 14: Comparison of mean WOMAC Score before and after intervention by Paired T test

Time of assessment		Mean	Std. Dev	Mean difference	P value
Pair 1	Before injection	55.22	2.459	9.922	<0.0001
	At 6th week	45.30	2.683		
Pair 2	At 6th week	45.30	2.683	9.703	<0.0001
	At 3rd month	35.59	2.428		
Pair 3	At 3rd month	35.59	2.428	9.781	<0.0001
	At 6th month	25.81	6.796		
Pair 4	Before injection	55.22	2.459	19.484	<0.0001
	At 3rd month	35.59	2.428		
Pair 5	Before injection	55.22	2.459	29.406	<0.0001
	At 6th month	25.81	6.796		

The decreasing trend which was measured by WOMAC score observed after intervention by S-PRP and Multiple-PRP injection at pre-injection, 6^{th} week, 3^{rd} month and 6^{th} month respectively. These differences were statistically significant by Paired T test.

Table 15:Comparison of mean WOMAC Score among S-PRP group before and after intervention by Paired T test

Time of assessment		Mean	Std. Dev	Mean difference	P value
Pair 1	Before injection	55.53	2.259	10.265	<0.0001
	At 6th week	45.26	2.885		
Pair 2	At 6th week	45.26	2.885	10.118	<0.0001
	At 3rd month	35.15	2.512		
Pair 3	At 3rd month	35.15	2.512	8.324	<0.0001
	At 6th month	26.82	8.919		
Pair 4	Before injection	55.53	2.259	20.380	<0.0001
	At 3rd month	35.15	2.512		
Pair 5	Before injection	55.53	2.259	28.706	<0.0001
	At 6th month	26.82	8.919		

The decreasing trend which was measured by WOMAC score observed after intervention by S-PRP injection at pre-injection, 6^{th} week, 3^{rd} month and 6^{th} month respectively. These differences were statistically significant by Paired T test.

Table 16: Comparison of mean WOMAC Score among Multiple-PRP group before and after intervention by Paired T test

Time of assessment		Mean	Std. Dev	Mean difference	P value
Pair 1	Before injection	54.87	2.662	9.533	<0.0001
	At 6th week	45.33	2.482		
Pair 2	At 6th week	45.33	2.482	9.233	<0.0001
	At 3rd month	36.10	2.264		
Pair 3	At 3rd month	36.10	2.264	11.433	<0.0001
	At 6th month	24.67	2.695		
Pair 4	Before injection	54.87	2.662	18.77	<0.0001
	At 3rd month	36.10	2.264		
Pair 5	Before injection	54.87	2.662	30.200	<0.0001
	At 6th month	24.67	2.695		

The decreasing trend which was measured by WOMAC score observed after intervention by Multiple-PRP injection at pre-injection, 6^{th} week, 3^{rd} month and 6^{th} month respectively. These differences were statistically significant by Paired T test.

Table 17: Association between S-PRP and M-PRP groups according to VAS scale difference between pre-injection and follow-up period (n=64 (S-PRP – 34 and M-PRP – 30))

	Group	Mean	Std. Deviation	Mean Difference	P - Value
VAS Pain scale difference at 3rd month	Single PRP injection	2.82	0.758	- 0.310	0.082
	Multiple PRP injection	3.13	0.629		
VAS Pain scale difference at 6th month	Single PRP injection	4.00	1.518	- 1.767	< 0.001
	Multiple PRP injection	5.77	1.223		

In the end of 6th month, the mean value of pain scale in S-PRP group is 4 and in M-PRP group is 5.77 and this difference in mean is statistically significant ($P < 0.001$). Thus, multiple PRP injection have greater response in reduction of pain when compared to single PRP injection according to VAS pain scale score. This association is shown in the above table.

Table 18: Association between S-PRP and M-PRP groups according to WOMAC score (n=64 (S-PRP – 34 and M-PRP – 30))

	Group	N	Mean	Mean Difference	P-Value
WOMAC Pre-injection	Single PRP injection	34	55.53	0.663	0.286
	Multiple PRP injection	30	54.87		
WOMAC 6 weeks	Single PRP injection	34	45.26	- 0.069	0.920
	Multiple PRP injection	30	45.33		
WOMAC 3 months	Single PRP injection	34	35.15	- 0.953	0.118
	Multiple PRP injection	30	36.10		
WOMAC 6 months	Single PRP injection	34	26.82	2.157	0.208
	Multiple PRP injection	30	24.67		

The mean score by using the WOMAC score in the S-PRP group is 45.26 and M-PRP group is 45.33 at the 6^{th} week of follow-up. This difference of means in both groups is not statistically significant (p = 0.920) by using the independent T-test. Similarly, the mean score in the S-PRP group is 35.15 and the M-PRP group is 36.10 in 3^{rd} month of follow-up. This difference of means in both groups is not statistically significant (p = 0.118) by using the independent T-test. Thus, according to the WOMAC scale score, there is no statistically significant difference in the treatment response with PRP injection between S-PRP and M-PRP groups. This association is shown in the above table.

DISCUSSION

PRP has gained popularity as a therapy option for early knee osteoarthritis. Patients with early stages of osteoarthritis were enrolled in the study, which took place at the R. L. Jalappa Hospital & Research Centre attached to Sri Devaraj Urs Medical College Affiliated to Sri Devaraj Urs Academy of Higher Education and Research Tamaka, Kolar.

The online random generator software assigned 64 people to our trial (34 in the single-dose PRP arm (S-PRP) and 30 in the multiple-dose PRP arm (M-PRP)). Patients in group I had a single intra-articular PRP injection, while patients in group II received two intra-articular PRP injections on presentation and at the end of third month.

With the terms "osteoarthritis of the knee" and "platelet rich plasma," a PubMed search in November 2021 yielded only a few studies have employed numerous IA-PRP injections in knee OA and these studies are of varying quality. Some are short pilot experiments with no controls, while others have utilised several injections for no apparent reason.

A lack of uniformity of study methods, platelet separation methodologies and outcome measurements complicates the current literature. As a result, the evidence supporting the therapeutic use of PRP and autologous blood concentrates as a therapy strategy for most orthopaedic disorders, let alone knee OA, is mixed.

Baseline Characteristics of Participants

Table 19: Comparison of Mean age of the participants with the similar studies

Author (year of study)	Single PRP injections group	Multiple PRP injections Group
Present study	**55.26 ± 4.889**	**51.13 ± 7.417**
Uslu Guvendi[131] (2018)	62.3 ± 1.6	60.4 ± 1.7
Kavadar et al[132] (2015)	53.6 ± 6.7	55.2 ± 5.7
Simental-Mendia et al[133] (2019)	54.6 ± 11.6	60.1 ± 10.6

The average age of the participants in the current study was 55.26 years in the S-PRP group and 51.13 years in the M-PRP group, with standard deviations of 4.8 and 7.4 years, respectively. But the mean age was higher in the Randomized blinded, controlled trial conducted by Uslu Guvendi et al in Turkey by 2018.[131] Similar findings were noted in the study conducted by Kavadar et al in Turkey in 2015.[132] The supporting results were observed in the recent study conducted by Simental Mentia et al., in Turkey in 2019.[133]

Table 20: Comparison of gender distribution of the participants with the similar studies

Author (year of study)	Single PRP injections group		Multiple PRP injections Group	
	Male (%)	Female (%)	Male (%)	Female (%)
Present study	**7 (20.6)**	**27 (79.4)**	**15(50)**	**15(50)**
Uslu Guvendi[131] (2018)	1(5.3)	18 (94.7)	1 (7.1)	13 (92.9)
Simental-Mendia et al[133] (2019)	1(5.6)	17 (94.4)	5(29.4)	12 (70.6)

Both genders were equally distributed among study participants in the M-PRP arm, but not in the S-PRP arm. Comparable findings were renowned in the study conducted by by Uslu Guvendi et al in Turkey by 2018.[131] The supportive results were observed in the current study conducted by Simental Mentia et al., in Turkey in 2019.[133] The reason behind this observation was that the above mentioned studies have been done at different settings and sampling technique used.

Table 21: Comparison of Mean BMI of the participants with the similar studies

Author (year of study)	Single PRP injections group	Multiple PRP injections Group
Present study	**27.94 ± 1.740**	**27.37 ± 1.542**
Uslu Guvendi[131] (2018)	31.4 ± 0.7	31.0 ± 1.0
Kavadar et al[132] (2015) Patel	24.9 ± 2.3	25.5 ± 1.9
Simental-Mendia et al[133] (2019)	29.6 ± 5.9	31.5 ± 4.8

The average BMI of the study participants was 27.94 in the S-PRP group and 27.37 in the M-PRP group in the current study. Analogous verdicts were noted in the study conducted by by Uslu Guvendi et al in Turkey by 2018.[131]Corresponding findings were renowned in the study conducted by Kavadar et al in Turkey by 2015[132]. The backup results were observed in the recent study conducted by Simental Mentia et al., in Turkey in 2019.[133]

Comparison of other Baseline Characteristics of Participants

In this study, roughly 67.6% of the S-PRP group experienced complaints in the right knee, which is identical to the M-PRP group's 73.3 percent. In all groups, about two-thirds of the participants felt right knee pain. Only 14% of people had problems with both knees.

In contrast to our findings, a study conducted by Montaez-Heredia et al in Spain in 2016 found that patients had discomfort in both knees in approximately 25 of 53 instances (47.2 percent), however the treated knee had more severe pain. Symptoms were unilateral in 28 of 53 patients (52.8%).[134]

Around 73.5 percent of those in the S-PRP group were diagnosed with grade 2 osteoarthritis, which is identical to the 60 percent in the M-PRP group. The study only looked at people who were in the early stages of osteoarthritis. Nearly two-thirds of the patients had grade 2 osteoarthritis, which could be attributed to the fact that patients with grade 2 osteoarthritis have severe symptoms like pain and swelling, which can be addressed with oral analgesics.

Comparison of VAS between groups before and after intervention

In the S-PRP group, the mean pain scale was 6.68 at the time of pre-injection and was reduced to 2.68 at the end of 6 months. The mean pain scale in the M-PRP group was 7.83 at the time of pre-injection, but it was reduced to 2.07 after injection. At pre-injection, 6^{th} week, 3^{rd} month and 6^{th} month, the decreasing trend of pain, as indicated by VAS scale, was observed after intervention by S-PRP and Multiple-PRP injections, respectively. The Paired T test revealed that these differences were statistically significant.

The pain scale difference in the S-PRP group is 4 and, in the M-PRP group is 5.77 at the end of the 6^{th} month, and this difference in mean is statistically significant (P 0.001) using Independent T test. According to VAS pain scales, several PRP injections show a better response in pain reduction than a single PRP injection.

Despite the fact that a significant reduction in knee scores was observed within 6 months of therapy, it is thought that IA PRP treatment would be useful to patients in all phases of OA. Numerous PRP injections resulted in much improved clinical results in patients with early OA; it is predicted that multiple PRP injections for these patients would result in an effective therapy technique.

Comparison of Western Ontario and McMaster Universities Osteoarthritis Index between groups before and after intervention

When it comes to the WOMAC scale, the mean score of study participants at the time of pre-injection in the S-PRP group is 55.53, which drops to 26.8 in the end of sixth month, while the mean score in study participants of M-PRP group is 54.87, which drops to 24.6 in the end of the sixth month. The lowering trend was detected after S-PRP and Multiple-PRP injections at pre-injection, 6^{th} week, 3^{rd} month and 6^{th} month respectively, as determined by WOMAC score. The Paired T test revealed that these differences were statistically significant. The decrease in WOMAC score is due to the fact that both therapies improved the subjects' functional status by reducing pain. The significance of the correlation test between Pain and WOMAC score at pre-injection, 6^{th} week, 3^{rd} month and 6^{th} month can be demonstrated.

At the 6^{th} week of follow-up, the S-PRP group's mean WOMAC score was 45.26, whereas the M-PRP groups was 45.33. Using the independent T-test, the difference in means between 2 groups is not statistically significant ($p = 0.920$). In the third month of follow-up, the S-PRP group's mean score is 35.15, whereas the M-PRP group's is 36.10. Using the independent T-test, the difference in averages between 2 groups is not statistically significant ($p = 0.118$). As a result, there is no statistically significant

difference in the therapeutic response with PRP injection between the S-PRP and M-PRP groups based on the WOMAC score.

Similar articles supporting the result of present study

The study's most noteworthy finding was that numerous PRP injections improved clinical outcomes, particularly in individuals with early OA. A single injection, on the other hand, was resulted to be much less effective than two injections. During the follow-up period of this investigation, significant improvements in the VAS and WOMAC values of both groups were seen when compared to their pre-injection values. However, the WOMAC score revealed a U-shaped pattern.

However, Carlos et al., in their systematic review published in United States in 2016 found that PRP administered three times at weekly intervals to patients with grade 3 and 4 knee OA reported improved quality of life, reduced pain and increased cartilage thickness as measured by ultrasonography at the 6-month follow-up.[135]

Chouhan et al. conducted a controlled laboratory investigation on guinea pigs in India by 2019 that sheds light on the histology foundation for the superiority of numerous PRP injections. In the short term, single and multiple injections of PRP had equal anti-inflammatory effects on the synovium, according to the researchers. However, this impact is only long-lasting when numerous injections are given. Multiple PRP injections have a chondroprotective effect, but only for a brief period of time. A single dose injection of PRP does not produce this effect.[136]

Tavassoli et al., published a randomised controlled trial in Iran in 2019 that included 95 patients and found that two PRP injections were more effective at each follow-up than a single injection.[137]

Multiple successive intra-articular PRP injections may have favourable results in adult patients with mild to moderate knee OA at roughly 6 months, according to a systematic review by Khoshbin et al., in Canada in 2013.[138] Patients treated with PRP appear to have a higher rate of nonspecific adverse events.

Patel et al conducted a RCT in India by 2013 states that at 6 months following injection, there was no gross change in WOMAC scores of groups treated with 1 or 2 PRP injections. When compared to saline injections, single or double PRP injections in knees with mild or moderate OA generated better results.[104]

In another randomized controlled trial, Gormeli et al in Turkey by 2017 states when compared to a single injection of PRP or hyaluronic acid, knees treated with three injections of PRP had considerably superior pain and functional scores.[16]

In a randomized controlled trial comparing 1, 2, and 3 injections of PRP, Kavadar et al in Turkey by 2015 concluded that in terms of pain and functional scores at 6 months, 2 and 3 PRP injections were significantly superior than a single injection.[132]

Simental Mentia et al. conducted a RTC in 2019 that included single application (18 patients) and triple application (18 patients) (17 patients). At baseline, 6, 12, 24, 36, and 48 weeks after therapy, both groups were assessed using the Visual Analogue Scale (VAS), WOMAC score, and the Health Survey 12v2 (SF-12). They found out that, both treatments considerably reduced the level of pain (VAS) and total WOMAC scores.[133] When comparing the final results between groups, the triple application demonstrated a higher improvement in the VAS and overall WOMAC ratings. According to the aforementioned clinical trials, numerous PRP injections are either equal to or superior to a single PRP injection.

The anti-inflammatory impact of PRP is found to be one of the processes by which it can help in OA knee. The pro-inflammatory cytokines interleukin-1 beta and tumour

necrosis factor-alpha have been demonstrated to be reduced by PRP. PRP leukocytes are hypothesised to result in anti-inflammatory action, immunological modulation, and angiogenesis stimulation. As a result, more experimental and clinical research is needed to fully cognize molecular mechanism by which PRP protects against osteoarthritis.

At this time, we believe that the improvement in our patients is due to the fact that injected platelets may work on multiple levels and are not promoting chondral anabolism or slowing catabolic processes. Platelet-rich plasma may influence overall joint homeostasis by lowering synovial membrane hyperplasia and modifying cytokine levels, resulting in a temporary improvement in clinical outcome without changing cartilage tissue structure or joint degenerative development.

CONCLUSION

The most significant finding of this study was that multiple PRP injections resulted in improved clinical results, mainly in patients with early OA. Though, the effectiveness of a single injection was found to be significantly lesser than that of two injections. However, no significant differences were noticed in the WOMAC values. A significant effect was observed in the initial period after a single injection of PRP, but the effect diminished in a brief period with regards to functional status.

In patients with symptomatic knee Osteoarthritis, PRP injection results in significant clinical progresses up to 6 months post injection. Considering the evidence, this nominally invasive injection procedure seems to be reliable and helpful, and since PRP injections biologically transform the articular cartilage, they may be a useful treatment option in primary knee osteoarthritis.

Based on the evidence PRP is a valuable and trustworthy treatment for functional status and pain for Grade 1 & 2 OA, and a minimum of two injections appears to be suitable.

RECOMMENDATION

Further studies are needed to confirm the results obtained and their longevity to understand the mechanism of PRP action and to evaluate if there is only a temporary symptom improvement or if PRP plays a more important role through disease-modifying properties. Standardization of PRP dosing regimens also to be considered as a prime important component of the study.

Future studies can improve on looking at longer-term follow-ups of at least 2 years, including post-injection rehabilitation protocols, and providing adequate and consistent description of injection techniques used.

To our knowledge, there are no studies in the literature which have compared various doses of PRP administered to patients with grade 3 knee osteoarthritis. Hence Randomized controlled double blinding studies are needed in future.

This study recommends 2 or more PRP injections for patients with early and moderate knee OA, and physicians decisions should be based on various factors such as the level of pain, level of activity, cost-effectiveness, and BMI. We further speculate that repeating the application after 6 months may further relieve symptoms for a longer period and delay OA progression.

LIMITATION

- This study comprised less bilateral knee OA, and randomization of patients was conducted rather than randomization of knees. It would have been better if knees were randomized and the same patient would have received different treatments in his or her 2 knees, but it would have made the procedure cumbersome, and there were patient-blinding issues.
- The primary imperatives of a new therapy remain the control of symptoms; because pain with daily activities is the most pressing problem in OA, this study evaluated only clinical parameters by using the WOMAC and VAS scoring systems.
- Radiographic follow-up investigation methods such as magnetic resonance imaging may be considered for evaluating cartilage regeneration (if any) in subsequent research efforts; These measurements were not taken up because of the cost and ethical issues.
- It's a single blinded study, could have done with double or triple blinding
- Longer-term follow-ups of up to 2 years will provide a better sense of the long-term benefits.
- Comparison with controls with no intervention or other groups receiving other treatments options like HA injections would have yield better results. Increasing the sample size would produce better results.

SUMMARY

- Osteoarthritis of the knee is a major issues that elderly adults face and to lessen the pain, morbidity associated with OA, physicians and orthopaedician around the world have tried a wide range of non-operative treatment modalities like oral chondro-protectives, intra-articular steroids and visco-supplements.
- Platelet-rich plasma is an autologous blood component with a triple concentration of platelets that is used to treat bone, tendon and ligament injuries in orthopaedic as well as in sports medicine practises.
- There is ambiguity on how many injections? How frequently can be administered for optimal efficiency, as well as the best treatment for various stages of gonarthrosis
- The purpose of this literature is to determine whether single IA-PRP injection when compared with multiple IA-PRP injections given in the early stages of osteoarthritis of the knee has better functional outcome when measured using WOMAC Score and for reduction in pain which is measured by VAS scale at 6^{th} week, 3^{rd} month and 6^{th} month.
- The comparative study was conducted among patients diagnosed with early osteoarthritis presented to department of Orthopaedics, in our tertiary care centre during the period, between January 2020 and June 2021.
- The Patients were divided into two groups, Group 1 (34 samples) received single intra-articular Platelet-rich plasma injection(S-PRP) and patients in group II (30 samples) received 2 intra-articular Platelet-rich plasma injections(M-PRP) on presentation and on 3^{rd} month.

- Visual Analogue Scale to measure pain and WOMAC Score to assess functional status was used at first visit before intervention and 6^{th} week, 3^{rd} month and 6^{th} month after intervention.
- The average age of the participants in the current study was 55.26 years in the S-PRP group and 51.13 years in the M-PRP group, with standard deviations of 4.8 and 7.4 years, respectively.
- Among the study participants, about 66 percent were females and the remaining were males.
- In all groups, about two-thirds of the participants felt right knee pain. Only 14% of people had problems with both knees.
- At the end of 6^{th} month, the mean pain scale in S-PRP group is 4 and in M-PRP group is 5.77 and this difference in mean is statistically significant ($P < 0.001$). Thus, multiple PRP injection have greater response in reduction of pain when compared to single PRP injection according to VAS pain scale score.
- The mean score by using the WOMAC Score in the S-PRP group is 45.26 and M-PRP group is 45.33 at the 6th week of follow-up. This difference of means in both groups is not statistically significant ($p = 0.920$) by using the independent T-test. Thus, according to the WOMAC Score, there is no statistically significant difference in the treatment response with PRP injection between S-PRP and M-PRP groups.
- The lowering trend was detected after S-PRP and Multiple-PRP injections at pre-injection, 6^{th} week, 3^{rd} month and 6^{th} month respectively, as determined by WOMAC score. The Paired T test revealed that these differences were statistically significant.

- The decrease in WOMAC score is due to the fact that both therapies improved the subject's functional status by reducing pain. The significance of the correlation test between Pain and WOMAC score at pre-injection, 6^{th} week, 3^{rd} month and 6^{th} month can be demonstrated.
- Intra-articular Platelet-rich plasma injection is a valuable and trustworthy treatment for improvement functional status and reduction in pain for Grade 1 and 2 Osteoarthritis up to 6 months post injection, and a minimum of two injections appears to be suitable.

REFERENCES

1. Pal C, Singh P, Chaturvedi S, Pruthi K, Vij A, Chandra Prakash P, et al. Epidemiology of knee osteoarthritis in India and related factors. Indian J Orthop. 2016 Sep 1;50(5):518–22.
2. Akinpelu A, Alonge T, Adekanla B, Odole A. Prevalence and Pattern of Symptomatic Knee Osteoarthritis in Nigeria: A Community-Based Study. Internet J Allied Heal Sci Pract. 2009;7(3):1–7.
3. Davis M, Ettinger W, Neuhaus J, Hauck W. Sex differences in osteoarthritis of the knee. The role of obesity. Am J Epidemiol. 1988;127(5):1019–30.
4. Roemer F, Kwoh C, Hayashi D, Felson D, Guermazi A. The role of radiography and MRI for eligibility assessment in DMOAD trials of knee OA. Nat Rev Rheumatol. 2018 Jun 1;14(6):372–80.
5. Malfait A-M, Tortorella MD. The "elusive DMOAD": Aggrecanase inhibition from laboratory to clinic. Clin Exp Rheumatol. 2019;37 Suppl 1(5):130–4.
6. Castrogiovanni P, Di Rosa M, Ravalli S, Castorina A, Guglielmino C, Imbesi R, et al. Moderate Physical Activity as a Prevention Method for Knee Osteoarthritis and the Role of Synoviocytes as Biological Key. Int J Mol Sci. 2019 Jan;20(3):1–18.
7. Roman-Blas JA, Bizzi E, Largo R, Migliore A, Herrero-Beaumont G. An update on the up and coming therapies to treat osteoarthritis, a multifaceted disease. Expert Opin Pharmacother. 2016 Sep;17(13):1745–56.
8. Rezuș E, Cardoneanu A, Burlui A, Luca A, Codreanu C, Tamba BI, et al. The Link Between Inflammaging and Degenerative Joint Diseases. Int J Mol Sci. 2019 Jan;20(3):1–20.
9. Martel-Pelletier J, Raynauld J-P, Mineau F, Abram F, Paiement P, Delorme P,

et al. Levels of serum biomarkers from a two-year multicentre trial are associated with treatment response on knee osteoarthritis cartilage loss as assessed by magnetic resonance imaging: an exploratory study. Arthritis Res Ther. 2017 Jul;19(1):169.

10. Rezuş E, Burlui A, Cardoneanu A, Macovei LA, Tamba BI, Rezuş C. From Pathogenesis to Therapy in Knee Osteoarthritis: Bench-to-Bedside. Int J Mol Sci. 2021 Mar 1;22(5):1–24.
11. Dhillon M, Patel S, John R. PRP in OA knee - update, current confusions and future options. SICOT-J. 2017;3:27.
12. Lopez-Vidriero E, Goulding KA, Simon DA, Sanchez M, Johnson DH. The use of platelet-rich plasma in arthroscopy and sports medicine: optimizing the healing environment. Arthrosc J Arthrosc Relat Surg Off Publ Arthrosc Assoc North Am Int Arthrosc Assoc. 2010 Feb;26(2):269–78.
13. Sundman EA, Cole BJ, Fortier LA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. Am J Sports Med. 2011 Oct;39(10):2135–40.
14. Filardo G, Kon E, Di Martino A, Di Matteo B, Merli ML, Cenacchi A, et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. BMC Musculoskelet Disord. 2012 Nov;13:229.
15. Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthrosc J Arthrosc Relat Surg Off Publ Arthrosc Assoc North Am Int Arthrosc Assoc. 2011 Nov;27(11):1490–501.

16. Görmeli G, Görmeli CA, Ataoglu B, Çolak C, Aslantürk O, Ertem K. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. Knee Surgery, Sport Traumatol Arthrosc. 2017 Mar 1;25(3):958–65.

17. Prieto-Alhambra D, Judge A, Javaid MK, Cooper C, Diez-Perez A, Arden NK. "Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints." Ann Rheum Dis. 2014;73(9):1659.

18. Hunter D, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. Nat Rev Rheumatol. 2014;10(7):437–41.

19. Carlson AK, Rawle RA, Wallace CW, Brooks EG, Adams E, Greenwood MC, et al. Characterization of synovial fluid metabolomic phenotypes of cartilage morphological changes associated with osteoarthritis. Osteoarthr Cartil. 2019 Aug 1;27(8):1174.

20. Nguyen U-SDT, Zhang Y, Zhu Y, Niu J, Zhang B, Aliabadi P, et al. Increasing Prevalence of Knee Pain and Symptomatic Knee Osteoarthritis. Ann Intern Med. 2011;155(11):725.

21. Hunter DJ,Bierma-Zeinstra S Osteoarthritis.Lancet. 2019;393(10182):1745–59.

22. Zhang Y, Jordan JM. Epidemiology of Osteoarthritis. Clin Geriatr Med. 2010 Aug;26(3):355.

23. Collaborators G 2015 D and II and P. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet (London, England). 2016 Oct 8;388(10053):1545.

24. Flandry F, Hommel G. Normal anatomy and biomechanics of the knee. Sports

Med Arthrosc. 2011;19(2):82–92.

25. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ. 2003;81(9):646–56.

26. Sinusas K. Osteoarthritis: Diagnosis and Treatment. Am Fam Physician. 2012 Jan 1;85(1):49–56.

27. Hunter D, Pietro-Alhambra D, Arden N. Osteoarthritis: the facts. 2nd editio. USA: Oxford: Oxford University Press; 2014. 208 p.

28. Fu K, Robbins SR, McDougall JJ. Osteoarthritis: the genesis of pain. Rheumatology. 2018;57(suppl_4):iv43–50.

29. Loeser RF, Collins JA, Diekman BO. Ageing and the pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2016;12(7):412–20.

30. Hsia AW, Emami AJ, Tarke FD, Cunningham HC, Tjandra PM, Wong A, et al. Osteophytes and fracture calluses share developmental milestones and are diminished by unloading. J Orthop Res. 2018;36(2):699–710.

31. Glyn-Jones S, Palmer AJR, Agricola R, Price AJ, Vincent TL, Weinans H, et al. Osteoarthritis. Lancet. 2015;386(9991):376–87.

32. Deveza LA, Loeser RF. Is osteoarthritis one disease or a collection of many? Rheumatology. 2018;57(suppl_4):iv34–42.

33. Scanzello CR. Role of low-grade inflammation in osteoarthritis. Curr Opin Rheumatol. 2017;29(1):79–85.

34. Bierma-Zeinstra SM, Van Middelkoop M. In search of phenotypes. Nat Rev Rheumatol. 2017;13(12):705–6.

35. Courties A, Sellam J, Berenbaum F. Metabolic syndrome-associated osteoarthritis. Curr Opin Rheumatol. 2017;29(2):214–22.

36. Jeon OH, Kim C, Laberge R-M, Demaria M, Rathod S, Vasserot AP, et al.

Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment. Nat Med. 2017;23(6):775–81.

37. Kohn MD, Sassoon AA, Fernando ND. Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. Clin Orthop Relat Res. 2016;474(8):1886–93.

38. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957 Dec;16(4):494–502.

39. Nelson AE. Osteoarthritis year in review 2017: clinical. Osteoarthr Cartil. 2018 Mar 1;26(3):319–25.

40. Atukorala I, Makovey J, Lawler L, Messier SP, Bennell K, Hunter DJ. Is there a dose response relationship between weight loss and symptom improvement in persons with knee osteoarthritis? Arthritis Care Res (Hoboken). 2016;68(8):1106–14.

41. King WC, Chen J-Y, Belle SH, Courcoulas AP, Dakin GF, Elder KA, et al. Change in pain and physical function following bariatric surgery for severe obesity. Jama. 2016;315(13):1362–71.

42. Bartels EM, Juhl CB, Christensen R, Hagen KB, Danneskiold Samsae B, Dagfinrud H, et al. Aquatic exercise for the treatment of knee and hip osteoarthritis. Cochrane Database Syst Rev. 2016;(3):CD005523.

43. Sihvonen R, Englund M, Turkiewicz A, Jarvinen TLN. Mechanical symptoms and arthroscopic partial meniscectomy in patients with degenerative meniscus tear: a secondary analysis of a randomized trial. Ann Intern Med. 2016;164(7):449–55.

44. Nissen SE, Yeomans ND, Solomon DH, Lascher TF, Libby P, Husni ME, et al.

Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med. 2016;375:2519–29.

45. Da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jani P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet. 2017;390(10090):e21–33.

46. Moore N, Salvo F, Duong M, Gulmez SE. Does paracetamol still have a future in osteoarthritis? Lancet (London, England). 2016 May;387(10033):2065–6.

47. Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet (London, England). 2013;382(9894):769–79.

48. Essex MN, O'connell MA, Behar R, Bao W. Efficacy and safety of nonsteroidal anti inflammatory drugs in Asian patients with knee osteoarthritis: summary of a randomized, placebo controlled study. Int J Rheum Dis. 2016;19(3):262–70.

49. Vanderstraeten G, Lejeune T, Piessevaux H, De Bacquer D, Walker C, De Beleyr B. Gastrointestinal risk assessment in patients requiring non-steroidal anti-inflammatory drugs for osteoarthritis: the GIRANO study. J Rehabil Med. 2016;48(8):705–10.

50. Derry S, Conaghan P, Da Silva JAP, Wiffen PJ, Moore RA. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev. 2016;4(4):CD007400.

51. Yataba I, Otsuka N, Matsushita I, Matsumoto H, Hoshino Y. Efficacy of S-flurbiprofen plaster in knee osteoarthritis treatment: Results from a phase III,

randomized, active-controlled, adequate, and well-controlled trial. Mod Rheumatol. 2017 Jan;27(1):130–6.

52. Arden NK, Cro S, Sheard S, Doré CJ, Bara A, Tebbs SA, et al. The effect of vitamin D supplementation on knee osteoarthritis, the VIDEO study: a randomised controlled trial. Osteoarthr Cartil. 2016 Nov;24(11):1858–66.

53. Peluso R, Caso F, Costa L, Sorbo D, Carraturo N, Di Minno MND, et al. Mud-bath therapy and oral glucosamine sulfate in patients with knee osteoarthritis: a randomized, controlled, crossover study. Clin Exp Rheumatol. 2016;34(4):618–24.

54. Tsuji T, Yoon J, Kitano N, Okura T, Tanaka K. Effects of N-acetyl glucosamine and chondroitin sulfate supplementation on knee pain and self-reported knee function in middle-aged and older Japanese adults: a randomized, double-blind, placebo-controlled trial. Aging Clin Exp Res. 2016 Apr;28(2):197–205.

55. Stebbings S, Beattie E, McNamara D, Hunt S. A pilot randomized, placebo-controlled clinical trial to investigate the efficacy and safety of an extract of Artemisia annua administered over 12 weeks, for managing pain, stiffness, and functional limitation associated with osteoarthritis of the hip an. Clin Rheumatol. 2016 Jul;35(7):1829–36.

56. Hunt S, Stebbings S, McNamara D. An open-label six-month extension study to investigate the safety and efficacy of an extract of Artemisia annua for managing pain, stiffness and functional limitation associated with osteoarthritis of the hip and knee. N Z Med J. 2016 Oct;129(1444):97–102.

57. Kasemsuk T, Saengpetch N, Sibmooh N, Unchern S. Improved WOMAC score following 16-week treatment with bromelain for knee osteoarthritis. Clin

Rheumatol. 2016 Oct;35(10):2531–40.

58. McCabe PS, Maricar N, Parkes MJ, Felson DT, O'Neill TW. The efficacy of intra-articular steroids in hip osteoarthritis: a systematic review. Osteoarthr Cartil. 2016 Sep;24(9):1509–17.

59. Van Middelkoop M, Arden NK, Atchia I, Birrell F, Chao J, Rezende MU, et al. The OA Trial Bank: meta-analysis of individual patient data from knee and hip osteoarthritis trials show that patients with severe pain exhibit greater benefit from intra-articular glucocorticoids. Osteoarthr Cartil. 2016 Jul;24(7):1143–52.

60. Zhang Q, Zhang T. Effect on Pain and Symptoms of Aspiration Before Hyaluronan Injection for Knee Osteoarthritis: A Prospective, Randomized, Single-blind Study. Am J Phys Med Rehabil. 2016 May;95(5):366–71.

61. Altman R, Fredericson M, Bhattacharyya SK, Bisson B, Abbott T, Yadalam S, et al. Association between Hyaluronic Acid Injections and Time-to-Total Knee Replacement Surgery. J Knee Surg. 2016 Oct;29(7):564–70.

62. Weick JW, Bawa HS, Dirschl DR. Hyaluronic Acid Injections for Treatment of Advanced Osteoarthritis of the Knee: Utilization and Cost in a National Population Sample. J Bone Joint Surg Am. 2016 Sep;98(17):1429–35.

63. Tammachote N, Kanitnate S, Yakumpor T, Panichkul P. Intra-Articular, Single-Shot Hylan G-F 20 Hyaluronic Acid Injection Compared with Corticosteroid in Knee Osteoarthritis: A Double-Blind, Randomized Controlled Trial. J Bone Joint Surg Am. 2016 Jun;98(11):885–92.

64. Bisicchia S, Bernardi G, Tudisco C. HYADD 4 versus methylprednisolone acetate in symptomatic knee osteoarthritis: a single-centre single blind prospective randomised controlled clinical study with 1-year follow-up. Clin Exp Rheumatol. 2016;34(5):857–63.

65. Rivera F. Single intra-articular injection of high molecular weight hyaluronic acid for hip osteoarthritis. J Orthop Traumatol Off J Ital Soc Orthop Traumatol. 2016 Mar;17(1):21–6.

66. Rivera F, Bertignone L, Grandi G, Camisassa R, Comaschi G, Trentini D, et al. Effectiveness of intra-articular injections of sodium hyaluronate-chondroitin sulfate in knee osteoarthritis: a multicenter prospective study. J Orthop Traumatol Off J Ital Soc Orthop Traumatol. 2016 Mar;17(1):27–33.

67. Martin Martin LS, Massafra U, Bizzi E, Migliore A. A double blind randomized active-controlled clinical trial on the intra-articular use of Md-Knee versus sodium hyaluronate in patients with knee osteoarthritis ("Joint"). BMC Musculoskelet Disord. 2016 Feb;17:94.

68. Benazzo F, Perticarini L, Padolino A, Castelli A, Gifuni P, Lovato M, et al. A multi-centre, open label, long-term follow-up study to evaluate the benefits of a new viscoelastic hydrogel (Hymovis®) in the treatment of knee osteoarthritis. Eur Rev Med Pharmacol Sci. 2016 Mar;20(5):959–68.

69. Xin Y, Jianhao L, Tiansheng S, Yongqiang H, Weimin F, Ming C, et al. The efficacy and safety of sodium hyaluronate injection (Adant®) in treating degenerative osteoarthritis: a multi-center, randomized, double-blind, positive-drug parallel-controlled and non-inferiority clinical study. Int J Rheum Dis. 2016 Mar;19(3):271–8.

70. Dahlberg LE, Aydemir A, Muurahainen N, Gühring H, Fredberg Edebo H, Krarup-Jensen N, et al. A first-in-human, double-blind, randomised, placebo-controlled, dose ascending study of intra-articular rhFGF18 (sprifermin) in patients with advanced knee osteoarthritis. Clin Exp Rheumatol. 2016;34(3):445–50.

71. Pers Y-M, Rackwitz L, Ferreira R, Pullig O, Delfour C, Barry F, et al. Adipose Mesenchymal Stromal Cell-Based Therapy for Severe Osteoarthritis of the Knee: A Phase I Dose-Escalation Trial. Stem Cells Transl Med. 2016 Jul;5(7):847–56.

72. Simental-Mendía M, Vílchez-Cavazos JF, Peña-Martínez VM, Said-Fernández S, Lara-Arias J, Martínez-Rodríguez HG. Leukocyte-poor platelet-rich plasma is more effective than the conventional therapy with acetaminophen for the treatment of early knee osteoarthritis. Arch Orthop Trauma Surg. 2016 Dec;136(12):1723–32.

73. Smith PA. Intra-articular Autologous Conditioned Plasma Injections Provide Safe and Efficacious Treatment for Knee Osteoarthritis: An FDA-Sanctioned, Randomized, Double-blind, Placebo-controlled Clinical Trial. Am J Sports Med. 2016 Apr;44(4):884–91.

74. Forogh B, Mianehsaz E, Shoaee S, Ahadi T, Raissi GR, Sajadi S. Effect of single injection of platelet-rich plasma in comparison with corticosteroid on knee osteoarthritis: a double-blind randomized clinical trial. J Sports Med Phys Fitness. 2016;56(7–8):901–8.

75. Dallari D, Stagni C, Rani N, Sabbioni G, Pelotti P, Torricelli P, et al. Ultrasound-guided injection of platelet-rich plasma and hyaluronic acid, separately and in combination, for hip osteoarthritis: a randomized controlled study. Am J Sports Med. 2016;44(3):664–71.

76. Andia I, Abate M. Platelet-rich plasma: underlying biology and clinical correlates. Regen Med. 2013 Sep;8(5):645–58.

77. Alves R, Grimalt R. A Review of Platelet-Rich Plasma: History, Biology, Mechanism of Action, and Classification. Ski Appendage Disord. 2018 Jan

1;4(1):18–24.

78. Conde Montero E, Fernández Santos M, Suárez Fernández R. Platelet-rich plasma: applications in dermatology. Actas Dermosifiliogr. 2015 Mar 1;106(2):104–11.

79. Lynch M, Bashir S. Applications of platelet-rich plasma in dermatology: A critical appraisal of the literature. J Dermatolog Treat. 2016 May 3;27(3):285–9.

80. Andia I, Rubio-Azpeitia E, Martin JI, Abate M. Current Concepts and Translational Uses of Platelet Rich Plasma Biotechnology. In: Biotechnology. Barakaldo, Spain: IntechOpen; 2015.

81. Li Z, Choi H, Choi D, Sohn K, Im M, Seo Y, et al. Autologous platelet-rich plasma: a potential therapeutic tool for promoting hair growth. Dermatol Surg. 2012 Jul;38(7 Pt 1):1040–6.

82. Sommeling C, Heyneman A, Hoeksema H, Verbelen J, Stillaert F, Monstrey S. The use of platelet-rich plasma in plastic surgery: a systematic review. J Plast Reconstr Aesthet Surg. 2013 Mar;66(3):301–11.

83. Picard F, Hersant B, Bosc R, Meningaud J. Should we use platelet-rich plasma as an adjunct therapy to treat “acute wounds,” “burns,” and “laser therapies”: A review and a proposal of a quality criteria checklist for further studies. Wound Repair Regen. 2015 Mar 1;23(2):163–70.

84. Cobos R, Aizpuru F, Parraza N, Anitua E, Orive G. Effectiveness and efficiency of platelet rich plasma in the treatment of diabetic ulcers. Curr Pharm Biotechnol. 2015 May 6;16(7):630–4.

85. Sclafani A, Azzi J. Platelet Preparations for Use in Facial Rejuvenation and Wound Healing: A Critical Review of Current Literature. Aesthetic Plast Surg.

2015 Aug 25;39(4):495–505.

86. Kim D, Je Y, Kim C, Lee Y, Seo Y, Lee J, et al. Can Platelet-rich Plasma Be Used for Skin Rejuvenation? Evaluation of Effects of Platelet-rich Plasma on Human Dermal Fibroblast. Ann Dermatol. 2011;23(4):424–31.

87. Dhillon MS, Patel S, Bansal T. Improvising PRP for use in osteoarthritis knee-upcoming trends and futuristic view. J Clin Orthop Trauma. 2019 Jan 1;10(1):32–5.

88. Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA. Platelet-rich plasma: a milieu of bioactive factors. Arthrosc J Arthrosc Relat Surg Off Publ Arthrosc Assoc North Am Int Arthrosc Assoc. 2012 Mar;28(3):429–39.

89. Akeda K, An HS, Okuma M, Attawia M, Miyamoto K, Thonar EJ-MA, et al. Platelet-rich plasma stimulates porcine articular chondrocyte proliferation and matrix biosynthesis. Osteoarthr Cartil. 2006 Dec;14(12):1272–80.

90. Pereira RC, Scaranari M, Benelli R, Strada P, Reis RL, Cancedda R, et al. Dual effect of platelet lysate on human articular cartilage: a maintenance of chondrogenic potential and a transient proinflammatory activity followed by an inflammation resolution. Tissue Eng Part A. 2013 Jun;19(11–12):1476–88.

91. Park S-I, Lee H-R, Kim S, Ahn M-W, Do SH. Time-sequential modulation in expression of growth factors from platelet-rich plasma (PRP) on the chondrocyte cultures. Mol Cell Biochem. 2012 Feb;361(1–2):9–17.

92. Yang SY, Ahn ST, Rhie JW, Lee KY, Choi JH, Lee BJ, et al. Platelet supernatant promotes proliferation of auricular chondrocytes and formation of chondrocyte mass. Ann Plast Surg. 2000 Apr;44(4):405–11.

93. Spreafico A, Chellini F, Frediani B, Bernardini G, Niccolini S, Serchi T, et al. Biochemical investigation of the effects of human platelet releasates on human

articular chondrocytes. J Cell Biochem. 2009 Dec;108(5):1153–65.

94. Gaissmaier C, Fritz J, Krackhardt T, Flesch I, Aicher WK, Ashammakhi N. Effect of human platelet supernatant on proliferation and matrix synthesis of human articular chondrocytes in monolayer and three-dimensional alginate cultures. Biomaterials. 2005 May;26(14):1953–60.

95. Anitua E, Sánchez M, Nurden AT, Zalduendo MM, de la Fuente M, Azofra J, et al. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts from arthritic patients. Rheumatology (Oxford). 2007 Dec;46(12):1769–72.

96. Sundman EA, Cole BJ, Karas V, Della Valle C, Tetreault MW, Mohammed HO, et al. The anti-inflammatory and matrix restorative mechanisms of platelet-rich plasma in osteoarthritis. Am J Sports Med. 2014 Jan;42(1):35–41.

97. Yin Z, Yang X, Jiang Y, Xing L, Xu Y, Lu Y, et al. Platelet-rich plasma combined with agarose as a bioactive scaffold to enhance cartilage repair: an in vitro study. J Biomater Appl. 2014 Mar;28(7):1039–50.

98. Mifune Y, Matsumoto T, Takayama K, Ota S, Li H, Meszaros LB, et al. The effect of platelet-rich plasma on the regenerative therapy of muscle derived stem cells articular cartilage repair. Osteoarthr Cartil. 2013 Jan;21(1):175–85.

99. Van Buul GM, Koevoet WLM, Kops N, Bos PK, Verhaar JAN, Weinans H, et al. Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes. Am J Sports Med. 2011 Nov;39(11):2362–70.

100. Bendinelli P, Matteucci E, Dogliotti G, Corsi MM, Banfi G, Maroni P, et al. Molecular basis of anti-inflammatory action of platelet-rich plasma on human chondrocytes: mechanisms of NF-κB inhibition via HGF. J Cell Physiol. 2010 Nov;225(3):757–66.

101. Wu C-C, Chen W-H, Zao B, Lai P-L, Lin T-C, Lo H-Y, et al. Regenerative potentials of platelet-rich plasma enhanced by collagen in retrieving pro-inflammatory cytokine-inhibited chondrogenesis. Biomaterials. 2011 Sep;32(25):5847–54.

102. Lee H-R, Park KM, Joung YK, Park KD, Do SH. Platelet-rich plasma loaded hydrogel scaffold enhances chondrogenic differentiation and maturation with up-regulation of CB1 and CB2. J Control Release. 2012 May;159(3):332–7.

103. Anitua E, Sanchez M, Orive G, Andia I. The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. Biomaterials. 2007;28(31):4551–60.

104. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: A prospective, double-blind, randomized trial. Am J Sports Med. 2013 Feb;41(2):356–64.

105. Kon E, Buda R, Filardo G, Di Martino A, Timoncini A, Cenacchi A, et al. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. Knee Surg Sports Traumatol Arthrosc. 2010 Apr;18(4):472–9.

106. Mishra A, Harmon K, Woodall J, Vieira A. Sports medicine applications of platelet rich plasma. Curr Pharm Biotechnol. 2012 Jun;13(7):1185–95.

107. DeLong JM, Russell RP, Mazzocca AD. Platelet-rich plasma: the PAW classification system. Arthrosc J Arthrosc Relat Surg Off Publ Arthrosc Assoc North Am Int Arthrosc Assoc. 2012 Jul;28(7):998–1009.

108. Arnoczky SP, Delos D, Rodeo SA. What is platelet-rich plasma? Oper Tech Sports Med. 2011;19(3):142–8.

109. Busilacchi A, Gigante A, Mattioli-Belmonte M, Manzotti S, Muzzarelli RAA. Chitosan stabilizes platelet growth factors and modulates stem cell differentiation tissue regeneration.Carbohydr Polym.2013;98(1):665–76.

110. Kutlu B, Ti l Ayd n RS, Akman AC, Gama derelioglu M e, Nohutcu RM. Platelet rich plasma loaded chitosan scaffolds: Preparation and growth factor release kinetics. Biomed Mater Res Part B Appl Biomater. 2013;101(1):28–35.

111. Saito M, Takahashi KA, Arai E, Inoue A, Sakao K, Tonomura H, et al. Intra-articular administration of platelet-rich plasma with biodegradable gelatin hydrogel microspheres prevents osteoarthritis progression in the rabbit knee. Clin Exp Rheumatol. 2009;27(2):201.

112. Magalon J, Bausset O, Serratrice N, Giraudo L, Aboudou H, Veran J, et al. Characterization and comparison of 5 platelet-rich plasma preparations in a single-donor model. Arthrosc J Arthrosc Relat Surg. 2014;30(5):629–38.

113. Mazzocca AD, McCarthy MBR, Chowaniec DM, Cote MP, Romeo AA, Bradley JP, et al. Platelet-rich plasma differs according to preparation method and human variability. JBJS. 2012;94(4):308–16.

114. Blajchman MA. Novel platelet products, substitutes and alternatives. Transfus Clin Biol. 2001;8(3):267–71.

115. Roffi A, Filardo G, Assirelli E, Cavallo C, Cenacchi A, Facchini A, et al. Does platelet-rich plasma freeze-thawing influence growth factor release and their effects on chondrocytes and synoviocytes? Biomed Res Int. 2014;2014:692913.

116. Cerza F, Carna S, Carcangiu A, Di Vavo I, Schiavilla V, Pecora A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. Am J Sports Med. 2012;40(12):2822–7.

117. Filardo G, Kon E, Buda R, Timoncini A, Di Martino A, Cenacchi A, et al. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. Knee Surgery, Sport Traumatol Arthrosc. 2011;19(4):528–35.

118. Filardo G, Di Matteo B, Di Martino A, Merli ML, Cenacchi A, Fornasari P, et al. Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: a randomized controlled trial. Am J Sports Med. 2015;43(7):1575–82.

119. Sanchez M, Fiz N, Azofra J, Usabiaga J, Recalde EA, Gutierrez AG, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. Arthrosc J Arthrosc Relat Surg. 2012;28(8):1070–8.

120. Ming L, Zhang C, Ai Z, Yuan T, Feng Y, Jia W. Therapeutic effectiveness of intra-knee-articular injection of platelet-rich plasma on knee articular cartilage degeneration. Zhongguo xiu fu chong jian wai ke za zhi= Zhongguo xiufu chongjian waike zazhi= Chinese J reparative Reconstr Surg. 2011;25(10):1192–6.

121. Say F, Galer D, Yener K, Balbal M, Malkoa M. Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. Acta Chir Orthop Traumatol Cech. 2013;80(4):278–83.

122. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res. 2020 Feb 1;72(2):149–62.

123. Gobbi A, Lad D, Karnatzikos G. The effects of repeated intra-articular PRP

injections on clinical outcomes of early osteoarthritis of the knee. Knee Surgery, Sport Traumatol Arthrosc. 2015;23(8):2170–7.

124. Hart R, Safi A, Komzak M, Jajtner P, Puskeiler M, Hartova P. Platelet-rich plasma in patients with tibiofemoral cartilage degeneration. Arch Orthop Trauma Surg. 2013;133(9):1295–301.

125. Hassan AS, El-Shafey AM, Ahmed HS, Hamed MS. Effectiveness of the intra-articular injection of platelet rich plasma in the treatment of patients with primary knee osteoarthritis. Egypt Rheumatol. 2015;37(3):119–24.

126. Sanchez M, Fiz N, Guadilla J, Padilla S, Anitua E, Sanchez P, et al. Intraosseous infiltration of platelet-rich plasma for severe knee osteoarthritis. Arthrosc Tech. 2014;3(6):e713–7.

127. Paterson KL, Nicholls M, Bennell KL, Bates D. Intra-articular injection of photo-activated platelet-rich plasma in patients with knee osteoarthritis: a double-blind, randomized controlled pilot study. BMC Musculoskelet Disord. 2016;17(1):1–9.

128. Sanchez M, Guadilla J, Fiz N, Andia I. Ultrasound-guided platelet-rich plasma injections for the treatment of osteoarthritis of the hip. Rheumatology. 2012;51(1):144–50.

129. Battaglia M, Guaraldi F, Vannini F, Rossi G, Timoncini A, Buda R, et al. Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritisOrthopedics. 2013;36(12):e1501–8.

130. Mei-Dan O, Carmont MR, Laver L, Mann G, Maffulli N, Nyska M. Platelet-rich plasma or hyaluronate in the management of osteochondral lesions of the talus. Am J Sports Med. 2012;40(3):534–41.

131. Uslu Güvendi E, Aşkin A, Güvendi G, Koçyiğit H. Comparison of efficiency

between corticosteroid and platelet rich plasma injection therapies in patients with knee osteoarthritis. Arch Rheumatol. 2018;33(3):273–81.

132. Kavadar G, Demircioglu DT, Celik MY, Emre TY. Effectiveness of platelet-rich plasma in the treatment of moderate knee osteoarthritis: A randomized prospective study. J Phys Ther Sci. 2015;27(12):3863–7.

133. Simental-Mendía M, Acosta-Olivo CA, Hernández-Rodríguez AN, Santos-Santos OR, de la Garza-Castro S, Peña-Martínez VM, et al. Intraarticular injection of platelet-rich plasma in knee osteoarthritis: single versus triple application approach. Pilot study. Acta Reumatol Port. 2019;44(2):138–44.

134. Montañez-Heredia E, Irízar S, Huertas PJ, Otero E, Del Valle M, Prat I, et al. Intra-articular injections of platelet-rich plasma versus hyaluronic acid in the treatment of osteoarthritic knee pain: A randomized clinical trial in the context of the Spanish national health care system. Int J Mol Sci. 2016 Jul 2;17(7):1064.

135. Meheux CJ, McCulloch PC, Lintner DM, Varner KE, Harris JD. Efficacy of Intra-articular Platelet-Rich Plasma Injections in Knee Osteoarthritis: A Systematic Review. Arthrosc - J Arthrosc Relat Surg. 2016 Mar 1;32(3):495–505.

136. Chouhan DK, Dhillon MS, Patel S, Bansal T, Bhatia A, Kanwat H. Multiple Platelet-Rich Plasma Injections Versus Single Platelet-Rich Plasma Injection in Early Osteoarthritis of the Knee: An Experimental Study in a Guinea Pig Model of Early Knee Osteoarthritis. Am J Sports Med. 2019;47(10):2300–7.

137. Tavassoli M, Janmohammadi N, Hosseini A, Khafri S, Esmaeilnejad-Ganji SM. Single-and double-dose of platelet-rich plasma versus hyaluronic acid for treatment of knee osteoarthritis: A randomized controlled trial. World J Orthop.

2019;10(9):311–26.

138. Khoshbin A, Leroux T, Wasserstein D, Marks P, Theodoropoulos J, Ogilvie-Harris D, et al. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: A systematic review with quantitative synthesis. Arthrosc - J Arthrosc Relat Surg. 2013;29(12):2037–48.

ANNEXURES

Study Tools

1.Visual Analogue Scale

An instrument used to support a person to rate the intensity of certain sensations and feelings such as pain. The Visual Analogue Scale for pain is a straight line with one end (0) denoting no pain and the other end (10) denoting worst pain imaginable as cited in Annexure. A patient marks a point on the line that matches the quantity of pain he/she senses.

2. Western Ontario and McMaster Universities Osteoarthritis Index

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is extensively employed in the assessment of Hip as well as Knee Osteoarthritis. This questionnaire entailing of 24 items split into 3 subscales:

- Pain (5 items): during walking, using stairs, in bed, sitting or lying and standing upright
- Stiffness (2 items): after first waking and later in the day
- Physical Function (17 items): using stairs, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy domestic duties, light domestic duties

WOMAC Index was developed in 1982 at Western Ontario and McMaster Universities. WOMAC is obtainable in over 65 languages and has been lingually validated.

The WOMAC takes about 12 minutes to complete. The test questions are scored on a scale of 0-4, which parallel to: None (0), Mild (1), Moderate (2), Severe (3) and Extreme (4).

The counts for each subscale are totalled up, with a likely score range of 0-20 for Pain, 0-8 for Stiffness, and 0-68 for Physical Function. Generally, a sum of the scores for all three subscales devotes a total WOMAC score. Higher scores on the WOMAC designate worse pain, stiffness, and functional limitations.

ANNEXURE.1

DATA COLLECTION PHOTOS

Figure 26: Double blood bag

A sterile double blood bag is used for collection of blood sample for PRP preparation

Figure 27: Blood collection

Under aseptic precautions about 150 ml of venous blood is drawn in a double blood bag

Figure 28: Blood separation

The blood bag is kept for 1 hour at temperature of 20-24 degree Celsius till separation

Figure 29: Blood bag centrifugation machine

Blood bag centrifugation machine, initially blood will be centrifuged using a light spin at 2630 Revolutions Per Minute (RPM) for 3 minutes and 1500RPM for another 15 minutes to sediment the RBCs and WBCs

Figure 30: Platelet Rich Plasma

A freshly prepared PRP sample after centrifugation the PRP is separated and transferred in to the second blood bag

Figure 31: Equipment's for IA injection

A Sterile tray with Betadine solution, Sterile gloves, Freshly prepared PRP loaded in the10CC syringe , Sterile cotton rolls, Bandage roll, 6 inch elastic compression bandage

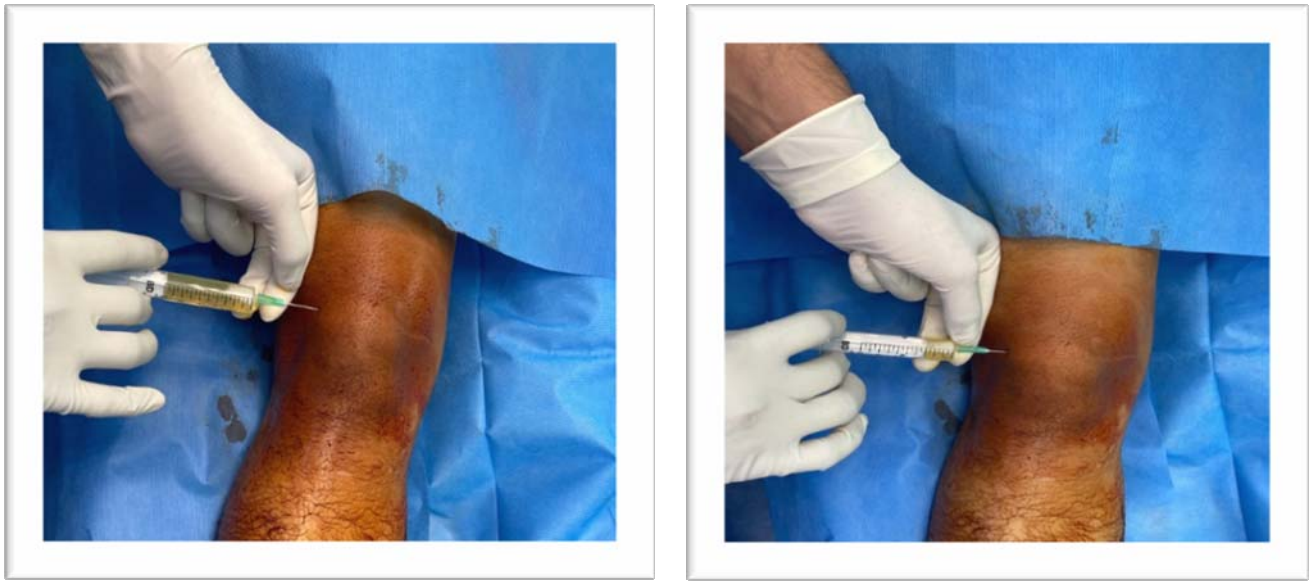
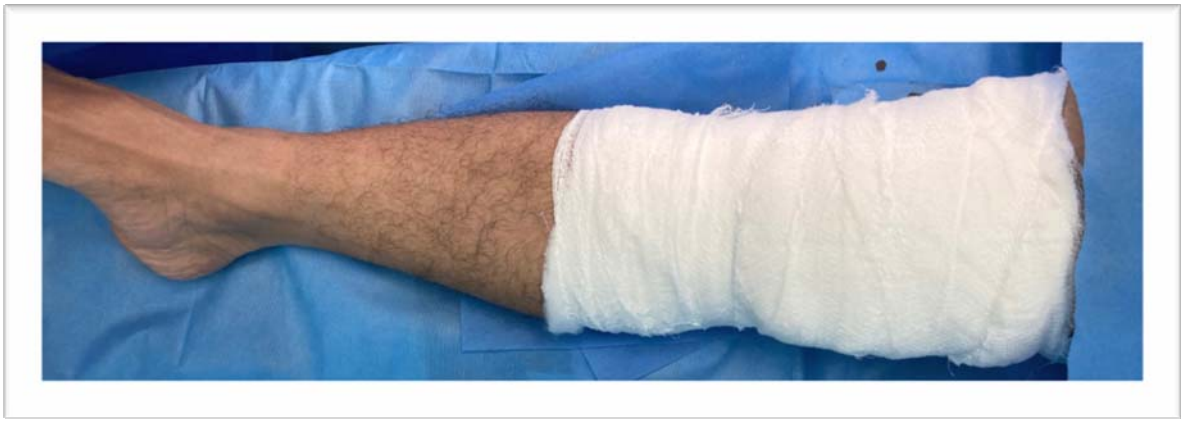


Figure 32: Administration of Intra-articular PRP injection

The affected knee is painted and draped, under aseptic precautions in the Lateral aspect of the knee in suprapatellar approach a 10ml of Freshly prepared PRP is injected



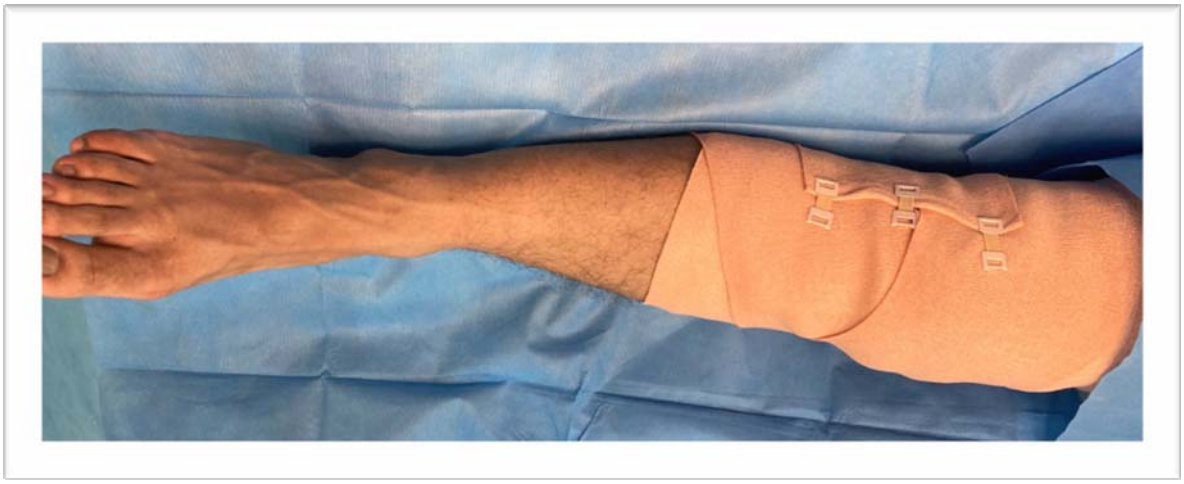


Figure 33: Sterile compression bandage of knee joint

Sterile dressing and jones compression bandage applied with cotton roll and elastic compression bandage is applied post injection

ANNEXURE-2

PROFORMA

Name : Case no :

Age : IP/op no :

Sex : DOB :

Address : Date :

Phone no:

Chief complaints :

History of presenting illness:

Past history:

Family history:

Personal history:

General physical examination:

Vital signs: Systemic examination:

BP - CVS-

RR - RS-

PR - PA-

Temp- CNS-

LOCAL EXAMINATION OF BILATERAL KNEE:

RIGHT LEFT

- Deformity
- Swelling
- Mid joint line Tenderness
- Lateral joint line Tenderness
- Retro Patellar Tenderness
- Retro patellar crepitus
- Patellar tap
- Synovial thickness
- ROM
- X ray of knee (both):- Kellergen and Lawrence grading:-

Routine:

Hb%	RBS
TC	Blood urea
DC	Serum creatinine
ESR	Blood group
BT	CT

Chest X-ray

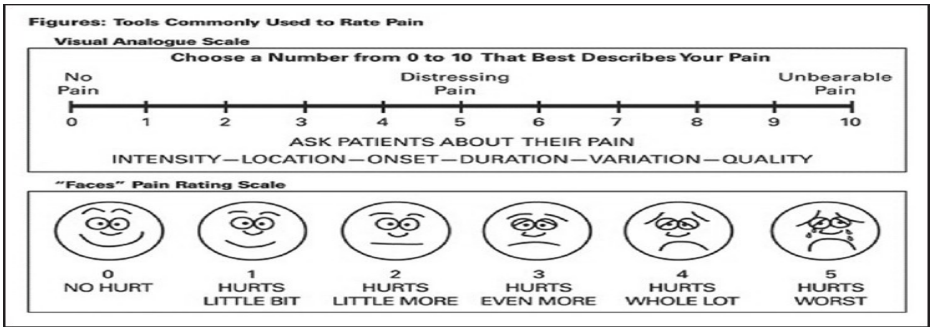
LAB INVESTIGATION OF PRP COLLECTED:

Volume: platelet count: sterility: serological tests: HIV

HBsAg

HCV

Diagnosis:



WOMAC AND VAS scoring during follow ups:

IA-PRP Injection	PRE-OP		6 WEEKS		3MONTHS		6MONTHS	
	VAS	WOMAC	VAS	WOMAC	VAS	WOMAC	VAS	WOMAC
SINGLE								
SECOND								

ASSESSMENT OF RESULT:

Signature of candidate: Signature of Guide: Signature of co-Guide

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

Name:_____Date:_____

Instructions:

Please rate the activities in each category according to the following scale of difficulty:

0=None, 1=Slight, 2 =Moderate, 3=Very, 4=Extremely

Circle one number for each activity Pain

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 later in the day	0	1	2	3	4
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 a 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= %

KANNADA CONSENT FORM

ರೋಗಿಯ ಸಮ್ಮತಿ ಪತ್ರ

ಕ್ರಮ ಸಂಖ್ಯೆ :

ರೋಗಿಯ ಹೆಸರು :

ಮೊಬೈಲ್ಸಂಖ್ಯೆ:

ಶೀರ್ಷಿಕೆ:ಮೊಣಕಾಲಿನ ಪ್ರಾರಂಭಿಕ ಸಂಧಿವಾತದಲ್ಲಿ ಕೀಲಿನ ನುಡುಭಾಗಕ್ಕೆ ಪ್ಲೇಟ್ಲೆಟ್ಸ್ (ಕಿರುಬಿಲ್ಲೆಗಳು) ಭರಿತ ಪ್ಲಾಸ್ಮಾಚುಚ್ಚುಮದ್ದನ್ನುಒಮ್ಮೆಅಥವ ಹಲವಾರು ಬಾರಿ ನೀಡುವುದರ ಕ್ರಿಯಾತ್ಮಕ ಫಲಿತಾಂಶದ ಒಂದು ತುಲನಾತ್ಮಕ ಅಧ್ಯಯನ.

ಈ ಕೆಳಗೆ ರುಜು ಮಾಡಿರುವ ನಾನು, ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು, ಅಧ್ಯಯನ ನಡೆಸಲು ಮತ್ತು ಈ ಸಮ್ಮತಿ ನಮೂನೆಯ ಅಂಶಗಳಂತೆ ನನ್ನ ವೈಯಕ್ತಿಕ ಮಾಹಿತಿಯನ್ನು ಬಹಿರಂಗ ಪಡಿಸುವ ಒಪ್ಪಿಗೆ ನೀಡಿರುತ್ತೇನೆ. ನನಗೆ ಈ ಅಧ್ಯಯನದ ಉದ್ದೇಶ ಹಾಗು ಗೋಪ್ಯತೆಯ ವಿಚಾರಗಳ ಬಗ್ಗೆ ನನ್ನ ಭಾಷೆ ಕನ್ನಡದಲ್ಲಿ ವಿವರಿಸಲಾಗಿದೆ.

ಈ ಅಧ್ಯಯನ ಕುರಿತಾದ ನನ್ನ ಎಲ್ಲಾ ಪ್ರಶ್ನೆಗಳಿಗೂ ಸಮಾಧಾನಕರ ಉತ್ತರ ನನಗೆ ದೊರಕಿರುತ್ತದೆ. ಎಲ್ಲಾ ಮಾಹಿತಿಗಳು ಸಂಶೋಧನೆಗಾಗಿಯೇ ಬಳಸಲಾಗುವುದು.

ಎಲ್ಲಾ ಮಾಹಿತಿಯನ್ನು ಗೌಪ್ಯವಾಗಿ ಇಡಲಾಗುತ್ತದೆ ಮತ್ತು ಇವನ್ನು ಹೊರಗಿನವರಿಗೆ ಬಹಿರಂಗಪಡಿಸಲಾಗುವುದಿಲ್ಲ.

ಈ ಅಧ್ಯಯನದಿಂದ ನನ್ನ ಜೀವಕ್ಕೆ ಯಾವುದೇ ರೀತಿಯ ಹಾನಿ ಆಗುವುದಿಲ್ಲ ಮತ್ತು ಹೆಚ್ಚು ಅನುಕುಲಕರವಗುತಡ ಎಂದು ನನಗೆ ಅರ್ಥವಾಗಿರುತ್ತದೆ.

ನಾನು ಯಾವಾಗ ಬೇಕಾದರೂ ಈ ಅಧ್ಯಯನದಿಂದ ಹೊರನಡೆಯಬಹುದು ಮತ್ತು ನನಗೆ ಇದರಿಂದ ಯಾವುದೇ ರೀತಿಯ ಅಧಿಕ ಖರ್ಚಾಗಿರುವುದಿಲ್ಲವೆಂದು ನಾನು ಒಪ್ಪಿಕೊಂಡಿರುತ್ತೇನೆ.

ರೋಗಿಯ ಹೆಸರು ಮತ್ತು ರುಜು/ಬೆರಳು ಗುರುತು

ಸಾಕ್ಷಿಗಳ ಹೆಸರು ಮತ್ತು ರುಜು

1.

2.

ಪ್ರಮುಖ ಸಂಶೋಧಕರ ಹೆಸರು ಮತ್ತು ರುಜು: ಡಾII ಪರಮಾನಂತಂ ಮಾಧವನ್.

ರೋಗಿಯ ತಿಳಿವಳಿಕೆಯ ಸಮ್ಮತಿ ನಮೂನೆ

ಅಧ್ಯಯನದ ಶೀರ್ಷಿಕೆ: ಮೊಣಕಾಲಿನ ಪ್ರಾರಂಭಿಕ ಸಂಧಿವಾತದಲ್ಲಿ ಕೀಲಿನ ನುಡುಭಾಗಕ್ಕೆ ಪ್ಲೇಟ್ಲೆಟ್ಸ್ (ಕಿರುಬಿಲ್ಲೆಗಳು) ಭರಿತ ಪ್ಲಾಸ್ಮಾ ಚುಚ್ಚುಮದ್ದನ್ನು ಒಮ್ಮೆ ಅಥವ ಹಲವಾರು ಬಾರಿ ನೀಡುವುದರ ಕ್ರಿಯಾತ್ಮಕ ಫಲಿತಾಂಶದ ಒಂದು ತುಲನಾತ್ಮಕ ಅಧ್ಯಯನ.

ಅಧ್ಯಯನದ ಸ್ಥಳ : ಆರ್ ಎಲ್ ಜಲಪ್ಪ ಆಸ್ಪತ್ರೆ ಮತ್ತು ಸಂಶೋಧನಾ ಕೇಂದ್ರ, ಶ್ರೀ ದೇವರಾಜ್ ಉರ್ಸ್ ವೈದ್ಯಕೀಯ ಕಾಲೇಜು, ತಮಕ, ಕೋಲಾರ.

ವಿವರಗಳು -

ಆರ್. ಎಲ್. ಜಲಪ್ಪಆಸ್ಪತ್ರೆಗೆ ಆರ್ಥೋಪೆಡಿಕ್ಸ್ವಿ ಭಾಗಕ್ಕೆ ಭೇಟಿ ನೀಡುವ ಅಸ್ಥಿಸಂಧಿವಾತ ಮೊಣಕಾಲು ಇರುವ 40 ರಿಂದ 60 ವರ್ಷ ವಯಸ್ಸಿನ ರೋಗಿಗಳನ್ನು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಎರಡು ಗುಂಪುಗಳಲ್ಲಿ ಸೇರಿಸಿಕೊಳ್ಳಲಾಗುವುದು. ಗುಂಪು ಎ ಏಕ ಅಂತರ- ಕೀಲಿನ ಪಿ.ಆರ್.ಪಿ ಚುಚ್ಚುಮದ್ದನ್ನು ಸ್ವೀಕರಿಸುತ್ತದೆ, ಗುಂಪು ಬಿ ಆಪರೇಷನ್ ಥಿಯೇಟರ್ನಲ್ಲಿ ಕಟ್ಟುನಿಟ್ಟಾದ ಅಸೆಪ್ಟಿಕ್ ಮುನ್ನೆಚ್ಚರಿಕೆಗಳ ಅಡಿಯಲ್ಲಿ ಅನೇಕ ಪಿ.ಆರ್.ಪಿ ಚುಚ್ಚುಮದ್ದನ್ನು ಸ್ವೀಕರಿಸುತ್ತದೆ ಮತ್ತು ಇದು ಅಸ್ಥಿಸಂಧಿವಾತ ಮೊಣಕಾಲಿಗೆ ಒಂದು ಹೊಸ ಚಿಕಿತ್ಸೆಯಾಗಿದ್ದು, ಇದು ತನಿಖಾ ಹಂತದಲ್ಲಿದೆ, ಇನ್ನೂ ಪ್ರಮಾಣೀಕರಿಸಲಾಗಿಲ್ಲ, ಆದರೂ ಈ ಚುಚ್ಚುಮದ್ದಿನ ಮಾದರಿಯನ್ನು ವೈಜ್ಞಾನಿಕ ಸಾಹಿತ್ಯದಲ್ಲಿ ಮೂಳೆಚಿಕಿತ್ಸೆಯ ಬಳಕೆಯಲ್ಲಿ ಪಿ.ಆರ್.ಪಿ ಚುಚ್ಚುಮದ್ದಿನಿಂದ ಉತ್ತಮ ಮಾದರಿ ಸ್ಥಾಪಿತವಾಗಿದೆ. ಈ ಅಧ್ಯಯನದ ರೋಗಿಗಳು ಎಪಿ ವೀಕ್ಷಣೆ ಮತ್ತು ಪೀಡಿತ ಮೊಣಕಾಲುಗಳ ಪಾರ್ಶ್ವ ವೀಕ್ಷಣೆಗಾಗಿ ನಿಂತಿರುವ ಸ್ಥಾನದಲ್ಲಿ ದಿನನಿತ್ಯದ ತನಿಖೆ ಮತ್ತು ಮೊಣಕಾಲಿನ ಎರಡೂ ಎಕ್ಸರೆಗಳಿಗೆ ಒಳಗಾಗಬೇಕಾಗುತ್ತದೆ. ಈ ಅಂತರ್- ಕೀಲಿನ ಪಿ.ಆರ್. ಪಿ. ಚುಚ್ಚುಮದ್ದಿನಿಂಧಾ

ಇ ಕೆಳಗಿನ ತೊಡಕುಗಳನ್ನು ಹೊಂದಬಹುದು – ಮೊಣಕಾಲು ಉಥಾ, ಎರಿಥೆಮಾ, ಚಲನೆಯ ಮೊಣಕಾಲಿನ ವ್ಯಾಪ್ತಿಯಲ್ಲಿ ತೊಂದರೆ, ಸೋಂಕು, ಸೆಪ್ಟಿಕ್ ಸಂಧಿವಾತ ಇತ್ಯಾದಿ.

ದಯವಿಟ್ಟು ಈ ಕೆಳಗಿನ ಮಾಹಿತಿಯನ್ನು ಓದಿ ಮತ್ತು ನಿಮ್ಮ ಕುಟುಂಬ ಸದಸ್ಯರೊಂದಿಗೆ ಚರ್ಚಿಸಿ. ಅಧ್ಯಯನಕ್ಕೆ ಸಂಬಂಧಿಸಿದಂತೆ ನೀವು ಯಾವುದೇ ಪ್ರಶ್ನೆಯನ್ನು ಕೇಳಬಹುದು. ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನೀವು ಒಪ್ಪಿದರೆ ನಾವು ನಿಮ್ಮಿಂದ ಅಥವಾ ನಿಮ್ಮ ಇಬ್ಬರ ಜವಾಬ್ದಾರಿಯುತ ವ್ಯಕ್ತಿಯಿಂದ ಮಾಹಿತಿಯನ್ನು (ಪ್ರೊಫಾರ್ಮಾದಪ್ರಕಾರ) ಸಂಗ್ರಹಿಸುತ್ತೇವೆ. ಸಂಗ್ರಹಿಸಿದ ಈ ಮಾಹಿತಿಯನ್ನು ಪ್ರಬಂಧ ಮತ್ತು ಪ್ರಕಟಣೆಗೆ ಮಾತ್ರ ಬಳಸಲಾಗುತ್ತದೆ.

ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಲಾದ ಎಲ್ಲಾ ಮಾಹಿತಿಯನ್ನು ಗೌಪ್ಯವಾಗಿಡಲಾಗುತ್ತದೆ ಮತ್ತು ಯಾವುದೇ ಹೊರಗಿನವರಿಗೆ ಬಹಿರಂಗಪಡಿಸುವುದಿಲ್ಲ. ನಿಮ್ಮ ಗುರುತು ಬಹಿರಂಗಗೊಳ್ಳುವುದಿಲ್ಲ. ಈ ಅಧ್ಯಯನವನ್ನು ಸಾಂಸ್ಥಿಕ ನೈತಿಕ ಸಮಿತಿಯು ಪರಿಶೀಲಿಸಿದೆ ಮತ್ತು ನೀವು ಸಾಂಸ್ಥಿಕ ನೈತಿಕ ಸಮಿತಿಯ ಕಾರ್ಯದರ್ಶಿಯನ್ನು ಸಂಪರ್ಕಿಸಲು ಮುಕ್ತರಾಗಿದ್ದೀರಿ. ಈ ಅಧ್ಯಯನವನ್ನು ಒಪ್ಪಿಕೊಳ್ಳಲು ಯಾವುದೇ ಬಲವಂತವಿಲ್ಲ. ನೀವು ಭಾಗವಹಿಸಲು ಬಯಸದಿದ್ದರೆ ನೀವು ಪಡೆಯುವ ಕಾಳಜಿ ಬದಲಾಗುವುದಿಲ್ಲ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನೀವು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಒಪ್ಪಿಕೊಂಡರೆ ಮಾತ್ರ ನೀವು ಹೆಬ್ಬೆರಳು ಅನಿಸಿಕೆಗೆ ಸಹಿ / ಒದಗಿಸುವ ಅಗತ್ಯವಿದೆ.

ರೋಗಿಯ ಸಹಿ / ಹೆಬ್ಬೆರಳಿನಗುರುತು-

ಹೆಸರು:

ಸಾಕ್ಷಿಸಹಿ(ರೋಗಿಗೆಸಂಬಂಧ):

ಹೆಚ್ಚಿನ ಮಾಹಿತಿಗಾಗಿ ಸಂಪರ್ಕಿಸಿ :

ಡಿ.ಆರ್. ಪರಮಾನಂತಂ ಮಾಧವನ್,

ಹೆಸರು:

ಪ್ರಥಮ ವರ್ಷದ

ಸ್ನಾತಕೋತ್ತರ,ಆರ್ಥೋಪೆಡಿಕ್ಸ್ ಇಲಾಖೆ,

ಎಸ್ಡಿಯುಎಂಸಿ, ತಮಕ, ಕೋಲಾರ.

ಸಂಪರ್ಕ ಸಂಖ್ಯೆ: 9945389639.

PATIENT INFORMATION SHEET

Study title: **FUNCTIONAL OUTCOME OF SINGLE VERSUS MULTIPLE INTRA-ARTICULAR PLATELET RICH PLASMA (PRP) INJECTIONS FOR EARLY OSTEOARTHRITIS KNEE- A COMPARATIVE STUDY**

Study location: R. L. Jalappa Hospital & Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Details-

Patients aged between 40 and 60 years diagnosed having osteoarthritis knee who visit to the department of Orthopaedics to R.L.Jalappa Hospital will be included in this study in one of two groups. Group I will receive single intra-articular PRP injection, group II will receive multiple PRP injections under strict aseptic precautions in operation theater and this a novel treatment for osteoarthritis knee which is under investigational stage not yet standardized ,yet the sampling of this injection has been well established, by the PRP injection for orthopaedic usage in scientific literatures. Patients in this study will have to undergo routine investigations and x ray of both knee in standing position for AP view and lateral view of affected knees. This intra-articular PRP injection can have the following complications like increase pain in the knee, swelling, erythema, difficulty in knee range of motions, infection, might leads to septic arthritis etc .

Please read the following information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or both. Relevant history will be taken. This information collected will be used only for dissertation and publication.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. This study has been reviewed by the Institutional Ethics Committee and you are free to contact the secretary of the Institutional Ethics Committee. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

For further information contact

DR. PARAMANANTHAM MADHAVAN

First year post graduate,

Department of ORTHOPAEDICS,

SDUMC, Tamaka, Kolar.

CONTACT NO: 9945389639

INFORMED CONSENT FORM

I/we the patient attenders have been explained about outpatient's condition i.e., osteoarthritis knee and the need for the procedure i.e., single versus multiple intra articular platelet rich plasma (PRP) injections in the treatment of osteoarthritis knee.

The procedure and complications associated with this procedure i.e., single versus Multiple intra articular platelet rich plasma (PRP) injections, have been explained to me in my own understandable language. I am willing to pay for the procedure and the treatment, and giving my consent for the publication and dissertation of the information collected.

I have been explained regarding the study design and I am participating in the study with my willful consent in group I (single PRP injection)/group II (multiple PRP injection). I have been also explained by the investigator that I am free to participate in the study, I can withdraw from the study at any point of time and I would continue to receive the standard care and treatment in this hospital as long as I wish to receive the treatment.

I/we the patient and the patient attenders hold the full responsibility for the procedure and the further consequences. I will not hold any treating doctor, nursing staff and hospital management for any untoward consequences.

I hereby give my consent for the same.

SIGNATURE OF THE PATIENT: **SIGNTURE OF DOCTOR:**

WITTNESS:

1.

2.

DATE

MASTER CHART

SL NO	UHID number	AGE	SEX	GROUP	KNEE AFFECTED		GRADE OF OA	DATE OF FIRST INJECTION	PLATELET COUNT		DATE OF SECOND INJECTION	PLATELET COUNT		CO-MORIDITIES		VAS				WOMAC				BMI	RANGE OF MOTION								COMPLICATIONS
																									PRE-INJECTIOI		1 MONTH		3 MONTH		6 MONTH		
									BLOOD PLATELET COUNT	PLATELET COUNT IN PRP		BLOOD PLATELET COUNT	PLATELET COUNT IN PRP	DIABETES	HYPERTENSION	INJECTION	6 WEEKS	3 MONTH	6 MONTH	INJECTION	6 WEEKS	3 MONTH	6 MONTH		RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	
1	930247	56	F	S-PRP	**RIGHT**	LEFT	GRADE 1	12/18/2019	100,000	813,000	NA	NA	NA	NO	NO	7	4	2	2	56	48	38	40	27	0-120	0-120	0-125	0-125	0-130	0-130	0-135	0-135	PAIN
2	930286	60	F	S-PRP	RIGHT		GRADE 2	12/20/2019	190,000	743,000	NA	NA	NA	NO	NO	6	3	3	3	54	48	34	44	30	0-120	0-135	0-120	0-135	0-125	0-135	0-130	0-135	
3	931146	55	F	S-PRP	**RIGHT**	LEFT	GRADE 2	12/22/2019	275,000	710,000	NA	NA	NA	NO	NO	7	6	4	2	56	42	36	24	30	0-120	0-125	0-125	0-130	0-130	0-130	0-130	0-130	
4	925470	58	F	S-PRP	**RIGHT**	LEFT	GRADE 2	1/2/2020	152,000	645,000	NA	NA	NA	NO	NO	6	4	3	2	56	50	38	20	28	0-120	0-125	0-125	0-130	0-125	0-130	0-130	0-130	PAIN
5	919935	50	F	S-PRP	**RIGHT**		GRADE 1	12/18/2019	125,000	630,000	NA	NA	NA	YES	NO	8	7	7	6	56	42	30	20	29	0-120	0-135	0-125	0-135	0-130	0-135	0-130	0-135	
6	931885	60	F	S-PRP	RIGHT	**LEFT**	GRADE 2	1/12/2020	150,000	625,000	NA	NA	NA	NO	NO	7	6	4	1	58	44	32	24	26	0-120	0-110	0-130	0-120	0-135	0-125	0-130	0-130	
7	931403	60	F	S-PRP	**RIGHT**	LEFT	GRADE 2	1/22/2020	110,000	900,000	NA	NA	NA	YES	YES	6	2	3	1	52	46	34	22	28	0-110	0-120	0-125	0-120	0-135	0-135	0-135	0-135	
8	932134	57	M	S-PRP	RIGHT	**LEFT**	GRADE 2	1/24/2020	290,000	655,000	NA	NA	NA	YES	NO	6	5	4	2	56	50	38	36	26	0-120	0-110	0-125	0-125	0-130	0-130	0-135	0-130	
9	920887	60	F	S-PRP	RIGHT	LEFT	GRADE 2	1/25/2020	160,000	540,000	NA	NA	NA	NO	NO	7	6	5	4	54	46	38	18	27	0-110	0-120	0-120	0-120	0-125	0-135	0-125	0-135	
10	931479	50	M	S-PRP	RIGHT		GRADE2	2/1/2020	218,000	540,000	NA	NA	NA	NO	NO	6	6	4	3	58	48	34	20	28	0-120	0-130	0-125	0-130	0-125	0-130	0-130	0-135	
11	934783	62	F	S-PRP	**RIGHT**	LEFT	GRADE 1	2/18/2020	190,000	680,000	NA	NA	NA	YES	NO	7	5	4	1	52	40	32	24	28	0-110	0-120	0-120	0-130	0-130	0-130	0-130	0-130	
12	935147	56	F	S-PRP	**RIGHT**	LEFT	GRADE 2	2/23/2020	138,000	590,000	NA	NA	NA	NO	NO	7	5	3	5	56	44	36	66	28	0-120	0-110	0-130	0-125	0-135	0-130	0-135	0-135	
13	933120	58	M	S-PRP	RIGHT	**LEFT**	GRADE 2	2/3/2020	275,000	730,000	NA	NA	NA	YES	NO	6	4	3	1	52	42	34	18	27	0-120	0-110	0-130	0-120	0-130	0-120	0-130	0-130	
14	936585	60	F	S-PRP	**RIGHT**	**LEFT**	GRADE 2	2/20/2020	273,000	640,000	NA	NA	NA	NO	NO	7	5	4	6	60	48	34	34	27	0-110	0-120	0-120	0-130	0-130	0-130	0-130	0-135	
15	939139	55	F	S-PRP	RIGHT	**LEFT**	GRADE 2	2/20/2020	188,000	740,000	NA	NA	NA	NO	YES	8	6	5	4	52	46	32	20	28	0-120	0-110	0-130	0-130	0-135	0-135	0-135	0-135	
16	934174	60	F	S-PRP	**RIGHT**	LEFT	GRADE 2	3/10/2020	280,000	680,000	NA	NA	NA	YES	YES	7	6	4	3	56	48	31	26	27	0-110	0-130	0-120	0-135	0-135	0-140	0-135	0-140	SWELLING
17	935197	46	M	S-PRP	**RIGHT**	LEFT	GRADE 2	3/12/2020	127,000	620,000	NA	NA	NA	NO	NO	6	5	3	4	56	46	36	22	28	0-120	0-130	0-125	0-130	0-130	0-135	0-135	0-135	
18	935268	55	F	S-PRP	RIGHT	**LEFT**	GRADE 1	3/20/2020	316,000	800,000	NA	NA	NA	NO	NO	7	6	4	3	58	48	36	24	26	0-130	0-120	0-130	0-125	0-130	0-125	0-135	0-130	
19	907621	56	F	S-PRP	RIGHT	**LEFT**	GRADE 2	3/16/2020	214,000	813,000	NA	NA	NA	NO	NO	6	5	3	5	56	46	38	28	27	0-110	0-120	0-120	0-130	0-130	0-130	0-130	0-130	
20	897216	52	F	S-PRP	RIGHT		GRADE 2	4/19/2020	140,000	630,000	NA	NA	NA	YES	NO	7	6	5	5	56	43	36	24	26	0-110	0-135	0-120	0-135	0-125	0-135	0-135	0-135	
21	896389	55	F	S-PRP	**RIGHT**		GRADE 2	4/20/2020	219,000	745,000	NA	NA	NA	NO	YES	6	6	4	3	54	44	34	28	27	0-110	0-120	0-120	0-135	0-130	0-140	0-135	0-140	
22	896388	59	F	S-PRP	**RIGHT**	**LEFT**	GRADE 2	4/28/2020	190,000	590,000	NA	NA	NA	NO	NO	8	6	4	2	52	48	32	26	29	0-110	0-110	0-120	0-130	0-130	0-135	0-135	0-140	
23	893914	54	F	S-PRP	**RIGHT**	LEFT	GRADE 2	5/4/2020	288,000	620,000	NA	NA	NA	NO	YES	7	6	4	5	56	48	34	24	27	0-110	0-120	0-120	0-135	0-130	0-135	0-135	0-135	
24	854382	57	F	S-PRP	**RIGHT**	LEFT	GRADE 2	5/13/2020	223,000	590,000	NA	NA	NA	NO	NO	7	5	4	1	54	46	38	28	30	0-110	0-110	0-120	0-120	0-125	0-130	0-130	0-135	
25	899526	60	F	S-PRP		LEFT	GRADE 2	5/20/2020	190,000	710,000	NA	NA	NA	NO	NO	6	5	4	3	52	42	32	24	32	0-130	0-110	0-135	0-120	0-130	0-130	0-135	0-140	
26	847174	52	F	S-PRP	**RIGHT**	LEFT	GRADE 2	5/21/2020	290,000	820,000	NA	NA	NA	NO	NO	7	5	4	1	56	42	34	26	27	0-110	0-125	0-120	0-130	0-130	0-135	0-135	0-135	
27	866677	58	F	S-PRP	RIGHT	**LEFT**	GRADE 2	5/28/2020	167,000	780,000	NA	NA	NA	NO	NO	7	6	4	2	58	40	36	24	28	0-120	0-110	0-130	0-120	0-130	0-125	0-135	0-135	
28	832922	56	M	S-PRP	**RIGHT**		GRADE 1	5/28/2020	219,000	685,000	NA	NA	NA	NO	YES	6	5	3	1	56	48	38	28	29	0-120	0-135	0-125	0-135	0-135	0-130	0-140	0-135	
29	850148	59	F	S-PRP	**RIGHT**	LEFT	GRADE 1	5/31/2020	183,000	625,000	NA	NA	NA	NO	NO	6	5	4	2	60	46	36	26	34	0-120	0-130	0-125	0-130	0-135	0-135	0-135	0-135	
30	849536	56	F	S-PRP	**RIGHT**	**LEFT**	GRADE 1	5/31/2020	236,000	610,000	NA	NA	NA	NO	NO	7	6	4	2	56	44	34	24	28	0-120	0-125	0-125	0-125	0-130	0-130	0-135	0-135	PAIN, SWELLING
31	-849142	54	F	S-PRP	**RIGHT**		GRADE 1	5/31/2020	230,000	840,000	NA	NA	NA	NO	NO	7	6	4	1	58	48	38	24	26	0-130	0-120	0-130	0-125	0-135	0-135	0-135	0-135	
32	848193	43	F	S-PRP	**RIGHT**	LEFT	GRADE 2	6/8/2020	217,000	900,000	NA	NA	NA	NO	NO	6	5	4	2	58	44	34	26	28	0-110	0-130	0-120	0-130	0-130	0-135	0-135	0-135	
33	836389	45	M	S-PRP	RIGHT	LEFT	GRADE 2	11/25/2019	290,000	780,000	NA	NA	NA	YES	YES	7	6	3	2	54	40	38	24	28	0-120	0-125	0-140	0-130	0-140	0-130	0-140	0-135	
34	897216	45	M	S-PRP	**RIGHT**	LEFT	GRADE 1	11/28/2019	156,000	826,000	NA	NA	NA	NO	NO	6	6	4	1	54	44	40	26	26	0-125	0-130	0-130	0-130	0-130	0-135	0-135	0-140	PAIN
35	896389	60	F	M-PRP	RIGHT	**LEFT**	GRADE 2	12/16/2019	167,000	945,000	14.03.2020	######	849,000	NO	NO	8	7	3	4	52	46	32	28	28	0-125	0-110	0-130	0-120	0-130	0-125	0-135	0-130	
36	884541	50	F	M-PRP	RIGHT	LEFT	GRADE 1	12/26/2020	237,000	925,000	2.02.2020	######	872,000	NO	NO	7	6	5	3	52	42	34	28	28	0-120	0-135	0-125	0-135	0-130	0-135	0-140	0-140	
37	892338	46	F	M-PRP	**RIGHT**	LEFT	GRADE 1	1/27/2020	240,000	930,000	26.03.2020	######	782,000	NO	YES	8	6	4	2	56	46	36	24	26	0-120	0-135	0-130	0-135	0-130	0-135	0-135	0-140	
38	893002	58	M	M-PRP	**RIGHT**	LEFT	GRADE 1	1/30/2020	265,000	670,000	4.04.2020	######	620,000	NO	NO	8	6	4	5	58	44	38	26	26	0-120	0-130	0-130	0-135	0-140	0-140	0-140	0-140	PAIN
39	874768	40	M	M-PRP	**RIGHT**	LEFT	GRADE 2	1/31/2020	256,000	930,000	23.03.2020	######	820,000	NO	NO	8	6	4	3	56	48	36	24	26	0-120	0-120	0-135	0-125	0-135	0-130	0-140	0-130	
40	892410	40	M	M-PRP	RIGHT	LEFT	GRADE 1	3/11/2020	288,000	848,000	12.05.2020	######	783,000	YES	NO	7	6	4	1	58	46	34	28	27	0-125	0-140	0-130	0-140	0-135	0-140	0-140	0-140	
41	876383	59	M	M-PRP	**RIGHT**	LEFT	GRADE 1	3/13/2020	295,000	1,032,000	1.06.2020	######	640,000	NO	YES	8	6	5	1	52	42	38	20	27	0-120	0-130	0-130	0-140	0-135	0-140	0-140	0-140	
42	890870	59	M	M-PRP	**RIGHT**	LEFT	GRADE 2	3/13/2020	102,000	860,000	2.05.2020	######	810,000	NO	NO	8	6	5	2	54	44	34	24	25	0-120	0-120	0-140	0-130	0-140	0-135	0-140	0-140	SWELLING
43	882246	41	F	M-PRP	**RIGHT**	LEFT	GRADE 2	3/15/2020	195,000	1,160,000	6.05.2020	######	790,000	YES	NO	8	6	5	1	54	46	36	28	29	0-120	0-135	0-135	0-135	0-135	0-135	0-135	0-140	
44	889605	60	F	M-PRP	**RIGHT**	**LEFT**	GRADE 2	3/15/2020	266,000	820,000	5.05.2020	######	823,000	YES	YES	8	6	5	1	58	44	38	24	26	0-115	0-130	0-125	0-135	0-130	0-135	0-135	0-135	
45	888198	57	F	M-PRP	**RIGHT**	LEFT	GRADE 2	4/4/2020	169,000	880,000	06.07.2020	######	670,000	YES	NO	8	6	5	2	52	48	32	26	26	0-120	0-130	0-125	0-130	0-130	0-135	0-135	0-135	

MASTER CHART

46	886796	53	F	M-PRP	**RIGHT**	LEFT	GRADE 1	4/8/2020	210,000	900,000	09.06.2020	######	740,000	NO	NO	8	6	5	2	58	46	38	24	28	0-120	0-120	0-130	0-130	0-135	0-140	0-140	0-140	PAIN, SWELLING
47	887454	50	M	M-PRP	RIGHT	**LEFT**	GRADE 1	4/11/2020	110,000	885,000	15.06.2020	######	670,000	NO	NO	7	6	4	2	56	48	32	28	27	0-120	0-120	0-125	0-130	0-125	0-130	0-130	0-130	SWELLING
48	888147	49	M	M-PRP	**RIGHT**		GRADE 1	4/15/2020	286,000	890,000	18.06.2020	######	990,000	YES	YES	8	6	4	5	54	48	33	24	29	0-120	0-120	0-125	0-130	0-125	0-130	0-130	0-135	
49	888183	49	F	M-PRP	**RIGHT**	**LEFT**	GRADE 1	4/18/2020	128,000	830,000	19.07.2020	######	820,000	NO	NO	8	6	5	1	58	40	36	26	26	0-120	0-110	0-125	0-120	0-130	0-125	0-130	0-130	
50	880977	54	F	M-PRP	**RIGHT**	LEFT	GRADE 2	4/21/2020	234,000	910,000	23.06.2020	######	780,000	YES	NO	8	6	5	1	52	48	38	26	26	0-110	0-120	0-120	0-130	0-125	0-130	0-125	0-130	
51	882684	56	M	M-PRP	**RIGHT**	LEFT	GRADE 1	4/26/2020	260,000	1,010,000	21.07.2020	######	670,000	NO	NO	8	6	5	1	52	46	34	24	27	0-120	0-130	0-125	0-130	0-130	0-130	0-135	0-135	
52	881428	57	M	M-PRP	RIGHT	**LEFT**	GRADE 1	4/28/2020	291,000	695,000	13.07.2020	######	562,000	YES	NO	8	6	5	2	58	48	38	28	28	0-120	0-110	0-125	0-120	0-130	0-130	0-135	0-135	
53	877027	60	M	M-PRP	**RIGHT**	LEFT	GRADE 2	4/30/2020	237,500	840,000	11.06.2020	######	670,000	NO	NO	8	6	4	1	56	44	36	24	27	0-110	0-130	0-120	0-130	0-125	0-130	0-130	0-130	
54	829822	64	M	M-PRP	**RIGHT**	**LEFT**	GRADE 2	5/4/2020	242,500	695,000	13.07.2020	######	762,000	YES	NO	9	6	6	4	54	42	38	26	29	0-120	0-135	0-125	0-135	0-130	0-135	0-135	0-135	
55	875390	42	M	M-PRP		LEFT	GRADE 1	5/6/2020	213,000	730,000	12.07.2020	######	820,000	NO	YES	8	6	5	2	52	44	34	24	25	0-135	0-120	0-135	0-120	0-135	0-125	0-135	0-130	
56	875311	44	M	M-PRP	**RIGHT**		GRADE 2	5/9/2020	232,600	815,000	13.08.2020	######	780,000	NO	NO	8	6	5	1	56	42	36	22	28	0-110	0-135	0-120	0-135	0-135	0-130	0-135	0-135	PAIN
57	874395	45	F	M-PRP	RIGHT		GRADE 2	5/13/2020	245,000	660,000	24.08.2020	######	450,000	NO	NO	8	6	5	2	52	46	38	16	26	0-120	0-135	0-130	0-135	0-130	0-135	0-135	0-140	PAIN
58	832922	45	F	M-PRP	**RIGHT**		GRADE 2	5/21/2020	260,000	845,000	17.08.2020	######	640,000	NO	NO	8	6	5	4	56	44	40	20	27	0-120	0-130	0-125	0-130	0-125	0-130	0-130	0-135	
59	873031	42	F	M-PRP	RIGHT		GRADE 2	5/25/2020	285,000	920,000	3.07.2020	######	789,000	NO	NO	8	6	5	1	58	50	36	24	29	0-110	0-135	0-120	0-135	0-135	0-135	0-125	0-135	
60	869920	56	F	M-PRP	**RIGHT**	LEFT	GRADE 2	5/26/2020	127,000	424,000	4.07.2020	######	568,000	NO	YES	7	6	4	2	54	46	38	24	31	0-110	0-120	0-120	0-130	0-130	0-130	0-135	0-135	
61	847174	48	F	M-PRP	**RIGHT**	LEFT	GRADE 2	5/30/2020	197,000	911,000	6.08.2020	######	793,000	YES	NO	7	6	5	2	52	48	36	26	27	0-110	0-120	0-130	0-130	0-130	0-130	0-135	0-135	
62	826154	40	M	M-PRP	**RIGHT**	**LEFT**	GRADE 2	5/30/2020	103,000	945,000	5.07.2020	######	548,000	NO	NO	8	6	5	2	50	42	36	24	31	0-120	0-110	0-130	0-120	0-130	0-125	0-135	0-135	
63	875903	50	M	M-PRP	**RIGHT**	LEFT	GRADE 2	5/30/2020	220,000	880,000	4.07.2020	######	624,000	NO	NO	7	6	5	1	60	44	38	24	27	0-110	0-120	0-120	0-130	0-130	0-130	0-135	0-135	PAIN, SWELLING
64	856342	60	F	M-PRP	**RIGHT**	LEFT	GRADE 2	5/31/2020	276,000	873,000	5.08.2020	######	873,000	YES	NO	8	6	5	1	56	48	40	26	29	0-120	0-110	0-130	0-120	0-130	0-125	0-135	0-130	