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Efficacy of platelet rich plasma in the management of early osteoarthritis of knee

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Abstract

Aim: To assess the efficacy of Platelet rich plasma in patients with early Osteoarthritis knee at AIMS, B.G.NAGARA during AUGUST 2018 to DECEMBER 2020.

Materials and Method: The study was conducted in the Department of Orthopaedics, Adichunchanagiri Institute of Medical Sciences, B. G. NAGARA after obtaining ethical clearance. This study consisted of 70 adult patients of either sex visiting outpatient department of the hospital. Patients diagnosed with early osteoarthritis knee were included in the study during the period from December 2018 to JUNE 2020.

Observation and Results: The mean age in our study is 56.5 years. The mean IKDC score increased from baseline of 38.99 to 63.86 at 6 months follow up. After 2 months of follow up, there was significant improvement of IKDC score in both the genders. The IKDC score showed improvement in all four age groups. Minor complications were reported.

Conclusion: On the basis of the current evidence, PRP injections reduced pain more effectively in Osteoarthritis of the knee. PRP injections can be used to treat early osteoarthritis of knee with significant improvement in function and possibly postpone the need for surgical intervention. More large randomized multicentric studies of good quality and less bias are needed to test whether PRP injections can be used as a routine treatment option in management of patients with Osteoarthritis of knee.

Keywords: osteoarthritis of knee, platelet rich plasma injection, IDKC score

Introduction

Osteoarthritis (OA) is a clinically heterogeneous degenerative condition characterized by destruction of articular cartilage, due to uncoupling of balance between cartilage degeneration and regeneration.

Knee osteoarthritis is one of the major causes of physical disability and pain in older people. Symptomatic knee Osteoarthritis occurs in approximately 13% of people who are aged >60yrs years old ^[1]. It is a clinical syndrome of joint pain with multifactorial etiopathogenesis that is characterized by the gradual loss of remodelling, and inflammation of the joint ^[1]. Because of the increased lifespan and obesity the prevalence of osteoarthritis is increased in Indian population. Prevalence of OA in India is reported to be in the range of 17 - 60.6% ^[2].

Although cartilage destruction is the hallmark of the disease, synovitis, subchondral bone remodelling (osteophyte formation, thickening, bone collapse, cyst), degradation of ligaments and menisci and hypertrophy of joint capsule take part in the pathogenesis of osteoarthritis ^[3]. OA is closely related to body mass index in weight-bearing joints. With life expectancy increasing and obesity rates approaching epidemic proportions, OA has become ever more frequent.

The pathogenesis involves uncoupling of balance between cartilage degeneration and regeneration resulting in net cartilage loss, bone hypertrophy and bone outgrowths called osteophytes ^[2]. OA prefers finger joints, knees, hips, shoulders and spine. It can also occur in an atypical joint, such as an elbow; when there is history of past trauma, congenital joint abnormality, underlying systemic disease, or chronic crystalline arthropathy. Multiple factors that cause destruction of articular cartilage, make OA a heterogenic condition.

Symptomatic OA of the knee which is described as having pain during most days of a month along with radiologic evidence of arthritis has a prevalence of 22% to 39% in India ^[4, 5].

Osteoarthritis is a chronic disease of synovial lined joints where articular cartilage is gradually weakened and disintegrated with new growth of cartilage and bone at the joint margins, formation of cysts and sclerosis at subchondral regions of bone, mild synovitis and capsular fibrosis.

Osteoarthritis differs from ordinary wear and tear in that it is distributed asymmetrically, often associated with atypical loading rather than frictional wear. It is not an inflammatory condition though local signs of inflammation often occur. Osteoarthritis in its most usual form is unaccompanied by any systemic disease. With emerging interest in regenerative medicine and tissue engineering, new treatment modalities are being developed for joint disorders including joint surface lesions and articular cartilage defects.

Platelets are natural source of growth factors and Platelet rich plasma (PRP) helps in regeneration of articular cartilage. Growth factors are effective in chemotaxis, differentiation of mesenchymal stem cells, chondrocyte proliferation and synthetic activities of osseous and cartilaginous cells and remodelling of cartilage tissue [6].

The application of biologic treatments such as Platelet Rich Plasma (PRP) in musculoskeletal disorders are growing significantly. It is used in muscular fibrosis, capsular relaxation in the shoulder, spinal fusions, pseudoarthrosis, arthritis, synovitis, tendinous inflammations and lesions of meniscus and articular cartilage [7-10]. PRP is most simply defined as a volume of plasma that has a platelet count above baseline blood levels [11]. The normal platelet count in human blood ranges from 150,000 to 350,000/ μ L [7], whereas PRP is often defined as at least 10^6 platelet/ μ L suspended in plasma. PRP is an autologous blood product that can be injected into damaged areas to deliver platelet derived growth factors (GFs) and promote healing [7]. The autologous nature of PRP theoretically reduces the risk of potential side effects and makes it a good treatment option [12, 13].

Platelets contain three types of granules: lysosomal granules, dense granules, and alpha granules. Alpha granules are the source of GFs, transforming growth factor (TGF- β), including platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1), fibroblastic growth factor (FGF), and epidermal growth factor (EGF); vascular endothelial growth factor (VEGF), platelet-derived epidermal growth factor (PDEGF), they also contain cytokines and chemokines, which are involved in stimulating chemotaxis, cell proliferation and maturation, modulating inflammatory molecules and attracting leukocytes [13]. Dopamine, histamine, serotonin, ADP, ATP, calcium ions, and are stored in dense granules which also have a complex role in tissue modulation and regeneration [13, 14]. Lysosomal granules contain acid cathepsin D and E, hydrolases, elastases and lysozyme [15], and other proteins whose physiological role is not well characterized.

On activation of platelets there is de-granulation and release of growth factors. The timing and cumulative release of growth factors is determined by the activation method but may continue throughout the platelet's 8–10day lifespan [10]. Platelet count correlates with the type and quantity of growth factors released. According to Sundman *et al.* there is positive correlations between platelet counts and both TGF- β 1 and PDGF-AB concentrations within PRP preparations [16]. TGF- β 1 and PDGF-AB are considered to be anabolic growth factors. The mechanism of action of PRP has still not been completely understood but several studies suggest that there is an anabolic effect on chondrocytes, synoviocytes, with a significant increase in cell proliferation and matrix production, as well as an antiinflammatory effect by means of

the regulation of the known catabolic signalling pathway. As per various studies PRP treatment in knee osteoarthritis [17-20] have promising clinical results with pain reduction, functional improvement, faster return to daily and sporting activities and consequent improvement of quality of life.

With our focus on disease progression and pathogenesis of osteoarthritis and increasing availability of novel biological treatments such as Platelet rich plasma, there is a need to study the effect of this newer modalities of treatment.

Aims And Objectives

1. To assess the efficacy of Platelet rich plasma in the patients with early Osteoarthritis of knee.
2. To assess whether it could be a cost-effective disease modifying measure, without major side effects and operative costs.
3. To assess whether it could halt the progression of disease.
4. To assess whether it could be used as a bridge to postpone surgery

Materials And Methods Source of Data

The study was conducted in the Department of Orthopaedics, Adichunchanagiri Institute of Medical Sciences, B.G.NAGARA after obtaining ethical clearance. This study consisted of 70 adult patients of either sex visiting outpatient department of the hospital. Patients diagnosed with early osteoarthritis knee were included in the study during the period from December 2018 to June 2020. The follow up visit was at 2 weeks, 3 months and 6 months in this prospective study.

Study Design: Prospective study Sample Size : $3.84 pq/d^2$ p = prevalence of Osteoarthritis of knee = 60% = 0.6 q = 1 - p = 1 - 0.6 = 0.4 d = degree of error = 12% Sample size = 63.98 rounded off to 64. "Considering loss of follow-up / attrition = 10% = 7. Total = 64 + 7 = 71 rounded of to 70.

Inclusion Criteria

1. Early OA of knee - Grade 1 & 2 Kellgren-Lawrence clarification
2. Age > 40years
3. Both genders
4. Pain and swelling of knee with duration of at least 4 months.
5. All the patients who have understood the content and signed the written informed consent will be part of the study.

Exclusion Criteria

1. Kellgren-Lawrence > Grade 2.
2. Patients with documented rheumatoid arthritis.
3. Patients with coagulopathies.
4. Immunosuppressed patients.
5. Patients with underlying infections.
6. Platelet count of < 1,50,000.
7. Patients with lower limb deformities.
8. Patients with secondary osteoarthritis of knee
9. Patients with coexisting backache
10. Patients who have received steroid injections within past 6 months.
11. Patients not willing for procedure.
12. Patients who have undergone previous surgery of knee joint.

Methodology: A detailed clinical history of the patient was elicited. A general physical examination and Local examination of the affected knee was done and required basic investigations done. Plain antero-posterior and lateral weight bearing radiograph of bilateral knee was taken. On the basis of the radiographs Kellegren-Lawrence grading was done.

Pre injection investigations

1. Routine Blood investigations: Complete hemogram, ESR, BT, CT.
2. CRP
3. X ray Knee (standing Anteroposterior view in full extension and Lateral view in partial flexion of 20 degrees).

Before subjecting the patients for investigations and required procedure, patients are informed about the diagnosis, treatment options, possible complications and a written/informed consent will be obtained from each patient/legal guardian.

Pre-Injection Precautions

The American Academy of Orthopaedic Surgeons recommends the following pre injection guidelines:

- a. Avoid corticosteroid medications for 2 to 3 weeks prior to the procedure
- b. Stop taking non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen, or arthritis medications.
- c. Do not take anticoagulation medication for 5 days before the procedure
- d. Drink plenty of fluids the day before the procedure.
- e. Some patients may require anti-anxiety medication immediately before the procedure.

Pre injection International Knee Documentation Committee (IKDC) score proforma was filled by the patients.

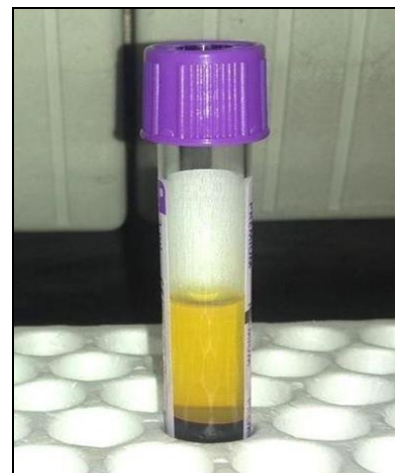
PRP preparation: The PRP extract was prepared at Adichunchanagiri Institute of Medical Sciences and Research Centre using double spin method which yielded adequate concentration of platelets over the baseline levels which is 4 to 5 times the baseline concentration. An 8.5 ml of venous blood was drawn from the cubital vein under aseptic precautions and mixed with acid citrate phosphate dextrose solution in vacutainer. The sample was then placed in a centrifuge and spin at 1200 rpm for 15 minutes. Now using a sterile needle and syringe separate plasma from the vacutainer to a sterile container and then centrifuged this separated plasma at 1500 rpm for 10 minutes. So, 2 ml of this sample was injected into the affected knee joint using an 18gauge needle. Patient received one injection of PRP.1.



Fig 1: blood drawn under sterile precautions



Blood is transferred into ACD tube. Centrifuge machine



Following initial separation centrifugation at 1200 rpm for 15 minutes



Following condensation centrifugation at 1500rpm for 10 minutes



PRP is taken in syringe for injection

Injection technique

The patient is placed in supine position, the knee being slightly bent with the help of popliteal cushion. Knee painted and draped. The infiltration technique used was superolateral approach and needle is inserted at an angle of approximately 45 degree towards the joint line until reaching the space between the patella and the femur.

With a sterile syringe, joint effusion, if any was aspirated and 2 ml PRP was injected into the joint. Sterile dressing was applied at the injection site. After 15-20 minutes of rest, patient is asked to actively flex and extend their knee so that the PRP could spread evenly across the joint space.



Knee painted with betadine, wiped with sterile spirit swab and draped with hole towel



Injection of PRP into the knee joint under aseptic precautions

Post injection protocol and follow up

Patients advised relative rest for 24-48 hours after the injections and limit weight bearing over the joints. patient advised to apply cold therapy three times a day for 10 minutes each time for initial 2 to 3 days. They were allowed Tramadol

(up to a maximum dose of 300 mg per day or Acetaminophen up to a maximum dose of 2 gm/day) for pain and prohibited from using any other analgesics, NSAIDS, steroids or medications influencing platelet count or function.

Results

A prospective study involving 70 patients was undertaken and patients were followed up at 2 weeks, 3 months and 6 months following the course. No patients were lost in follow up. Results were analysed in terms of functional outcome with respect to age, sex and grades of osteoarthritis in the study.

1. Age distribution

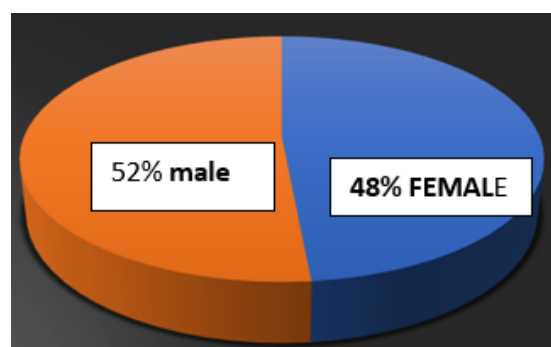
The study shows that the majority of patients were between 41-50 years old (40 %) and 61-70 years old (30 %), the youngest patient was 41 years old and the eldest patient was 78 years old. (Table no.1)

Table 1: Distribution of age of the patients

Age in years	Number of patients	Percentage
41-50	28	40
51-60	14	20
61-70	21	30
70 and above	07	10
Total	70	100

2. Gender distribution

The male (48.5%) to female (51.5%) distribution was almost equal. (Graph 1)



Graph 1: Distribution of Gender

3. Side distribution

Among the 70 patients, 42 patients (60 %) had osteoarthritis of knee on right side and 28 patients (40%) on the left side. (Table no.2)

Table 2: side involved

Side	Number of patients	Percentage
Right	42	60
Left	28	40
Total	70	100

4. Kellgren-Lawrence grading distribution

Majority of patients in the study had Kellgren- Lawrence Grade 2 (70 % patients) as compared to Kellgren - Lawrence Grade 1 (30 % patients). (Table no.3)

Table 3: Distribution of Kellgren – Lawrence Grade

Kellgren-Lawrence grade	Number of patients	Percentage
Grade 1	21	30
Grade 2	49	70
Total	70	100

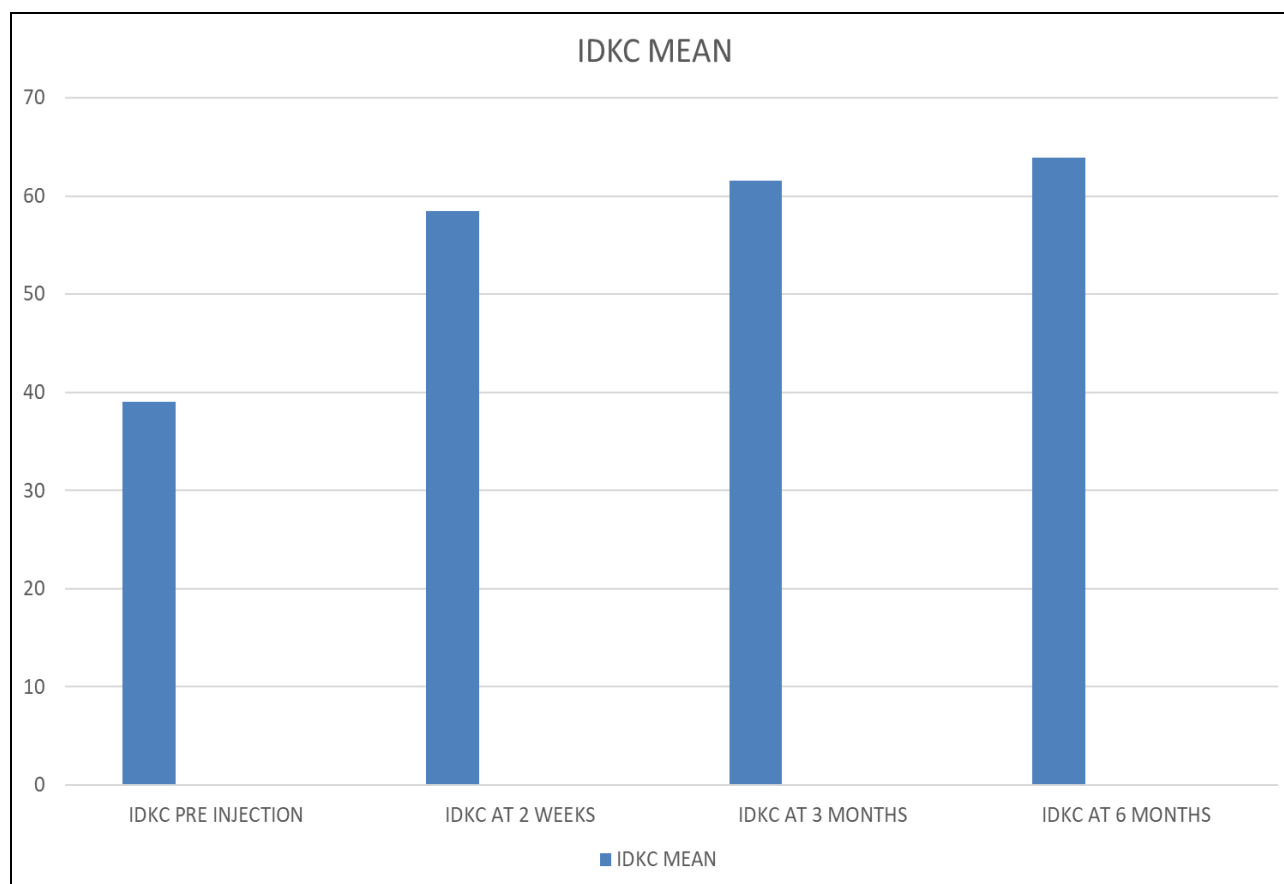
5. IKDC score

The IKDC score showed highly significant improvement in patients with mean pre injection IKDC of 38.99 to mean of

58.46 at 2 weeks, 61.57 at 3 months and 63.86 at 6 months follow up. (Table no.4)

Table 4: IKDC score

	IKDC preinjection	IKDC at 2 weeks	IKDC at 3months	IKDC at 6months
Mean	38.99	58.4614	61.5757	63.8671
Median	39.65	58.9	61.7	63.9
Standard deviation	3.4379	3.2075	2.9249	3.2695



Graph 2: IKDC Score

Discussion

Osteoarthritis is the most common form of degenerative arthritis, affects the elderly resulting in physical, mental and social distress. Osteoarthritis most commonly affects the knee and is more common in elderly women.

Many treatment options were used in the past with the goal of decreasing pain and improve the joint function. They included physiotherapy, life style modifications such as weight reduction and activity modifications and pharmacological therapy such as oral Opioids, NSAIDs, Chondroitin supplementation, glucosamine and Intraarticular injections of steroids and Hyaluronic acid. Surgical options included arthroscopic lavage, debridement in cases of loose bodies, osteotomies and total knee replacement which is the last option in whom all medical management have failed and patients strive with intractable pain and disability.

Intra-articular injectables include corticosteroids, hyaluronic acid, visco supplementation and autologous platelet rich plasma. Intra articular autologous Platelet rich plasma is rich in growth factors, a promising agent for cartilage healing in osteoarthritis of knee, had also disease limiting activities and reduce pain in patients with osteoarthritis of knee. This treatment modality is an opportunity to reduce overall cost for

healthcare system.

Physicians, now are increasingly concentrating in treatment modalities that also reverse disease process and repair damaged tissues. Option available was the intraarticular autologous platelet rich plasma injection, which is recent and have more striking relief in patients.

Keeping this in mind, we decided to do this study to find the efficacy of autologous intra-articular platelet rich plasma injection in osteoarthritis of knee and its functional outcome in early osteoarthritis of knee patients.

With regards to usage of PRP, we injected freshly prepared 2 ml of PRP. As different authors used various plans of PRP injection. Filardo *et al.* used 2 injections of 5 ml volume at 4 weeks interval ^[21]. Cerza *et al.* used 4 injections at 1week interval of volume 5.5 ml. ^[22] Kon *et al* used 3 injections at 2 weeks interval of volume 5ml. ^[23] Spakova *et al.* used 3 injections at 1week interval with volume of 3 ml. ^[24]

AGE - The mean age in our study was 56.5 years and it is similar with other studies. The PRP prepared and used in this study had platelets amplified with an average of 4.2 times that of the baseline count. Aseptic precautions were followed in each and every step of the PRP preparation process. Spakova *et al*, in their study, had an average of 4.5 times amplification

of platelet count [24].

In age wise comparison, individuals were divided into four clusters in our study

cluster one 41-50 years, cluster two 51-60 years and cluster three 61-70 years and cluster 4 more than 70 years. All clusters showed significant increase in IKDC score at 6 months follow up.

Table 5: mean age distribution in various studies

Study	Total number of patients	Mean age
Patel <i>et al.</i>	78	52.8
Bagherifard A <i>et al.</i>	39	55.24
Filardo <i>et al.</i>	32	54.5
Present study	70	56.5

IKDC- In our study the mean IKDC score initially at baseline was with 38.99. There was increase in the IKDC score during follow up. The IKDC score at 6 months of follow up was 63.86 which is a significant increase. This is consistent with

the study by Filardo in which IKDC score increased from 47% of normal and nearly normal knees before the treatment to 78% at the end, then to 73% and 67% at 6 months and 12 months follow-up, respectively, showing a significant improvement at all these follow-up times with respect to the basal level.¹⁹ But our study is better when compared to the study by Lin *et al.* in which the IKDC score increased from baseline score of 35.71% to 47.33% at 6 months follow up.

In our study, from the 2nd week follow up there was a significant reduction of IKDC score up to our 6 months follow up.

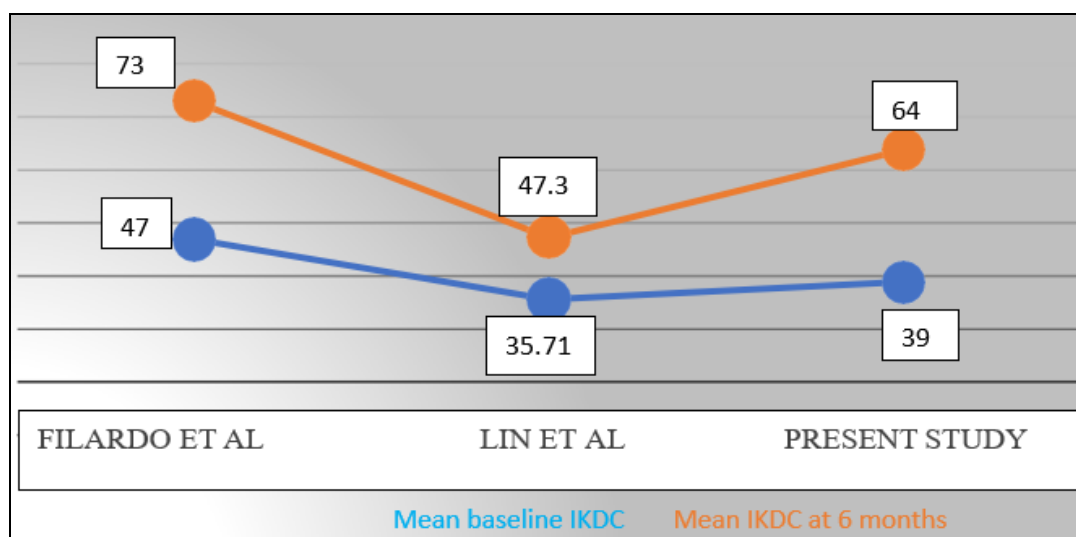
In our study both males and females showed similar trend of increase in IKDC score from mean baseline to 6 months follow up.

In our study both Grade I as well as Grade II showed significant better outcome with

PRP injections, IKDC increased from mean baseline to 6 months follow up in both the Grades. Filardo *et al.*, in their study found that PRP had a better outcome in Grade I and II compared to Grade III and IV [21].

Table 6: Comparison of improvement in IKDC scores in various studies

Study	Mean Baseline IKDC	Mean IKDC at 6 months
Filardo <i>et al</i>	47%	73%
Lin <i>et al</i>	35.71%	47.33%
Present study	38.99%	63.86%



Graph 3: Comparison of improvement in IKDC scores in various studies

Complications

In our study there were no complications except moderate pain in 15 knees with lasted maximum up to 4 days. Similarly, Kon *et al* mentioned about local minor adverse events like mild pain and effusion in some cases (exact number not mentioned) and none persisted more than 2 days except for 1 case which spontaneously resolved after two weeks. The complications in our study were probably due to the stimulation of the body's natural response to inflammatory mediators

Conclusion

On the basis of the current evidence, PRP injections reduced pain more effectively in Osteoarthritis of the knee. PRP injections can be used to treat early osteoarthritis of knee with significant improvement in function and possibly postpone the need for surgical intervention. More large randomized studies of good quality and less bias are needed to test

whether PRP injections can be used as a routine treatment option in management of patients with Osteoarthritis of knee.

Summary

Intra-articular injection of PRP is effective in treating early Grade I and II Osteoarthritis of knee. The study shows outcome with significant improvement of symptoms in patients with age group between 40 and 60.

Our study group did not require analgesics following 1 week after injections till follow up of 6 months. Complications like infection, stiffness and effusions is nil in this study. Unlike steroids it does not increase the risk of infection in future procedures.

This is a cost effective minimally invasive therapy with better outcome improving the quality of life in patients which gives symptomatic pain relief and delays the need for surgical intervention.

However, there are some limitations in this study

- Smaller sample size.
- All grades of Osteoarthritis were not included, for generalization of outcome.
- Our study's follow up duration of 6 months is not enough. However, we are following the patients and looking forward to re-evaluate them at 12 months, 18 months and 24 months.
- We evaluated only clinical parameters by using IKDC scoring system. Radiographic follow up by MRI, may be considered to evaluate the cartilage regeneration (if any) in subsequent research efforts, we could not do this due to the cost and ethical issues.
- We did not evaluate for the contained growth factors in our PRP product.

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