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**ORIGINAL RESEARCH**

# Clinical outcome of Serial Intra-articular injections of Growth Factor Concentrate on long term pain and functional scores in early Knee Osteoarthritis patients

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**Abstract**

**Background**: Osteoarthritis knee is a chronic degenerative joint disease,limiting movement and quality of life of many patients especially elderly. Pharmacological management do not alter the basic joint pathology and can be harmful in long run. Focus is shifted to regenerative medicine in the form of Platelet rich plasma (PRP)/ Growth factor concentrate (GFC).The objective of this study was to retrospectively evaluate the efficacy, safety, and clinical outcome of platelet derived growth factor concentrate in early osteoarthritis knee.

**Methods**: Patients with early knee OA, underwent monthly injections of GFCfor 3 times under ultrasound guidance and evaluated at 3, 6 and 12 months intervals in the pain medicine unit of our anaesthesia department.Outcome was measured in the form of VAS and WOMAC scores, and complications were reported.

**Results:** Out of a total of 35 patients, 30 were available for follow up at the end of 12 months. There was significant improvement in VAS and WOMAC scores at 3, 6 and 12 months from baseline scores. Minimal complications were reported.

**Conclusions:** GFC injections inknee at monthly intervals for 3 months can be an efficient and safe treatment for pain and functional outcome scores in early OA knee patients.

**Keywords:** Regenerative therapy, Osteoarthritis knee,WOMAC score, Growth factor concentrate (GFC)

## Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease affecting millions of people worldwide.[1]The diseaseis a leading cause of disability in the elderly, causing pain, stiffness, and loss of function in articulating joints. OA is characterized by changes in the anatomy of load-bearing joints that lead to degradation of articular cartilage, inflammation of the synovium (synovitis), changes to subchondral bone, and growth of new bone and cartilage (osteophytes) at the joint edge.[2,3]

The most common joints affected by osteoarthritis is knees,followed by hips, joints of hand and spine. Knee OA constitutes 85% of the global disease burdenof OA.[4,5] The main risk factors for primary OAinclude old age, female gender, African American race,obesity, and genetic predisposition.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 05, 2024

Patients present with pain, limitation of movement, varying degrees of stiffness, occasionally effusion, and deformity in severe grades. Radiographically KOA has 4 grades [Kellgren-Lawrence(K-L) classification], based on presence of osteophytes and joint space reduction.[6]
The management goals in Knee OA are to decrease the patient's symptoms while maintaining or improving joint function. Non operative treatment in the form of acetaminophen, NSAIDS, physical therapy, are usually the first line of management, but these agents do not alter the basic joint pathology and they need long term consumption which may lead to adverse events. Interventional methods consist of intra articular (IA) injections, which avert the systemic side effects of oral medications by direct delivery of the drug at the site of disease. With an aim at reverting or stopping the degenerative process, the recent focus has shifted towards regenerative medicine.
Autologous platelet rich plasma(PRP) in different forms has generated a lot of interest with its safety and clinical efficacy reported by many studies, particularly in early grades when compared to hyaluronic acid(HA), steroids or placebo, although its capability to change joint structure is still a matter of debate.[7.8]
Studies have reported favorable pain and function outcomes with intra-articular PRP injections in Knee OA, compared to placebo and other IA therapies, particularly in early grades.[7.8.9]
The concentration of platelets is very high in PRP and the growth factors released by platelet alpha granules not only have favourable effects on chondrocytes and mesenchymal stem cell (MSC)proliferation but also have anti-nociceptive and anti-inflammatory properties via inhibition of nuclear factor kB.[10,11]
Plasma rich in growth factors (PRGF)/ growth factor concentrate (GFC) is a low concentrate PRP devoid of cellular components, with proven safety and efficacy.[12,13] It facilitates delivery of growth factors(GFs) (IGF, VEGF, TGF β1, BMPs, vitronectin, fibronectin among others) directly at the target site without need for in vivo activation and may have lesser adverse reactions related to cellular components.[11] All these GFs have anabolic, anti-inflammatory, chondroprotective and immunomodulatory properties.[14,15]
There are very few studies evaluating the long term efficacy of GFC for Knee OA, therefore we aimed to retrospectively evaluate the clinical efficacy of GFC in OA knee and were available for follow up at 1 year.

## Methods

This study was a retrospective analysis and included 35 patients who visited the pain clinic of our hospital between October 2021 and December 2022 and were followed up for 1year post procedure.Patients who were included were, aged 35-70 yrs with clinical features of unilateral OA (based on American College of Rheumatology criteria) and showing K-L grade I, II on standing anteroposterior and lateral knee radiographs with moderate pain on VAS(>4). Patients had pain for more than 3 months and had received conservative management of short term analgesics with precautions and exercises for at least 1 mth.
Patients were excluded if they had bilateral OA, previous knee surgery, secondary knee arthritis(including inflammatory arthritis), received previous injections in the same knee for last 6 months, presence of local infection, uncontrolled diabetes, patients on steroids or having multiple joint OA, malignancy, coagulopathy, NSAID intake in previous 2 weeks, platelet count of less than 1.5 lakh/µl.
All patients received Growth factor concentrate (GFC) for three times, one month apart.

## Procedure

The commercially available PRGF kit was used in this study. Under full aseptic precautions 8 ml of patient's blood was drawn in the vacutainer. The solution was mixed by inverting

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 05, 2024

several times and then kept upright for 30 min. This results in platelet activation and release of GFs from platelet granules. This solution was then centrifuged at 3400 rpm for 10mins in the centrifuge (Remi 4C). This centrifugation lead to GFC separation from rest of blood components. The tube final components are the propriety solution + cellular components at bottom with GFC (yellowish fluid) at the top and thixotropic gel in between them. This GFC was transferred to another sterile syringe. The final volume of 2-2.5 ml of GFC concentrate was obtained.

Again under full aseptic precautions and USG guidance the GFC was administered in the suprapatellar recess of the knee after local anaesthetic administration at the level of skin only.

After 30 min of the procedure, patients were sent home. Tablet paracetamol 650 mg was advised TDS for 3-5 days and then as and when required. Antibiotics were given for 3 days. Patients were instructed regarding life style modifications andto start exercises as soon as possible and avoid any other drugs like NSAIDS and steroids. A total of 3 injections one month apart were given in each patients.

The primary outcome measures were visual analogue scale (VAS) for pain and Western Ontario and McMaster Universities Arthritis Index(WOMAC). The patients were evaluated for subjective improvement in pain, stiffness and physical function by the WOMAC score.

WOMAC score is widely used in the evaluation of Hip and Knee Osteoarthritis. It is a self-administered questionnaire consisting of 24 items divided 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

The test questions are scored on a scale of 0-4, which correspond to: None (0), Mild (1), Moderate (2), Severe (3), and Extreme

The scores for each subscale are summed up, with a possible score range of 0-20 for Pain, 0-8 for Stiffness, and 0-68 for Physical Function. Usually a sum of the scores for all three subscales gives a total WOMAC score. Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.

For VAS the Minimal clinically important difference[MCID] of >2 point difference of mean was considered significant and it was measured on a 10cm line (0-3 mild pain, 4-6 moderate pain ,7-10 –severe pain). For WOMAC score, MCID was >12% of baseline. VAS and WOMAC were calculated at baseline and then at 3,6 and 12 months of last injection. Complications of procedure and side effects if any were noted.

Data were organized, tabulated, and statistically analysed using SPSS Statistics v 29.0. The difference between all the scores was represented in the form of mean and standard deviation (SD) and comparison was done using paired t test.$p < 0.05$ was considered statistically significant.

## Results

Out of 30 patients who were available for final follow up at 1 year, there were more females (n=22)than males (n= 8). Most of the patients belonged to 45 to 55 years (n = 20) followed by the age group >55 years (n = 10). Most of the patients were in K-L grade II (n=24) (Table 1).

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 05, 2024

**Table 1: Relation between various patient-related factors (sex, age, KL grade)**

| Parameters | | No. of patients ( 30) |
|---|---|---|
| Sex | Male<br>Female | 8<br>22 |
| Age | 45-55 yrs<br>>55 yrs | 20<br>10 |
| KL Grading | Grade I<br>Grade II | 6<br>24 |

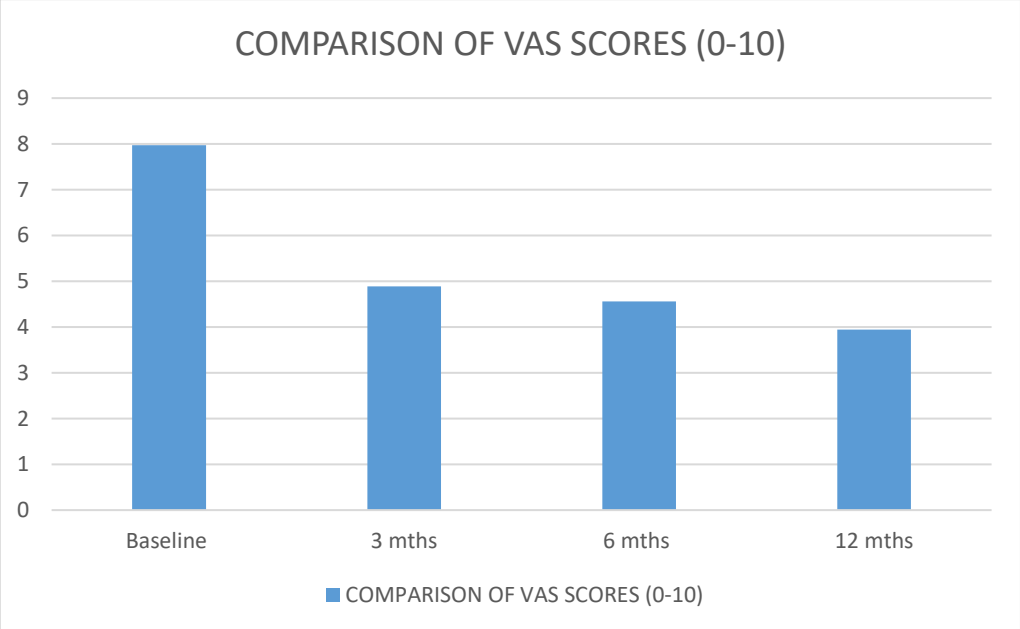
There was significant reduction in VAS scores at 3, 6 and 12 mth of follow up. ($p< 0.05$). Mean VAS scores improved to 4.89 ± 1.20, 4.56 ± 1.22 and 3.94 ± 1.36 at 3,6 and 12 months respectively. This improvement from baseline (7.97 ± 0.66) was statistically significant ($P < 0.001$). (Table 2 and Fig 1).

A reduction in WOMAC scores was evident from the first follow-up at 3 mth. Baseline mean WOMAC was61.15 ± 5.282. The patients reported maximum improvement in WOMAC Scores to 25.23 ± 7.818 at 3 mth($p<0.001$). The benefit was statistically significant at 6 months, score of 31.70 ± 6.003($p<0.001$) and at 12 months,score of 36.20 ± 4.727 ($p < 0.02$). These scores were less as compared to scores at 3 mths follow up.(Table 2 and Fig 2).

**Table 2: WOMAC and VAS scores at baseline and at follow up after the last intervention**

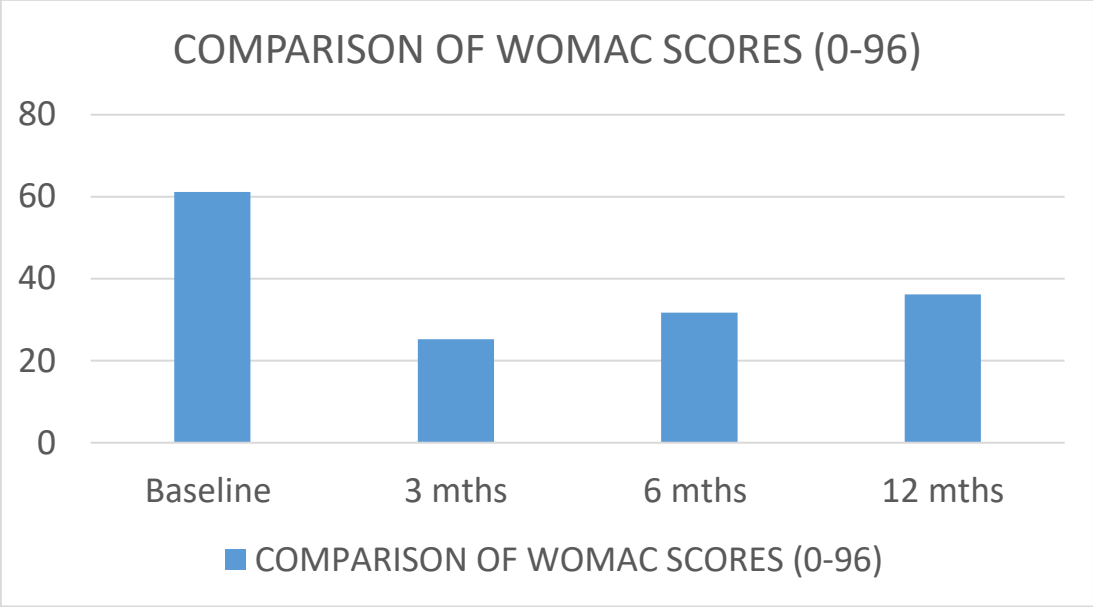
| | VAS (1-10) | | WOMAC score (0-96) | |
|---|---|---|---|---|
| | **Mean ± SD** | **p value** | **Mean ± SD** | **p value** |
| Baseline | 7.97 ± 0.66 | - | 61.15 ± 5.282 | - |
| 3 mth | 4.89 ± 1.20 | < 0.001 | 25.23 ± 7.818 | < 0.001 |
| 6 mth | 4.56 ± 1.22 | < 0.001 | 31.70 ± 6.003 | < 0.001 |
| 12 mth | 3.94 ± 1.36 | < 0.001 | 36.20 ± 4.727 | < 0.02 |

**Fig 1: Comparison of VAS Scores at baseline and at 3, 6 and 12 months follow up**



ISSN: 0975-3583,0976-2833 VOL15, ISSUE 05, 2024

**Fig 2: Comparison of WOMAC Scores at baseline and at 3, 6 and 12 months follow up**




Procedural complications were minimal. Incidence of mild knee pain following monthly injections was 10%, 8% and 8% respectively and lasted for 2-3 days. No other complication was reported.

**Discussion**

Our study shows that GFC injections at monthly intervals for 3 times, improve the pain VAS and functional WOMAC scores significantly even at a follow up of 1 year in early knee osteoarthritis patients.

Blood derived products in different forms (PRP or autologous conditioned plasma[ACP], autologous conditioned Serum[ACS], concentrated growth factor[CGF], homologous platelet lysate[PL]) have been used for treatment of Knee OA for many years now. They differ in method of preparation mainly and are reported to have different concentration of cells, cytokines and growth factors. PRP or ACP is obtained from whole blood collected in anticoagulant containing tubes which are subjected to differential centrifugation, the final product yields a plasma which is rich in platelets.[16]

Platelet Rich Plasma (PRP) is a biologic therapy that uses the patient's own blood to obtain final product with a higher platelet concentration than patient's blood. The platelets are rich in growth factors which are released in vivo, thus delivering them for regeneration to the desired place. The biological effects of PRP mimic and influence biological processes such as inflammation, analgesia, and cell stimulation, thus promising therapeutic potential of the method. These processes are required for maintenance, correct function and homeostasis of the joint, influencing all tissues. Changes in one joint element have an impact on the rest, outstanding the cellular and molecular interaction between the cartilage and subchondral bone.Therefore the joint is an optimal therapeutic target for PRP therapy, which favours biological environment for joint repair.[17]The yield of growth factors from PRP in vivo can be variable due to various factors like quality of PRP, that is, amount, frequency, concentration and type (leucocyte rich or poor) and patient factors like platelet count, age, gender, grade of OA) and thus variable results reported in some studies.[18]GFC is an activated platelet concentrate, devoid of RBCs and WBCs, requires single centrifugation and small volume of patient's blood. According to one school of thought, PRP activation prior to application ensures GFs are released optimally, but the other argument states that appropriate GF release will occur in response to in vivo environment.[19]

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 05, 2024

Recently the PRGF intraosseous infiltration application in Knee OA has been reported to delay the need for knee arthroplasty between 1.5 and 5 years.[20]Antonio Rios Luna et al devised an office based intraosseous infiltration of PRGF to treat KOA, making this therapy less cumbersome, more accessible, and cost-efficient.[21]M Sanchez et al compared knee infiltrations with PRGF-Endoret or with hyaluronic acid (HA) (three injections on a weekly basis). The primary outcome measure was a 50 percent decrease in knee pain from baseline to week 24, the WOMAC Index; the rate of response using the criteria of the OMERACT-OARSI and safety.They found that PRGF-Endoret has both a faster time to response and more enduring beneficial effect than hyaluronic acid. Treatment with PRGF-Endoret resulted in clinically significant reductions in knee pain, stiffness and physical function.[22]

Sayed et al compared the candidates with symptomatic knee osteoarthritis who received two intra-articular injections of PRGF, 3 weeks apart or received three weekly injections of HA. There was significant improvement in VAS score and global, pain, and ADL score of Lequesne by passing 12 months from injection in PRGF compared to HA.[23,24]Saraf et al concluded that injections of GFC result in improvement of subjective pain and function outcome scores, sustaining up to 12 months in KOA grade II and III. GFC also lead to significant reduction in serum levels of cartilage degradation biomarker coll2-1.[25]

Our patients did not report any complications. Side effects of GFC such as mild knee pain following monthly injections had an incidence of 10%, 8% and 8% respectively and lasted for 2-3 days.The limitations of this retrospective observational study are a small sample size, no comparison group, and inclusion of patients with grade 1, 2 OA knee only. No growth factor quantification could be done in this study. Further comparative studies, providing further long term outcomes are needed.

## Conclusion

GFC injections in knee at monthly intervals for 3 months can be an efficient and safe treatment for pain and functional outcome scores in early OA knee patients.

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## Conflicts of Interest

The author declares that there is no conflict of interest regarding the publication of this paper.

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ISSN: 0975-3583,0976-2833 VOL15, ISSUE 05, 2024


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ISSN: 0975-3583,0976-2833 VOL15, ISSUE 05, 2024

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