



Efficacy of intra-articular concentrated growth factor, platelet-rich plasma, and hyaluronic acid in knee osteoarthritis: A comparative analysis

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Abstract

Aim: Knee osteoarthritis (KOA) is a prevalent chronic joint condition causing substantial pain and disability. In recent years, intra-articular injections of platelet-rich plasma (PRP), concentrated growth factor (CGF), and hyaluronic acid (HA) have emerged as promising KOA therapies. We aimed to compare the effects of intra-articular CGF, PRP, and HA in KOA patients.

Materials and Methods: Patients diagnosed with KOA and who were grade 2-3 according to the Kellgren-Lawrence classification in radiological imaging were included in the study. Patients were randomized into three groups receiving a single injection of either HA, PRP, or CGF. Patients were evaluated for pain scores using the visual analog scale (VAS) and for pain, stiffness, and physical function using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) before and 1 and 6 months after the procedure.

Results: Of 60 patients, 41 were female and 19 were male. According to the Kellgren-Lawrence classification, 27 patients had grade II and 33 patients had grade III KOA, with a similar distribution among the three groups. The VAS scores showed a statistically significant decrease in all groups at 1-month and 6-month follow-up compared to pre-procedural scores. However, there was no significant difference among the groups in terms of VAS scores. The WOMAC-pain, -stiffness, -physical function scores also showed a significant decrease in all groups at 1-month and 6-month follow-up compared to pre-procedural scores. The CGF group had the lowest WOMAC scores at both time points, with a statistically significant difference compared to the PRP group ($p < 0.05$). Patient satisfaction rates were high in all groups, while the satisfaction rate was highest in the CGF group.

Conclusion: CGF demonstrated superior pain alleviation and functional improvement compared to PRP and HA. Although the results of this study demonstrate the potential of regenerative treatments for KOA, more research with larger samples and longer follow-up is needed for robust validation. Additionally, the standardization of treatment protocols is important.

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Introduction

Knee osteoarthritis (KOA) is a chronic joint disease, with its prevalence increasing with age and obesity. Worldwide estimates suggest that approximately 13% of women and 10% of men aged 60 years and older experience symptoms of KOA. This prevalence significantly rises to around 40% for individuals aged over 70 years. Additionally, asymptomatic KOA is estimated at 240 cases per 100,000 persons per year [1]. Risk factors for KOA include age, gender, obesity, joint injuries (resulting from work or sports activities), and geographic region. KOA reduces individuals'

quality of life by causing joint pain, muscle weakness, and physical disability. Additionally, chronic pain can lead to anxiety, depression, and cognitive dysfunction, which affect daily life socially and economically [2].

The management of KOA typically involves conservative treatment options, such as exercise, physiotherapy, pharmacotherapy, and joint injections [3]. In recent years, the use of intra-articular injections of platelet-rich plasma (PRP), concentrated growth factor (CGF), and hyaluronic acid (HA) has emerged as a promising treatment option for KOA [3-5]. These treatments are minimally invasive, safe, and effective in reducing pain and improving joint function [6].

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CGF is a third-generation platelet concentrate that contains more growth factors than PRP and has a harder fibrin structure [7,8]. Previous studies have demonstrated that CGF can enhance osteogenesis and angiogenesis, leading to improved bone regeneration [9]. PRP is a concentrate of platelets and growth factors obtained from the patient's blood through centrifugation. It has been shown to reduce pain and improve function in patients with KOA [10]. HA is a high molecular weight biological polymer that is naturally present in the synovial fluid and cartilage matrix. It acts as a lubricant and shock absorber in the joint and has been used as a treatment option for KOA for many years [11,12].

Several clinical trials have investigated the effectiveness of these treatments in patients with KOA. However, there is a lack of consensus on the comparative effectiveness of these treatments. Some studies have shown that PRP is more effective than HA in reducing pain and improving function in patients with KOA [13-16]. However, there is still no consensus on the optimal dose and frequency of PRP use for KOA. The literature reports varying recommendations, ranging from weekly to every 3-4 weeks schedule with single to multiple injections [17,18].

The lack of agreement on the comparative effectiveness of these treatments may be attributed to the absence of uniformity in PRP preparation techniques, as well as variations in patient-related factors such as disease severity and activity level. Furthermore, several studies have investigated the effectiveness of CGF in treating KOA, and the results have been promising [19,20]. In contrast to the controversy surrounding PRP, some studies have shown that CGF is more effective than PRP and HA in improving knee function and reducing pain in patients with KOA [7,19,20]. CGF has a higher concentration of growth factors than PRP, and its fibrin structure is harder, which may lead to better growth factor release over time [21,22]. CGF has also been found to enhance osteogenesis and angiogenesis, resulting in improved bone regeneration, which could further contribute to the observed improvements in pain and function [7]. Although the comparative effectiveness of these treatments is not yet clear, they all offer a promising alternative to traditional treatments and have the potential to enhance the quality of life of patients with KOA. Given the rising prevalence of KOA, identifying the most effective treatments for this debilitating disease is crucial.

In this study, we aimed to compare the effects of intra-articular CGF, PRP, and HA in patients with KOA. Our study will help clinicians make informed decisions about the most effective treatment options for their patients with KOA, considering the comparative effectiveness of these treatments.

Materials and Methods

The current study was approved by the local ethical committee of Firat University, registration number 2023/06-28. Written informed consent was obtained from all the patients. Patients who presented to the pain clinic with knee pain, whose clinical and physical examination was compatible with KOA, and who were grade 2-3 according to the Kellgren-Lawrence classification in radiological

imaging were included in the study. Patients with a history of knee trauma or surgery, who had received intra-articular injection in the past 6 months, who have bleeding, infection, or skin lesions at the injection site, and who have history of allergy or hypersensitivity to the medication used were excluded from the study.

A total of 60 patients were randomized into three groups. The first group received 3 ml of intra-articular HA (n=20). In the second group, approximately 10 ml of venous blood was collected in anticoagulated tubes, centrifuged at 3200 rpm for 8 minutes, and 3 ml of intra-articular PRP, consisting of 2 ml of plasma and buffy coat, was obtained (n=20). In the third group, approximately 10 ml of blood was collected in anticoagulated tubes, centrifuged at 3200 rpm for 8 minutes, and transferred to an activation tube containing 0.5 ml of calcium chloride in plasma and buffy coat. The resulting 3 ml of intra-articular CGF was obtained after centrifugation at 3500 rpm for 4 minutes (n=20). All patients received a single injection.

Demographic characteristics such as age, weight, and height were recorded, and body mass index (BMI) was calculated. Patients were evaluated for pain scores using the visual analog scale (VAS) and for pain, stiffness, and physical function using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) before and 1 and 6 months after the procedure. Patient satisfaction was evaluated at the 6-month follow-up. Any side effects or complications were also recorded.

Statistical analysis

To determine the minimum number of participants required for adequate statistical power, G-power Analysis software (G Power 3.1.9, University of Düsseldorf, Germany) was used. The sample size for each group was calculated to be 20 individuals, considering previous studies with $\alpha=0.05$, power of 90%. All data were presented as mean \pm standard deviation (mean \pm SD). One-way analysis of variance (ANOVA) was used to evaluate the demographic characteristics of the patients (age, weight, gender, BMI), but first, the homogeneity of variances was determined by the Levene test. To determine differences between groups, the Tukey HSD test was used as a post-hoc test for ANOVA. For within-group analysis, variance analysis was used for repeated measurements. $P < 0.05$ was considered statistically significant.

Results

The study enrolled a total of 60 patients, with a mean age of 66.33 years (range: 41-93 years). Among them, 41 were female and 19 were male. According to the Kellgren-Lawrence classification, 27 patients had grade II and 33 patients had grade III KOA, with a similar distribution among the three groups. There was no difference among the groups in terms of demographic characteristics. The demographic characteristics of the patients are summarized in Table 1.

The VAS scores showed a statistically significant decrease in all groups at 1-month and 6-month follow-up compared to pre-procedural scores. However, there was no significant difference among the groups in terms of VAS scores.

Table 1. The demographic characteristics of the patients.

	Group I (HA) n=20	Group II (PRP) n=20	Group III (CGF) n=20
Sex (Female/Male)	14/6	16/4	11/9
Age (year)	70.05	69.05	59.9
Length (cm)	166.35	162.75	165.35
Weight (kg)	81.5	78.75	83.5
BMI (kg/m ²)	29.61	29.83	30.21
Side (Right/Left)	10/10	12/8	11/9
Kellgren-Lawrence Classification (Stage II/III)	11/9	8/12	8/12

Values are expressed as mean or number. BMI; body mass index, HA; hyaluronic acid, PRP; platelet-rich plasma, CGF; concentrated growth factor.

Table 2. Comparison of pre- and post-procedure VAS scores in the groups.

VAS score	Group I (HA) n=20	Group II (PRP) n=20	Group III (CGF) n=20
Pre-procedure	7.25±0.16	6.75±0.22	6.40±0.15
1 st month	3.75±0.29	4.30±0.37	3.35±0.39
6 th month	3.75±0.21	4.40±0.35	3.35±0.39
p-value	<0.05	<0.05	<0.05

Values are expressed as mean±standart deviation VAS; visual analog scale, HA; hyaluronic acid, PRP; platelet-rich plasma, CGF; concentrated growth factor P-value is obtained with ANOVA; Tukey HSD.

Table 3. Comparison of pre- and post-procedure total WOMAC scores in the groups.

WOMAC-Total	Group I (HA) n=20	Group II (PRP) n=20	Group III (CGF) n=20
Pre-procedure	57.96±3.16	63.74±3.59	50.57±2.34
1 st month	37.80±3.92	44.73±4.07	28.99±3.19*
6 th month	30.77±4.49	39.37±4.30	23.53±3.45*
p-value	<0.05	<0.05	<0.05

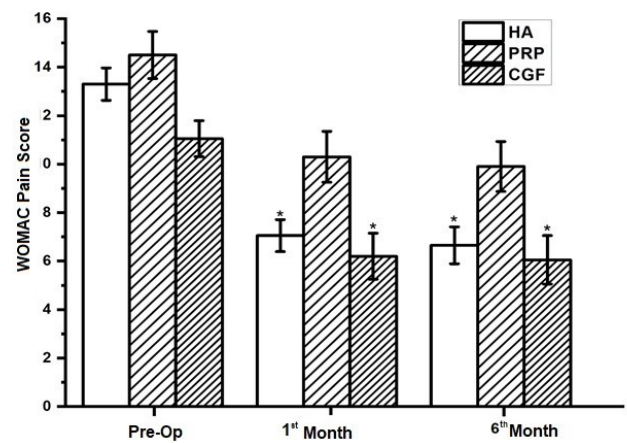
Values are expressed as mean±standart deviation WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index, HA; hyaluronic acid, PRP; platelet-rich plasma, CGF; concentrated growth factor P-value is obtained with ANOVA; Tukey HSD

* When comparing the 1st and 6th month scores of CGF group with the PRP group, p-value <0.05.

Table 4. The patient satisfaction rates for each group.

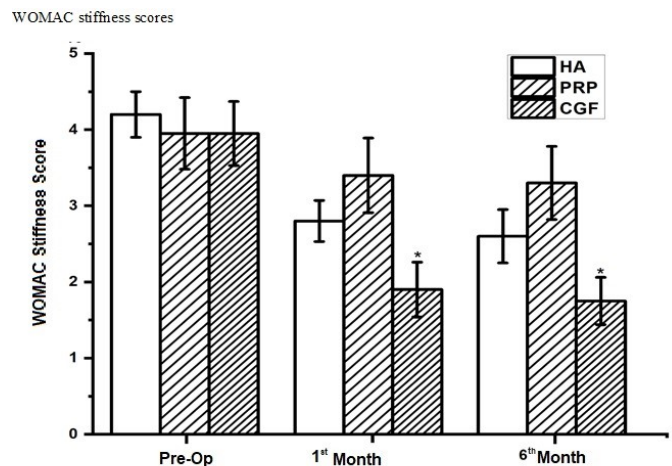
Satisfaction	Group I (HA) n=20	Group II (PRP) n=20	Group III (CGF) n=20
Very-satisfied	6 (30%)	3 (15%)	7 (35%)
Satisfied	6 (30%)	2 (10%)	7 (35%)
Semi-satisfied	2 (10%)	14 (70%)	4 (20%)
Not-satisfied	6 (30%)	1 (5%)	2 (10%)

Values are expressed as number (percent) HA; hyaluronic acid, PRP; platelet-rich plasma, CGF; concentrated growth factor.



WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index, HA; hyaluronic acid, PRP; platelet-rich plasma, CGF; concentrated growth factor P-value is obtained with ANOVA; Tukey HSD *When the 1st and 6th month scores of HA and CGF groups were compared with the PRP group, p<.05.

Figure 1. The differences in WOMAC- pain scores among the groups.



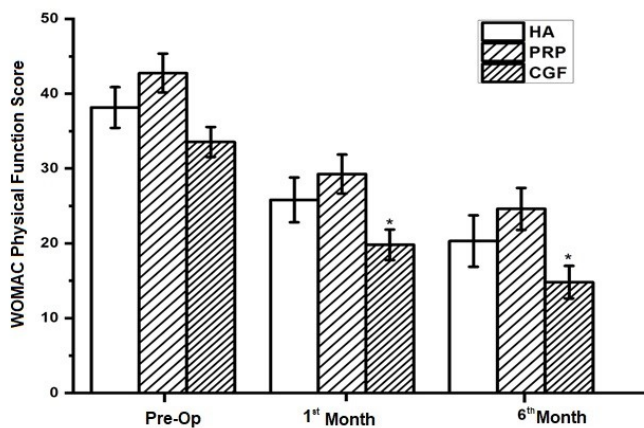
WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index, HA; hyaluronic acid, PRP; platelet-rich plasma, CGF; concentrated growth factor P-value is obtained with ANOVA; Tukey HSD * When the 1st and 6th month scores of CGF group was compared with the PRP group, p<.05.

Figure 2. The differences in WOMAC-stiffness scores among the groups .

Details of the VAS scores for each group are presented in Table 2.

The WOMAC-pain score also showed a significant decrease in all groups at 1-month and 6-month follow-up compared to pre-procedural scores. The CGF group had the lowest pain score at both time points, with a statistically significant difference compared to the PRP group (p<0.05). The HA group had a significantly lower pain score at 1-month and 6-month follow-up compared to the PRP group (p<0.05). The differences in WOMAC-pain scores among the groups are presented in Figure 1.

The WOMAC-stiffness score also showed a significant decrease in all groups at 1-month and 6-month follow-up



WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index, HA; hyaluronic acid, PRP; platelet-rich plasma, CGF; concentrated growth factor P-value is obtained with ANOVA; Tukey HSD * When the 1st and 6th month scores of CGF group was compared with the PRP group, $p < .05$.

Figure 3. The differences in WOMAC-physical function scores among the group

compared to pre-procedural scores. The CGF group had the lowest stiffness score at both time points, with a statistically significant difference compared to the PRP group ($p < 0.05$). There was no significant difference among the other groups. The differences in WOMAC-stiffness scores among the groups are presented in Figure 2.

The WOMAC-physical function score showed a significant decrease in all groups at 1-month and 6-month follow-up compared to pre-procedural scores. The CGF group had the lowest physical function score at both time points, with a statistically significant difference compared to the PRP group ($p < 0.05$). There was no significant difference among the other groups. The differences in WOMAC-physical function scores among the groups are presented in Figure 3.

The total-WOMAC score showed a statistically significant decrease in all groups at 1-month and 6-month follow-up compared to pre-procedural scores. The CGF group had the lowest total WOMAC score, with a statistically significant difference compared to the PRP group ($p < 0.05$). There was no significant difference among the other groups. The differences in total-WOMAC scores among the groups are presented in Table 3.

Patient satisfaction rates were high in all groups, with 85% of patients reporting that they were satisfied with the treatment at 6th month, while the satisfaction rate was highest in the CGF group. However, there was no significant difference in patient satisfaction rates among the groups. The patient satisfaction rates for each group are presented in Table 4.

After the procedure, 5 patients in the PRP group and 4 patients in the CGF group had knee swelling and pain, and their complaints lasted for 1 week. No significant adverse effects or complications were reported in other patients.

Discussion

In this study, we conducted a comprehensive comparison of the effects of HA, PRP, and CGF applications, which are commonly employed in the treatment of KOA, focusing on their impact on pain and WOMAC scores. Our findings underscored significant improvements in both pain levels and WOMAC scores for all three treatments, following a single-session application at the 6-month evaluation. Particularly noteworthy was the discernibly greater improvement observed within the CGF group, coupled with higher patient satisfaction in this cohort.

The fundamental objectives in treating KOA encompass pain management, reduction of physical restrictions, enhancement of the overall quality of life, and ideally, halting the progression of the underlying pathological processes. Tailoring treatment strategies to individual patients is imperative, factoring in considerations such as disease severity, activity level, comorbidities, and patient expectations [23]. Among the interventions, intra-articular injections yield positive effects on pain and functional status in KOA. Notably, while intra-articular steroid injections effectively alleviate pain, inflammation, and stiffness, they exhibit no impact on disease progression and have even been linked to adverse effects on joint cartilage [24,25]. In contrast, HA, a high molecular weight biological polymer, holds the potential to enhance the viscosity and elasticity of synovial fluid, exerting a lubricating effect on cartilage. This, in conjunction with its anabolic effect promoting proteoglycan synthesis and mitigation of fibronectin-related cartilage harm, positions HA as a preferred alternative to corticosteroids for addressing pain, particularly in the later stages of KOA [26].

Recent years have witnessed the ascendancy of regenerative therapies, aimed at not merely restoring joint functionality but also inducing tissue regeneration. Regenerative medicine, an emerging field, encapsulates the utilization of naturally occurring repair mechanisms or biomimetic products to rectify pathological tissues [5]. PRP, prolotherapy, CGF, and stem cell therapies constitute integral components of this therapeutic realm [4]. PRP, for instance, serves as a readily accessible autologous agent infused with growth factors like insulin-like growth factor, platelet-derived growth factor, and fibroblast growth factor, which collectively quell inflammation, foster tissue regeneration, and spur local stem cells into action. PRP injections have demonstrated significant clinical enhancements in pain, physical function, and stiffness in moderate KOA patients [27-30]. Yet, the optimal dosage and frequency remain to be definitively established. Although single-dose PRP manifests comparable pain improvement to multiple doses, the latter exhibits more pronounced enhancement in joint functionality. Meanwhile, early-stage KOA patients tend to benefit more from multiple PRP injections, whereas advanced-stage patients seem to derive no discernible difference from various dosing regimens [13,16]. The current study, focusing on stage II and III patients, corroborates the potency of single-dose PRP injections, resulting in notable improvements across the board.

The third generation of platelet derivatives, encompassed within the framework of CGF, presents a notable devel-

opment. Contrasted with PRP, CGF necessitates a dual centrifugation technique along with the addition of thrombin and anticoagulants. The resultant CGF releases a spectrum of growth factors that stimulate proliferation, extracellular matrix mineralization, angiogenesis, and tissue remodeling [31-33]. Additionally, CGF's propensity to promote osteogenesis adds another layer of therapeutic potential [31,34,35]. While CGF holds promise, its application in treating KOA is relatively underexplored, with experimental studies and case reports remaining the primary sources of information. Originally introduced and popularized by Anitua et al., the employment of plasma rich in growth factors (PRGF-Endoret) marked a pivotal advancement [36]. Their investigation showcased augmented WOMAC and VAS scores in contrast to HA. Subsequent to this, Vaquerizo et al. exhibited enhanced outcomes through a regimen involving three weekly PRGF injections as opposed to a singular long-acting HA injection, observed at both the 24 and 48-week marks [37]. PRGF is recognized for its propensity to engender anti-inflammatory effects, with its concomitant growth factors aiding the process of cartilage repair. Similarly, a serialized approach to administering CGF via three monthly injections has evinced substantial amelioration in subjective pain and functional outcome scores, persisting for a duration of up to 12 months in patients with grades II and III KOA. Notably, this protocol was also associated with a significant reduction in serum levels of the cartilage degradation biomarker coll2-1 [19].

In our present study, the cohort treated with CGF manifested a superior degree of enhancement in relation to pain and functional outcomes compared to both the PRP and HA groups. This noteworthy finding might potentially be attributed to the heightened concentration of growth factors inherent in CGF, in contrast to PRP. Prior research underscores the variability in growth factor concentrations within PRP, a consequence of variances in processing techniques and equipment [28]. Importantly, the structural composition of CGF's fibrin was found to be denser than that of PRP, a characteristic that plausibly augments sustained growth factor release over an extended period [31]. Additionally, antecedent studies have demonstrated CGF's ability to elicit osteogenesis and angiogenesis, mechanisms that potentially contribute to improved bone regeneration, thereby potentially explaining the observed enhancements in pain and functionality within the CGF group [33,35]. Impressively, patients within the CGF cohort also exhibited higher satisfaction rates, a phenomenon possibly attributable to the more pronounced enhancements in both pain alleviation and functional improvement observed within this subgroup [38].

However, acknowledging the limitations of our study is crucial. The relatively small sample size and the need for an extended follow-up period to ascertain the durability of the effects represent important considerations. Additionally, the study's applicability is restricted to KOA patients within Kellgren-Lawrence stages II-III, warranting caution when extending the results to patients with more advanced disease stages. Moreover, the absence of a control group mandates careful interpretation of the findings, as the placebo effect cannot be entirely ruled out.

Conclusion

Our study underscores the potential of intra-articular CGF, PRP, and HA injections to alleviate pain and improve functional status in KOA patients. Among these interventions, CGF demonstrates notable promise. However, further research with larger cohorts and extended follow-up periods is required for validation and optimization of treatment approaches. Our investigation also highlights the need for standardized PRP and CGF administration practices due to significant concerns related to solution procurement, platelet concentration determination, and equipment variations. Ultimately, our findings provide valuable insights to guide clinicians in developing tailored strategies for enhanced KOA patient management.

Ethical approval

Firat University ethics committee approval was obtained (No: 2023/06-28).

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