A Prospective, Randomized, Controlled Trial Comparing Clinical Outcomes of Intraarticular Platelet Plasma Concentrate and Growth Factors versus Corticosteroid Injections in the Treatment of Knee Osteoarthritis

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Abstract

OBJECTIVES: To compare and evaluate the efficacy of intraarticular platelet-rich growth factor (PRGF) versus intraarticular steroid injections.

MATERIAL AND METHODS: A prospective, blinded, randomized controlled trial was conducted by enrolling 650 patients with knee osteoarthritis (OA) who did not respond to the combination of oral medication and physiotherapy. After computer-based randomization and exclusion, the number of patients in our study was 557. Patients were divided into 2 groups. Group 1 (310 patients) received intraarticular PRGF injection and group 2 (247 patients) received intraarticular injection of 40-mg triamcinolone solution. The post-trial follow-up period ranged from 12 to 18.5 months. The primary endpoints were the International Knee Documentation Committee (IKDC) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores and the secondary endpoints were the Visual Analog Scale (VAS) pain scores.

RESULT: The IKDC scores were measured at baseline, 2-, 4-, 6-, and 12-month follow-up after the injection. The IKDC scores of group 1 (PRGF treatment) were 39.48 ± 7.94, 48.47 ± 8.49, 51.04 ± 8.26, 51.54 ± 8.07, and 52.14 ± 9.86, and the IKDC scores of group 2 (steroid treatment) were 38.30 ± 7.26, 45.64 ± 9.45, 45.60 ± 10.24, 45.79 ± 9.96, and 43.14 ± 11.63, respectively. WOMAC scores were collected at the same period. The WOMAC scores of group 1 (PRGF treatment) were 56.91 ± 14.89, 42.54 ± 15.64, 38.13 ± 14.95, 36.41 ± 15.23, and 36.28 ± 17.86 and, for group 2 (steroid treatment), the scores were 56.73 ± 11.69, 45.22 ± 17.00, 46.37 ± 17.52, 46.47 ± 17.47, and 50.84 ± 20.29, respectively. Patients in group 1 and 2 both showed improvement after the treatment. The data showed significant statistical difference ($p < 0.01$) in almost all of the scoring, in favor of the PRGF injection, except no significance at the first 2 months (WOMAC, $p = 0.053$). The secondary outcome revealed a similar trend with significant statistical difference ($p < 0.01$) as the primary outcome did. PRGF was collected according to our novel Plasma Platelet Concentrate and Growth Factors (PP&GF) protocol. The average platelet concentration prepared by PP&GF protocol was 6 times (3-8.69) higher than the normal platelet concentration. There was no knee infection at the end of the follow up.

CONCLUSION: PRGF and intraarticular steroid injection result in good outcomes, however in terms of functional scoring (WOMAC and IKDC), PRGF treatment demonstrated significantly better clinical outcomes at 6- to 12-month follow-up. PRGF treatment can become an effective alternative treatment in knee OA. However, optimal preparation techniques are essential for improved clinical outcomes, and further investigation with long-term follow-up is recommended.

Keywords: knee osteoarthritis, corticosteroid injection, platelet-rich plasma, platelet-rich growth factor, Kellgren-Lawrence, surgical intervention

Knee Osteoarthritis (OA) is steadily increasing, affecting the patient's quality of life by the progressive loss of cartilage thickness and accelerated cartilage degeneration to end-stage arthritis.[1,2] The guideline of OA initial treatments is patient education, oral medication, intraarticular injections, and physical therapy. Furthermore, intraarticular injection of corticosteroid is the standard treatment in many guidelines. According to the

2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee, intra-articular steroid injection is strongly recommended as one of the pharmacological approaches.[3] Moreover, the NICE pathway for management of osteoarthritis 2020 states that intra-articular corticosteroid injections should be considered an adjunct to core treatments for the relief of moderate to severe pain in people with osteoarthritis.[4] However, long-term medical complications are concerning.[5,6]

Controversies related to clinical efficacy and platelet concentrated preparations remain.[7,8] Previous meta-analysis revealed the outcome of pain and functional performance assessment of corticosteroid treatment was better than the platelet-concentrated group.[9] With a simple preparation protocol, the recent treatment of platelet rich growth factors, adjusted for platelet concentration, fibrin concentration, leukocyte population, and activator status, demonstrated improved clinical efficacy, safety, and effectiveness for the treatment of knee OA.[10] There was no study comparing the clinical data of platelet-rich growth factors, and the standard treatment of intraarticular corticosteroid injection. The aim of this study was to compare the efficacy of intraarticular injection of platelet-rich growth factor (PRGF) and intraarticular injection of corticosteroid, using clinical parameters such as the International Knee Documentation Committee (IKDC), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Visual Analog Scale (VAS) scores.

Materials and Methods

The prospective, randomized, controlled trial study was conducted from February 2018 to May 2019 at the Biomedical Technology Research and Development Center, Police General Hospital, Bangkok, Thailand after it was approved by the Police General Hospital's ethics committee and The Institutional Review Board (IRB). All patients, who provided written informed consent for participation in this investigation, were treated at the outpatient clinic.

The inclusion criteria were as follows:

1. Knee OA patients above 55 years old who experienced conservative treatment failures from physical rehabilitation and pharmacologic management, such as pain and NSAIDs medications for at least 6 months.
2. Patients with knee OA conditions that were classified according to KL classification (I, II, III, and IV).
3. Knee OA patients with hemoglobin concentrations greater than 11 g/dL and platelet counts greater than $150x10^3$ cells/μL.

The exclusion criteria were as follows:

1. Patients with meniscus and ligament injuries (from physical examination).
2. Patients with deformity (tibiofemoral angle) more than 5 degrees.
3. Patients with inflammatory arthritis.
4. Patients with uncontrolled bleeding disorder.
5. Patients who received treatments of anticoagulants-antiaggregant, nonsteroidal anti-inflammatory drugs in the past 5 days, and intraarticular injection of hyaluronic acid in past 6 months.

650 patients with diagnosis of knee OA according to the American College of Rheumatology (ACR) were enrolled in the study and divided into 2 groups. 63 patients were excluded because of previous intraarticular hyaluronic injection and loss to follow-up (18 patients in group 1 and 12 patients in group 2). After the exclusion criteria, the remaining participants were 557. The first group had 310 patients who were treated with PRGF injection. The second group, with 247 patients, was treated with 40-mg triamcinolone acetonide and 5 mL of 1% lidocaine hydrochloride with 1:100,000 epinephrine. All patients were evaluated prospectively at enrollment at baseline and at 2-, 4-, 6- and 12-month follow-up time points.

Evaluation methods

The primary endpoints were the clinical outcome of IKDC and WOMAC scores. The secondary endpoints were clinical outcomes of VAS pain scores. Adverse events and patient satisfaction were also recorded. Radiography was performed on every patient to determine the OA grade (the joint was classified according to the most degenerated compartment).

PRGF preparation and Injection protocol

30 mL venous blood sample was collected. A complete peripheral platelet count was performed at the time of the initial blood draw and after the finishing preparation. The PRGF was prepared by the Plasma Platelet Concentrate and Growth Factors (PP&GF) system. The blood was mixed with the appropriate condition of anti-coagulant. The first 20 mL of blood was centrifuged twice. The first centrifuge was to separate red blood cell, buffy coat, platelet-rich plasma (PRP), and platelet-poor plasma. The second centrifuge was to concentrate the platelets. The second 10 mL of blood was centrifuged for natural activators. The platelet concentrations (total number of platelets/mL) were measured before and after centrifugation (URIT-3000Plus). Then, the PRGF was intraarticularly injected into the joint of knee OA patients. All open procedures were performed in an A-class sterile hood. The sterile double syringe injections were prepared for knee injection under sterile preparation.

Corticosteroid preparation and injection protocol

The intraarticular corticosteroid injection contained 40 mg of triamcinolone acetonide and 5 mL of 1% lidocaine hydrochloride with 1:100,000 epinephrine. Patients were in a supine position. The knee was flexed approximately 60 degrees and prepared in a sterile fashion. Under sterile preparation, the injection utilized a 25-gauge needle for patient comfort.

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Figure 1: Plasma Platelet Concentrate and Growth Factors (PP&GF) centrifuges machine

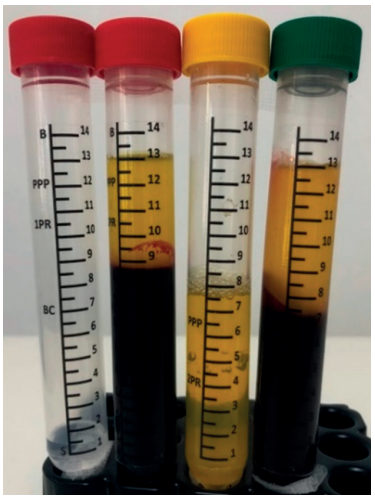

Figure 2: Plasma Platelet Concentrate and Growth Factors (PP&GF) preparation process (red-solution tube, red-first spin, yellow-second spin, green-platelet gel

Statistical analysis

All continuous data were expressed in terms of the mean and the standard deviation. Discrete data were accessed using percentage and proportion. To assess the differences of parametric independent data, independent t-test with statistical significance ($p < 0.05$) was used. The influence of grouping variables on scores at different follow-up times was investigated by a generalized linear model for repeated measures with the grouping variable as the fixed effect. The nonparametric Pearson 2 test was performed to investigate the relations between grouping variables. Pearson correlation was used to assess the correlation between continuous variables. If patients were cross treated between groups, they will be analyzed as the assigned group (intention to treat analysis). The data were reported as box plots. Statistical analysis was performed by means of the Stata software, version 16.0 (Stata Corp, Texas).

Results

There was no significant difference in the baseline characteristic between the two groups as shown in Table 1. According to Table 2, the baseline clinical parameters (IKDC, WOMAC, VAS pain scores) were not statistically different between the two treatments. No patient was cross treated between groups. All patients showed clinical improvement after the treatment, which was reflected by the IKDC and WOMAC scores at baseline, 2-, 4-, 6-, and 12-month follow-up post-injection.

Table 1: Baseline demographic data

Characteristics	PRGF (n = 310)	Corticosteroid (n = 247)	Total (n = 557)	*p*
Sex (Female/Male)	228/82	176/71	404/153	0.547
Mean age (years)	66.11 ± 9.78	66.26 ± 9.49	66.18 ± 9.64	0.855
Mean body mass index (kg/m2)	25.04 ± 4.38	24.83 ± 4.16	24.95 ± 4.28	0.582
Side of injection (Left/Right)	158/152	119/128	277/280	0.513
Kellgren Lawrence grading				
Grade I	5 (1.61%)	5 (2.02%)	10 (1.80%)	
Grade II	132 (39.68%)	87 (35.22%)	210 (37.70%)	
Grade III	72 (23.23%)	53 (21.46%)	125 (22.44%)	
Grade IV	110 (35.48%)	102 (41.30%)	212 (38.06%)	

Notes: Values are presented as the mean ± SD or n (%).

Table 2: Baseline clinical parameter for patients

	PRGF (n = 310)	Corticosteroid (n = 247)	Total (n = 557)	*p*
IKDC score	39.48 ± 7.94	38.30 ± 7.26	38.96 ± 7.66	0.070
Modified WOMAC score	56.91 ± 14.89	56.73 ± 11.69	56.83 ± 13.55	0.877
VAS pain score	65.77 ± 18.25	68.87 ± 20.09	67.15 ± 19.13	0.058

Notes: Values are presented as the mean ± SD

The primary outcome of IKDC score in group 1 (PRGF treatment) at baseline, 2-, 4-, 6-, and 12-month follow-up post-injection were 39.48 ± 7.94, 48.47 ± 8.49, 51.04 ± 8.26, 51.54 ± 8.07, and 52.14 ± 9.86, respectively (Figure 3). According to Figure 4, the WOMAC scores were measured at the same time points (56.91 ± 14.89, 42.54 ± 15.64, 38.13 ± 14.95, 36.41 ± 15.23, and 36.28 ± 17.86, respectively). For the clinical parameters of primary outcome in group 2 (corticosteroid treatment), the IKDC score at baseline, 2-, 4-, 6-, and 12-month follow-up post-injection were 38.30 ± 7.26, 45.64 ± 9.45, 45.60 ± 10.24, 45.79 ± 9.96, and 43.14 ± 11.63, respectively (Figure 3). In addition, the WOMAC scores, represented in Figure 4, were measured at the same time points (56.73 ± 11.69, 45.22 ± 17.00, 46.37 ± 17.52, 46.47 ± 17.47, and 50.84 ± 20.29, respectively).

The IKDC scores at all time points and the WOMAC scores at 4-, 6-, 12-month follow-up revealed a statistical difference between the two treatments, in favor of the PRGF injection at all point of time. Noticeably, the difference in IKDC scores between group 1 (PRGF treatment) and group 2 (corticosteroid treatment) increased with longer follow-up time points (Table 3, $p < 0.05$). Although the secondary outcome of VAS pain scores showed improvement in all groups, the analysis demonstrated the increased statistical significance in favor of the PRGF injection (Figure 5).

The average platelet concentration before and after centrifugation were $1.97x10^5$ cells/μL ($1.20\text{-}3.36x10^5$ cells/μL) and $1.2x10^6$ cells/μL ($5.56x10^5\text{-}3.9\ x10^6$) cells/μL, respectively. The average platelet concentration prepared by our novel protocol for PRGF was 6 times (3-8.69) higher than the normal platelet concentration. There was no knee infection at the end of follow-up.

Table 3: Outcomes comparing clinical parameter between groups at 0, 2-, 4-, 6-month follow-up period

	PRGF (n = 310)	Corticosteroid (n = 247)	Total (n = 557)	*p*
IKDC score				
Baseline	39.48 ± 7.94	38.30 ± 7.26	38.96 ± 7.66	0.070
2 months	48.47 ± 8.49	45.64 ± 9.45	47.22 ± 9.03	< 0.001
4 months	51.04 ± 8.26	45.60 ± 10.24	48.63 ± 9.57	< 0.001
6 months	51.54 ± 8.07	45.79 ± 9.96	48.99 ± 9.40	< 0.001
12 months	52.14 ± 9.86	43.14 ± 11.63	48.15 ± 11.57	< 0.001
Modified WOMAC score				
Baseline	56.91 ± 14.89	56.73 ± 11.69	56.83 ± 13.55	0.877
2 months	42.54 ± 15.64	45.22 ± 17.00	43.72 ± 16.30	0.053
4 months	38.13 ± 14.95	46.37 ± 17.52	41.78 ± 16.63	< 0.001
6 months	36.41 ± 15.23	46.47 ± 17.47	40.87 ± 17.00	< 0.001
12 months	36.28 ± 17.86	50.84 ± 20.29	42.74 ± 20.30	< 0.001
VAS pain score				
Baseline	65.77 ± 18.25	68.87 ± 20.09	67.15 ± 19.13	0.058
2 months	38.65 ± 18.42	47.21 ± 21.79	42.44 ± 20.41	< 0.001
4 months	35.00 ± 16.70	50.73 ± 24.28	41.96 ± 21.83	< 0.001
6 months	34.97 ± 17.60	47.09 ± 23.00	40.34 ± 21.04	< 0.001
12 months	34.42 ± 21.08	52.26 ± 25.99	43.66 ± 25.56	< 0.001

Notes: Values are presented as the mean ± SD

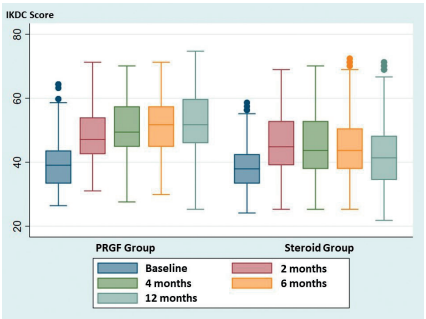

Figure 3: Comparison of IKDC scores between PRGF and corticosteroid treatment groups measured at baseline (blue), 2- (red), 4- (green), 6- (yellow), 12-month (grey) follow-up

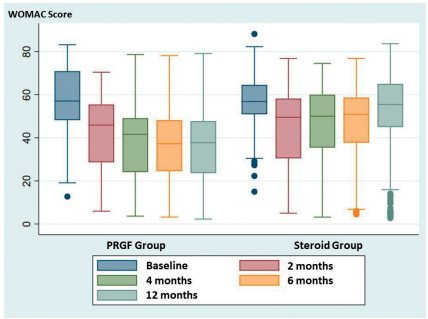

Figure 4: Comparison of WOMAC scores between PRGF and corticosteroid treatment groups measured at baseline (blue), 2- (red), 4- (green), 6- (yellow), 12-month (grey) follow-up

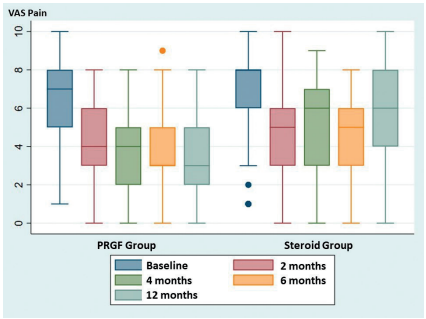

Figure 5: Comparison of VAS pain scores between PRGF and corticosteroid treatment groups measured at baseline (blue), 2- (red), 4- (green), 6- (yellow), 12-month (grey) follow-up

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Discussion

The clinical outcomes of PRGF and PRP remain controversial in the treatment of knee osteoarthritis. Although the uses of PRGF and PRP are not considered as conservative treatments of knee OA, they have shown clinical efficacy.[11]

PRGF contains a combination of natural activators and a diverse group of growth factors, including platelet-derived growth factor (PDGF), transforming growth factor (TGF), and insulin-like growth factor (IGF).[12] These components have been reported to improve chondrocyte proliferation and hyaluronic acid production and promote stem cell migration and anti-inflammatory activities.[13] Intraarticular corticosteroid treatment can trigger cartilage cell apoptosis during repetitive and long-term uses.[14] However, promising clinical results are observed in short-term treatments. Previously, a meta-analysis presented a final accumulative rank of all knee OA treatment outcomes. The pain and functions from cumulative rank number 1, number 2, and number 3 were naproxen, corticosteroid injection, and PRP treatment, respectively.[15] Kon et al.,[16] studied the effect of PRP injection compared to low molecular weight hyaluronic acid (LMHA) and high molecular weight hyaluronic acid (HMHA) using IKDC scores and reported that PRP treatment provided better results at 6-month follow-up ($p < 0.0005$). LMHA demonstrated improved treatment outcomes when compared to HMHA treatment. After the subgroup analysis between patient age and stage of OA, PRP had a similar outcome to LWHA in patients over 50 years old with advanced OA (Kellgren-Lawrence grade IV). However, the results were in favor of PRP, compared to hyaluronic acid (HA) in younger patients with early OA (Kellgren-Lawrence grade III).[16]

A 6-months duration study compared the effect of intraarticular platelet-rich plasma and corticosteroids in the treatment of moderate knee osteoarthritis, and revealed the same trend where PRP is a safe and efficient treatment option in symptom control up to 6 months after application. Treatment response obtained with corticosteroid injection has a shorter duration than PRP treatment. [17]

Furthermore, one study utilized meta-analyses assessing pharmacological or medical device interventions for knee OA treatments and compared the treatment effect sizes. Although the findings revealed that PRP had the highest point estimate in treatment effect, optimal formulations are needed to decrease the variability of PRP clinical outcomes.[18]

To optimize and improve PRP formulations, it is important to have a good understanding of the following factors: platelet concentration and recovery, inclusion of white blood cells (WBCs), platelet activation (such as thrombin and calcium ions), kinetics of cytokines released from platelets, preservation/function of platelets and WBCs, ratio between fibrinogen and thrombin concentration, formation of fibrin matrix (polymerization), microstructure of the final fibrin network (the ability to trap cytokines and bioactive factors), the appropriate injection technique, and thermal profile during PRP preparation.[19,20] Modulation of these factors could maximally increase the release of growth factors from alpha granules and platelet reservoir in a sustained release fashion and promote pericyte migration via indirect activation by PDGF.[21]

We developed the PP&GF method to create a unique formulation that reduces the variability of and improves patient outcomes. The novel preparation techniques involve adjusting PRGF, fibrin, protein concentrations, and leukocyte population in an optimal, controlled thermal environment. In addition, the formulation contains natural activators, which has been reported to increase the effectiveness of PRGF treatment for knee OA.[22-25] Based on our unique protocol, the platelet concentration was approximately 6 times higher than the normal platelet concentration. Our findings suggest that intraarticular PRGF injection was, at least, as effective as corticosteroid injection in the short-term. However, at longer follow-up time points, PRGF treatment displayed more significant clinical benefits. Since the longest follow-up time point in this study was 12-months, we acknowledge that further studies should examine the clinical outcomes of long-term (>12-month follow-up) PRGF treatment.

PRGF is a safe, simple, and effective treatment for patients who have failed to respond to conservative treatment of knee OA. We have designed a novel approach for PRGF preparation that improves the concentration of platelets (6x higher), increases platelet activity through the abundance of natural activators, and enhances the release of growth factors and anti-inflammatory molecules.[10]

CONCLUSION

PRGF and intraarticular steroid injection result in good outcomes. However, in terms of functional scoring (WOMAC and IKDC), PRGF treatment demonstrated significantly better clinical outcomes at 6- to 12-month follow-up. PRGF treatment can become an effective alternative treatment in knee OA. optional preparation techniques are essential for improved clinical outcomes, and further investigation with long-term follow-up is recommended.

Declaration of conflicting interests

The authors declared that no potential conflicts of interest exist with respect to the article's research and/or publication.

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