

SAFETY AND CLINICAL EFFICACY OF PLATELET RICH GROWTH FACTORS (PRGF) IN MANAGING KNEE OSTEOARTHRITIS AFTER FAILED CONSERVATIVE TREATMENT: EVIDENCE FROM REAL PRACTICES

Thana Turajane*, Chaivat Sriratanavudhi*, Pamok Saengsirinavin*, Ukrit Chaweewannakorn*, Wanpen Lappaiwong**, Jongjate Aojanepong*

*Biomedical Technology Research and Development Center, Department of Orthopedics, Police General Hospital, Bangkok, Thailand

**THAISTemLife, Bangkok, Thailand

Abstract

Background: Platelet rich growth factors (PRGF) comprise a biological treatment of knee osteoarthritis (OA). Due to its limitation concerning the articular cartilage lesions' healing potential, chondrocyte differentiation and external environment factors, clinical improvement of knee OA using PRGF treatment depends on preparation techniques.

Objectives: The study aimed to demonstrate clinical outcomes of PRGF treatment in real practices.

Methods: A prospective cohort study was conducted from February 2018 to 2019 at the Biomedical Technology Research and Development Center, Police General Hospital, Bangkok, Thailand. We enrolled patients above 60 years old with knee OA that failed conservative treatment. The exclusion criteria included meniscus and ligament injury and knee deformity of the tibiofemoral angle more than 5 degrees. The primary endpoint was safe PRGF while secondary endpoints included changes of weight bearing pain and delayed surgery until an appropriate time for intervention.

Results: A total of 240 patients with knee OA, Kellgren-Lawrence (KL) grades II, III or IV were enrolled including 90 males and 150 females. The average age was 68 (60-81) years. Mode of conservative treatment failure included 140 cases of oral medication, 60 cases of oral medication and steroid injection and 40 cases of oral medication, steroid and intra-articular hyaluronic injections (IA-HA). Based on the KL system, 194 were classified as grades II-III, and 46 patients were grade IV. The PRGF was collected according to the protocol. The average initial platelet concentration before and after centrifugation was 165×10^3 cells/ μ L (140 - 195×10^3 cells/ μ L) and 990×10^3 cells/ μ L (825 - $1,650 \times 10^3$ cells/ μ L), respectively. At average of 3.3 (3-8) months follow-up, no major complications were observed, but 17 cases (7.9%) had minor complications. Average VAS (visual-analog-scale for pain: 0-100) scores before and after injection were 71 (65-80) and 52 (50-72), respectively. Surgical intervention in KL II-III totaled 11 cases (5.6%) and KL IV totaled 5 cases (10.8%).

Conclusion: Our technique of adjusting platelet concentration, fibrin concentration, leukocyte population and activator status improved clinical efficacy of PRGF treatment. PRGF is a safe, simple and effective treatment for patients with knee OA experiencing conservative treatment failure.

Keywords : Osteoarthritis, Platelet rich plasma, Platelet rich growth factor, Knee arthroplasty, Total knee arthroplasty, Kellgren-Lawrence, Surgical intervention

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Correspondence to:

Turajane T, Biomedical Technology Research and Development Center, Department of Orthopedics, Police General Hospital, Thailand

E-mail : thanaturajane@yahoo.com

Introduction

Knee OA has been steadily increasing affecting patients' quality of life as well as financial impact.⁽¹⁾ Limitation in the healing potential of articular cartilage lesions involves a lack of vessels, chondrocyte differentiation and external environment factors. The repairable process cannot generate properly for cartilage because of its restricted cell migration to repair the lesion. Also, the progressive loss of tissue homeostasis accelerates cartilage degeneration to end stage arthritis.⁽²⁾ Numerous treatments have been shown to control pain, improve function and quality of life and to modify the natural history of knee OA. Pharmacologic management usually begins with pain relievers and anti-inflammatory agents. However, adverse effects have been noted concerning the gastrointestinal, nephrologic and cardiovascular systems.^(3,4) Intra-articular injection of steroids only provides short term improvement for pain and functions. IA-HA injections have been introduced to alleviate pain and delay surgical intervention and recommendation can be found in many guidelines.⁽⁵⁾ However, controversies exist related to clinical efficacy and preparations. Platelet rich plasma (PRP) is a popular biologic agent used to treat knee OA and clinical improvements depend on preparation techniques. A recent meta-analysis revealed the outcomes of pain and function assessment of corticosteroid treatment was better than those of PRP treatment while those of PRP treatment were better than those of IA-HA treatment. Many studies have investigated knee OA treatment. However, failure of conservative treatment due to medication and injection techniques has not been widely discussed. Conservative failure and severe damage after surgical intervention could possibly indicate complications including unicompartmental knee arthroplasty (UKA) and total knee arthroplasty (TKA). The recent treatment of PRGF needs to be addressed regarding its safety and clinical effectiveness involving delayed surgical intervention.

Methods

Patient Grouping

After obtaining the approved IRB, a prospective cohort study was conducted from February 2018 to 2019 at the Biomedical Technology Research and Development Center, Police General Hospital, Bangkok, Thailand.

All patients were treated in the outpatient clinic and provided written informed consent to participate in this investigation. The inclusion criteria comprised 1) patients above 60 years old, 2) knee OA revealing failure after conservative treatment from physical rehabilitation and pharmacologic management such as pain and NSIADs medication, intra-articular steroid injections, and IA-HA injection, 3) all stages of knee OA severity according to KL classification (II, III, IV); and 4) hemoglobin concentrations greater than 11 g/dL and platelet counts greater than 150×10^3 cells/ μ L. The exclusion criteria comprised 1) patients having meniscus and ligament injuries, 2) having deformity (tibiofemoral angle) more than 5 degrees, 3) having inflammatory arthritis, and 4) having uncontrolled bleeding disorder. The primary end point was safety of treatment after PRGF intra-articular injection. The secondary endpoints were change of weight bearing pain after minimal follow-up after 3 months of injections and delayed surgery until an appropriate for intervention.

PRGF Preparation

Thirty milliliters of venous blood samples were collected from patients. A complete peripheral platelet count was performed at the time of the initial blood draw before and after PRGF preparation. The blood was mixed using appropriate conditions. The first 20 mL of blood were centrifuged twice. The first centrifuge was to separate red blood cell, buffy coat, PRP and platelet poor plasma. The second centrifuge was to concentrate the platelets. The second 10 mL of blood was centrifuged to obtain natural activator, while sterile double syringe injections were prepared for knee injection.

Injection Technique

Patients were placed in the supine position. One knee was flexed 70 degrees and prepared in sterile fashion. The injection site was identified by soft spot at the anteromedial knee. A 22 gauge-needle was inserted through the same area in the joint capsule. In case any effusion presented, the fluid was aspirated. The needle remained in place and then the two syringes prefilled with PRGF were injected. When pain persisted, 2 tablets of paracetamol were given for rescue medication.

Results

Ninety male and 150 female patients with knee OA (KL grade II, III and IV) were enrolled with an average age of 68 years (range 60-81 years). Patients with failed conservative treatment who had been suggested to undergo surgical inter-

vention included 140 cases not responding to oral medication; 60 cases not responding to oral medication and steroid injection and 40 cases not responding to oral medication, steroid and IA-HA injection. One hundred and ninety-four patients were KL grades II-III, 46 patients were KL grade IV (**Table 1**).

Table 1. Baseline demographic data and clinical parameters

Characteristics	Total
Number of patients (male: female)	249 (90:150)
Mean age (years) (range)	68 (60-81)
Body Mass Index (kg/m^2)(mean \pm SD)(range)	24.8 \pm 3.5 (20-35)
Mean height (cm)	165 (160-172)
Number of knees (Right: Left)	240 (130:110)
Number of patients with Kellgren Lawrence II-III: IV	194:46
Mean Tibiofemoral angle (degrees) (range)	3 (0-5)
Failed conservative treatment	
Oral: Oral and Steroid: Oral and Steroid and IAHA	140:60:40
Average follow-up months (range)	3.3 (3-8)

The average initial platelet concentration before centrifugation was 165×10^3 cells/ μL (range from 150 - 195×10^3 cells/ μL). The average initial platelet concentration after centrifugation was 990×10^3 cells/ μL (range from 825 - $1,650 \times 10^3$ cells/ μL) (**Table 2**).

Table 2. Baseline clinical parameters of patients

Platelet Rich Growth Factor (PRGF)	Before PRGF	After PRGF
Average platelet concentration x 10 ³ cells/uL (range)	165 (150-159)	990 (825-1,650)
VAS pain (points)	73±13	52±15
Range of motion (degrees)	125±10	16±8

At an average of 3.3 (3-8) months follow-up, no major complications were observed after PRGF treatment. In all, 17 cases involved minor complications (7.9%). The VAS score before injection was an average of 73 (60-86) and after injection the average was 52 (43-65). The surgical intervention in KL stages II-III totaled 11 cases (5.6%).

All cases were treated by arthroscopic partial meniscectomy for complex tear of the meniscus (medial 9 cases, medial and lateral 2 cases), plica resection and micro drilling technique with PRGF intra-operative injection. KL IV totaled 5 cases (10.8%) and all were treated with TKA (**Table 3**).

Table 3. Adverse effects and surgical interventions

Adverse effects and surgical interventions	Number of patients
Injection site pain and pruritus more than 3 days	12
Pain swelling more than 3 days	5
Effusion	2
Hemorrhage and Erythrema	0
Aseptic Athritis	0
Major complication for surgical intervention	0
Surgical intervention Kellgren Lawrence II, III (Anthroscopic Surgery)	11
Surgical Kellgren Lawrence IV (Total Knee Arthroplasty)	5

Discussion

The conservative treatment of knee OA by pharmacologic intervention proved to have clinical efficacy by many guidelines.⁽⁶⁾ Most treatments involve oral medication and steroid injections. AI-HA injection is commonly used as stated in standard practices.⁽⁷⁾ Because patients now live longer and have more demands, surgical interventions have to be considered at appropriate times. The new biologic interventions have shown potential in improving effective conservative treatment. PRP contains a number of different growth factors including basic metabolic panel (BMP), Platelet-derived growth factor (PDGF), transforming growth factor (TGF), and insulin-like growth factor, which improve chondrocyte proliferation and viability, increase proteoglycan, glycosaminoglycan, hyaluronic acid production, nociceptive, anti-inflammatory role and promote stem cell migration and chondrocyte differentiation.⁽⁸⁾ The chemokine constitutions of PRP are growth factors such as PDGF, TGF, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), proteases/antiproteases (alpha-2 macroglobulin), adhesive proteins (fibrinogen, fibronectin), cytokines (interleukin 1 beta, tumor necrosis factor) exhibiting differences resulting from hyaluronic acid.⁽⁹⁾ PRP therapies have been reported in many studies regarding its treatment effectiveness in knee OA, and thus, widely used in clinical practices. However, different of platelet concentrations as well as preparation methods can influence the outcomes. Double spin PRP with activator enhanced chondrogenic differentiation concerning cartilage regeneration.^(10, 11) Controversy regarding its effective usefulness involved different types of platelet concentrations and preparation methods.^(12, 13) Recently, a meta-analysis presented the final accumulative ranks of all knee OA treatment outcomes. The pain and functions from cumulative rank number 1 is naproxen, number 2 is corticosteroid injection, number 3 is PRP and number 7 is IAHA.⁽¹⁴⁾ To increase the capability of the treatment, understanding platelet concentrations, platelet recovery, inclusion of white blood cells (WBCs), platelet activation (thrombin, Ca²⁺), kinetics of cytokines released from platelets, preservation/function of platelets and WBCs, ratio between fibrinogen and thrombin

concentration, formation of the fibrin matrix (fibrin polymerization), microstructure of the final fibrin network (ability to trap cytokines and bioactive factors) and appropriate injection techniques are needed.^(15, 16) PRGF was developed to improve the treatment quality of knee OA.⁽¹⁷⁾ Understanding all these factors mentioned in the methods section could improve the maximally released growth factors from alpha granules and platelet reservoir to increase sustained releases and pericyte migration by PDGF to activate stem cells.^(18, 19) Based on our established technique, steps of platelet preparation increased the platelet concentration on an average of 5 to 10 times the normal platelet concentration. The results of this study revealed its easy administration in clinical practices, minimal risks, anti-inflammatory effects and possible effective adjunct to particular arthroscopic procedures. This technique is safe, simple and low cost because no major complications after PRGF treatment were observed except 17 cases (7.9%) presenting minor complications. PRGF treatment improved pain and slightly improved range of motion. The surgical intervention in KL II-III involved 11 cases (5.6%). Most of the pathologies involved complex tear of the meniscus, cartilage lesion in medial femoral condyle and undiagnosed plica. To decrease the failure rate, MRI is recommended in doubtful cases. Five cases (10.8%) comprised KL IV using tri-compartment arthritis as standard TKA.

Even though PRGF is safe, improved VAS scores and delayed surgical intervention, the basic science of the PRGF needs further studies to understand platelet kinematics and functional activity. Further studies should be conducted regarding tissue biology and stimulating repair or replacing damaged cartilage highlighting a complex regulation of growth factors (GFs) for normal tissue structures and reaction to tissue lesions is recommended. Intermediate and long term follow-up are also suggested for further investigation.

In conclusion, our technique of adjusting the platelet concentration, fibrin concentration, leukocyte population and activator status improved clinical efficacy of PRGF treatment. PRGF is a safe, simple and effective treatment for patients with knee OA who have conservative treatment failure.

Declaration of Conflicting Interests

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

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