



Patient Factors Associated with the Good Outcome after a Single Injection of Plasma-Rich Growth Factors in Patients with Osteoarthritic Knee

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Purpose: This study aimed to evaluate patient factors for a good outcome of a single intra-articular (IA) plasma-rich growth factor (PRGF) 12 months after injection in patients with varying severities of knee osteoarthritis (KOA) using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score.

Methods: Patients with mild-to-severe KOA who received a single IA PRGF injection at an outpatient clinic were eligible to participate in this study. An observational analytical cohort study and clinical evaluation using WOMAC scores for the baseline and five follow-up periods were performed. A good outcome was defined as $\geq 50\%$ improvement in pain or in function of WOMAC score at 12 months after injection compared to baseline. Logistic regression was performed to determine the factors associated with good outcomes of a single IA PRGF injection.

Results: A total of 215 knees with osteoarthritis (OA) were recruited in this study; 30.7% of them had severe KOA. The mean age of the participants was 65.26 ± 7.96 years (range; 41-87 years), and the mean body mass index (BMI) was 25.74 ± 3.56 kg/m² (range; 17-38 kg/m²). The mean difference in WOMAC scores between baseline and at 12 months after injection were 82.71 ± 36.53 in good response group and 23.20 ± 30.15 in short response group. Overall, 72.56% of the participants had good outcomes. Multivariate analysis revealed that demographic patient factors, including age, sex, and BMI, did not affect good outcomes. Hypertension (HT) and KOA severity were significant negative factors associated with good outcomes.

Conclusions: 72.56% of the patients had good outcome in terms of WOMAC score improvement in pain or function, 72.56% of the patients had good outcomes 12 months after a single injection of IA PRGF. The patient factors that negatively affected good outcomes were not only underlying diseases, including HT, but also KOA severity. Further clinical studies should be conducted to obtain more details on HT, including severity, disease control, and treatment, which may have affected our results.

Keywords: PRGF, Osteoarthritic Knee, predictive factors, good outcome, 12 months

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Knee osteoarthritis (KOA) has emerged as one of the most common symptomatic degenerative diseases in recent years, and its incidence has been increasing owing to patient activities and a rapidly aging society. The prevalence in individuals aged > 18 and > 70 years was approximately 22.7% and 40%, respectively. Late-stage KOA is often characterized by structural damage, patient-reported joint pain, stiffness, and disability⁽¹⁾. Each year in the USA, the estimated cost of job-related osteoarthritis (OA) is US\$ 60 billion⁽²⁾, while the median cost induced by KOA in France could be as high as EUR 2 billion per year⁽³⁾. Thai patients were willing to pay (WTP) for treatments that delayed disease progression rather than for pain relief⁽⁴⁾.

Good knee function and pain relief are major goals of KOA treatment. Another concern for KOA treatment is the reduction in structural destruction with fewer adverse reactions or complications. Quality-adjusted life years (QALYs) is another index used to evaluate cost-effective investments for the longevity of well-being. If the incidence of activation in the inactive KOA population could be reduced by 20%, it would be another factor for meaningful life expectancy gain, as well as a reduction in the incidence of cancers, cardiovascular diseases (CVD), and diabetes mellitus (DM)⁽⁵⁾. Many nonsurgical treatments with different guidelines have been used to achieve the goal of KOA treatment. Each KOA treatment option has several factors that affect the results.

Plasma-rich growth factor (PRGF) has been reported to be beneficial in many conditions including cutaneous, dental, and reproductive conditions. Numerous studies have investigated the efficacy of PRGF in KOA and meta-analyses have reported significant pain reduction and functional improvements with PRGF⁽⁶⁻⁹⁾. Some studies have reported cytokine responses and cartilage regeneration following platelet-based therapies^(10,11). Factors were reported to affect the results of KOA treatment with PRGF including age of patient, severity of KOA and excessive body mass index (BMI)^(12,13). This study aimed to identify patient factors associated with a good outcome in terms of pain or functional improvement at 12 months after a single intra-articular (IA) PRGF

injection in patients with mild-to-severe KOA to predict the clinical results.

METHODS

This single-center observational analytical cohort study was conducted at the outpatient clinic of the Orthopedic Department using data recorded in the medical files of patients treated for KOA between January 2023 and September 2023. All participants underwent clinical and radiological evaluations by an orthopedic surgeon to exclude patients who did not meet the criteria. The anteroposterior standing knee plain radiography was done in every patient to classify severity of KOA using the Kellgren–Lawrence classification (KL), KL grade 1-2 (KL1 and KL2) were considered as mild KOA, KL grade 3 (KL3) was moderate KOA and KL grade 4 (KL4) was severe KOA respectively. Underlying DM, hypertension (HT), and current medications were recorded for each participant. All patients were instructed not to stop their current medications before the PRGF injection.

The inclusion criteria were male or female adults aged > 18 years who were diagnosed with KOA. Exclusion criteria were diagnosis of secondary osteoarthritis, hyaluronic acid infiltration or corticosteroid use within the last 3 months, diagnosis of systemic inflammatory disease or inflammatory arthritis, meniscal or knee ligament injuries (determined by history and physical examination) or intra-articular lesions such as fractures, calcific loose bodies, and osteolytic lesions (diagnosed via plain radiography), blood disorders (thrombopathy, thrombocytopenia, anemia with hemoglobin < 9), cancer or ongoing immunosuppressive therapies, or pregnancy.

Outcome Measurement

After this recruitment and screening process, 215 patients received a single IA injection of PRGF, following the protocol technique⁽¹⁴⁾. Patient responses were evaluated by using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total scores. Data were collected at baseline before injection (WM0). Five questionnaire visits were scheduled for each participant: one week, one month, three months, six

months, and 12 months (WM1, WM2, WM3, WM4, and WM5, respectively) after the injection, and the medications used were evaluated. In this study, the clinically significant difference (CSD) in the WOMAC at 12 months after injection was used to categorize patients into two groups: good responders and short responders. Patients were classified as good responders if their overall WOMAC score (pain, stiffness, and function) at 12 months after injection (WM5) was reduced from baseline (WM0) by more than 50% (adapted from the OARSI responder criteria⁽¹⁵⁾), while the others were short responders.

PRGF Preparation

Platelet-rich Growth Factor, a combination of Leukocyte Rich – Platelet Rich Plasma (LR-PRP) and injectable platelet-rich fibrin (iPRF), formulations were prepared using the Alpas® system^(9,14,16) by certified technicians. A nurse drew a peripheral blood sample of 30 mL, then the sample was centrifuged according to the manufacturer's instructions and subsequently cryoprecipitated. All procedures were performed under sterile conditions in a clean and well-controlled environment as Figure 1. A double-syringe system was used to obtain 7 mL PRGF.

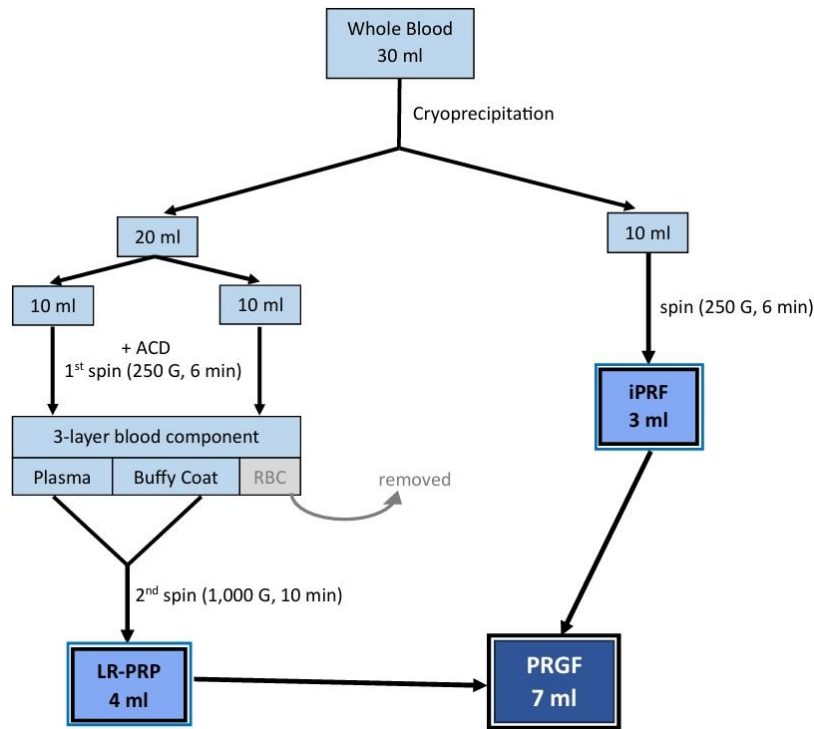


Fig. 1 Preparation of PRGF for single Intra-articular Knee injection.

Injection Protocol

All IA knee injections were administered by a single orthopedic surgeon. Using the inferomedial patellar approach with the knee flexed to 30°, an 18G needle was used to administer PRGF via the single-needle and two-syringe technique: 4 mL of LR-PRP followed by 3 mL of iPRF. No synovial fluid aspiration was performed prior to the injection. The knee was extended immediately after

PRGF administration. All participants were permitted full weight-bearing after injection. Cold compression was applied around the injection site for 10 min and clinical observations were conducted immediately thereafter. At 30 min post-injection, local appearance, active range of motion, ability to stand on the injected limb, and performance on a 10-meter walk were assessed. The participants were then allowed to resume their

daily activities. Acetaminophen was prescribed every 8 h for pain control. In cases of persistent pain, patients were instructed to contact their orthopedist via the provided contact channels before taking other analgesics with antiplatelet effects, such as NSAIDs and steroids. Full activity was permitted two days after injection. Adverse events were also recorded.

Rehabilitation Protocol

All participants were instructed to begin exercise therapy two days after injection. Exercise therapy was explained to all participants prior to injection. The rehabilitation regimen included fixed-arc quadriceps exercises, such as sitting on a chair with one leg extended forward for 100 s on each side. Multiangle isometric exercises were performed to target the knee muscles, quadriceps femoris, thigh abductors, and adductors. In addition, hamstring stretching exercises were prescribed: three sets of 10 repetitions of 10 seconds stretches per day. After one month, the participants were encouraged to gradually transition to closed-chain isotonic exercises.

Statistical Analysis

Observational analytical cohort and clinical evaluations. Categorical variables were presented as frequencies and percentages. Continuous variables are expressed as mean \pm standard deviation for normally distributed data or as median and percentiles for non-normally distributed data. Comparisons between groups were performed using the Fisher's exact test for categorical variables, independent t-test for normally distributed continuous variables, and signed-rank test for non-normally distributed continuous variables. Potential factors associated with the outcomes were evaluated using univariate and multivariate logistic regression analyses. All statistical analyses were performed using Stata Program version 15.0 (StataCorp LLC, College Station, TX, USA), with statistical significance set at $p < 0.05$.

Ethical Considerations

This study was approved by the Ethics Committee in Human Research Chiangrai Prachanukroh Hospital (Approval No. EC.68-742). All data were anonymized and kept confidential.

Table 1 Baseline demographics of all participants.

Population	n	%
Number of Participant	215	100.00
Sex		
Male	41	19.07
Female	174	80.93
Age (year) (mean \pm SD)	(65.26	\pm 7.96)
≤ 59	53	24.65
60-69	105	48.84
≥ 70	57	25.51
BMI (kg/m ²) (mean \pm SD)	(25.74	\pm 3.56)
≤ 24	94	43.72
25-29.99	101	46.98
≥ 30	20	9.30
DM	28	13.02
HT	108	50.23
KL		
1	1	0.47
2	71	33.02
3	77	35.81
4	66	30.70

RESULTS

The demographics of the 215 IA PRGF knees with OA included in this study are shown in Table 1. Among the patients, 33.49% had mild KOA (KL1-2), 35.81% had moderate KOA (KL3), and 30.7% had severe KOA (KL4). 80.93% Of the participants, 80.93% were female, 13.02% had DM involvement, and 50.23% had HT. A total of 73.49% of the participants were aged < 70 years. The mean age was 65.26 ±7.96 years (range, 41-87 years), and the mean body mass index (BMI) was 25.74 ±3.56 kg/m² (range, 17-38 kg/m²). (Table 1)

Good response group comprised 72.56% of the patients. In the comparison of demographic and clinical characteristics between patients with good and short responses, no statistically significant differences were observed in any of the analyzed variables, including sex, age, body mass index (BMI), diabetes mellitus (DM), hypertension (HT), and Kellgren–Lawrence (KL) grade. However,

trends were noted showing that patients with a Short Response tended to have a higher proportion of KL grade 4 and HT, whereas patients with a Good Response had a higher proportion of DM. (Table 2)

In the unadjusted comparison, a higher prevalence of advanced radiographic osteoarthritis (KL 3–4) was found in the short-response group than in the good-response group (76.3% vs. 62.8%). However, this difference was not statistically significant (p = 0.089).

On Day 0 (baseline), the WOMAC scores between the good- and short-response groups were not significantly different (p = 0.714). From 1 week to 12 months after treatment, the Good Response group consistently demonstrated significantly lower WOMAC scores than the Short Response group (p < 0.05 at all-time points). Lower WOMAC scores indicate reduced pain and functional impairment, reflecting better clinical outcomes. (Table 3)

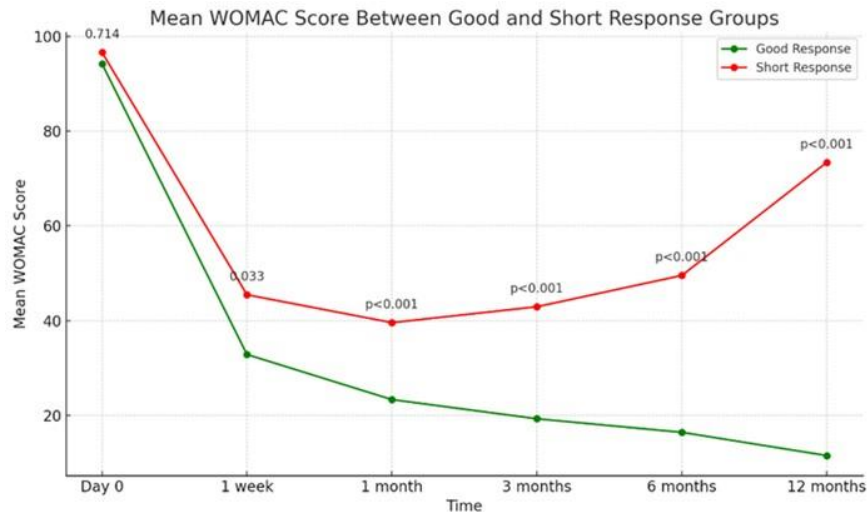
Table 2 Demographics of the studied population in good responders and short responders.

Characteristics	Good Response (N=156)		Short Response (N=59)		p-value
	n	%	n	%	
Sex					0.331
Male	27	17.31	14	23.73	
Female	129	82.69	45	76.27	
Age (year)					0.832
≤ 59	40	25.64	13	22.03	
60-69	76	48.72	29	49.15	
≥ 70	40	25.64	17	28.81	
BMI (kg/m ²)					0.974
≤ 24	67	42.95	27	45.76	
25-29.99	74	47.44	27	45.76	
≥ 30	15	9.62	5	8.47	
DM	24	15.38	4	6.78	0.114
HT	73	46.79	35	59.32	0.126
KL					0.135
1	1	0.64	0	0	
2	57	36.54	14	23.73	
3	56	35.90	21	35.59	
4	42	26.92	24	40.68	
Group comparison					0.089
KL 1-2	58	37.18	14	23.73	
KL 3-4	98	62.82	45	76.27	

Table 3 Mean of WOMAC score between good response group and short response group.

Time	Good Response mean±SD (Median; P25, P75)	Short Response mean±SD (Median; P25, P75)	p-value
Day 0	94.22±42.81 (93; 62.5, 122.5)	96.63±43.48 (98; 61, 129)	0.714*
1 week	32.85±37.35 (18; 3.5, 52.5)	45.46±41.71 (33; 10, 82)	0.033**
1 month	23.33±28.26 (12.5; 2.5, 34)	39.58±34.90 (31; 9, 70)	0.001**
3 months	19.28±29.08 (5; 0, 25)	42.93±42.38 (32; 11, 66)	<0.001**
6 months	16.42±27.35 (4; 0, 22)	49.54±44.95 (37; 12, 77)	<0.001**
12 months	11.51±17.42 (3; 0, 16.5)	73.42±36.05 (71; 44, 98)	<0.001**

* t-test ** sign rank test

**Fig. 2** Mean WOMAC scores in the good response and short response KOA groups at baseline and at follow-up after PRGF injection. Regression analysis of repeated responses.

At 1-week post-injection, the WOMAC scores decreased in both groups, with a continued decline observed up to 3 months post-injection. At 6 months post-injection, WOMAC scores showed a slight increase compared to the 3 months scores but remained lower than baseline levels (Figure 2). At

12 months, 72.56% of the patients demonstrated that pain or function WOMAC subscale scores decreased from baseline by more than 50% and were defined as the Good Response group. The Short Response group showed a different pattern.

Table 4 Mean Difference of WOMAC score between Good Response group and Short Response group. (Day 0, baseline)

Time	Good Response mean±SD	Short Response mean±SD
1 week	61.37±35.75	51.17±42.39
1 month	70.89±39.03	57.05±41.47
3 months	74.94±38.56	53.69±41.89
6 months	77.79±43.67	47.08±35.73
12 months	82.71±36.53	23.20±30.15

Univariate logistic regression analysis of factors associated with a Short Response showed that KL grade 4 was significantly associated with an increased likelihood of a short response compared with the reference group (OR = 2.37, $p = 0.028$).

Other factors, including female sex, age, BMI, DM, and HT, showed trends toward either an increased or decreased likelihood of a Short Response; however, these differences were not statistically significant. (Table 5)

Table 5 Univariable comparison of Good Response and Short Response.

Characteristics	Odds ratio	95% Confide interval	p-value
Female	0.67	0.324 - 1.395	0.287
Age (year)			
60-69	1.17	0.550 - 2.505	0.678
≥ 70	1.31	0.562 - 3.043	0.534
BMI (kg/m ²)			
25-29.99	0.91	0.483 - 1.696	0.756
≥ 30	0.83	0.274 - 2.501	0.737
DM	0.40	0.133 - 1.207	0.104
HT	1.66	0.903 - 3.043	0.103
KL			
3	1.55	0.720 - 3.354	0.262
4	2.37	1.010 - 5.110	0.028

Patients with KL grade 4 KOA had a significantly higher likelihood of experiencing a Short Response compared to KL 2, with an odds ratio of 3.49 (95% CI 1.446–8.437, $p = 0.005$). Patients with KL grade 3 showed a tendency toward an increased likelihood of a Short Response compared

to those with KL grade 2, approximately 1.8 times, but this was not statistically significant (OR = 1.83, 95% CI 0.800–4.189, $p = 0.152$). In addition, patients with HT had a 2.1-fold higher likelihood of a Short Response (OR = 2.13, 95% CI = 1.081–4.195, $p = 0.029$). (Table 6)

Table 6 Multivariable association between clinical factors and Short Response outcome.

Factor	Adjusted Odds Ratio	95% Confidence Interval	p-value
KL 4	3.49	1.446 – 8.437	0.005
KL 3	1.83	0.800 – 4.189	0.152
HT	2.13	1.081 – 4.195	0.029

DISCUSSION

Platelet-rich plasma (PRP) is an optional treatment for KOA, which is still inconclusive from recent standard guidelines⁽¹⁷⁻¹⁹⁾ due to variability in preparation and injection protocols. PRGF, a combination of LR-PRP and iPRF, is a PRP-based treatment classified as a subtype of LR-PRP according to the MARSPILL classification. In this study, PRGF was prepared using a specific protocol that was reported to improve the WOMAC score,

even in patients with KL4 KOA, while requiring fewer sessions of injection^(8, 13, 14).

Theoretically, numerous components of PRGF influence the progression and regeneration of KOA. Platelets contain more than 30 bioactive proteins, including those from mesenchymal stem cells, osteoblasts, fibroblasts, endothelial cells, and epidermal cells, which contribute to cellular proliferation, matrix formation, osteoid production, and cartilage and collagen synthesis. Activated

platelets secrete growth factors from their alpha granules, which start within 10 min after activation. More than 95% of these pre-synthesized growth factors are secreted within 1 h, causing antinociceptive effects and reducing the secretion of proinflammatory mediators during tissue repair and regeneration. Due to this unstable process, the timing from blood drawing to PRGF injection, sterile techniques, and temperature control of the PRGF preparation are the major technical factors for a good response to KOA treatment.

Some studies reported that the results of PRGF treatment were comparable with those of other options of intra-articular injection, such as Turajane, who reported that PRGF was superior to corticosteroid⁽⁷⁾. A meta-analysis publication by F. Migliorini⁽⁸⁾ summarized the use of PRGF might be associated with more favorable clinical outcomes than the use of hyaluronic acid (HA), especially in the functional subscale of WOMAC. In the RIAT project, Sánchez reported the superiority of PRGF over HA in alleviating the symptoms of mild-to-moderate KOA, with a similar safety profile in the short term,⁽²⁰⁾ whereas Saiz⁽⁶⁾ reported the similarity of PRGF and HA in pain reduction and unexpected adverse events. In cases of HA failure, PRGF may be a response⁽⁹⁾. The combination of HA and PRGF is another treatment option for KOA patients.

In this study, a single-dose technique was employed^(14,21-23) with the expected results. A single PRGF injection is more beneficial than multiple injections in terms of cost effectiveness, safety, and comfort, particularly for high-risk patients. A few studies have concluded that multiple doses offer superior outcomes only in early stage KOA⁽²⁴⁾. Ngarmukos et al.⁽²⁵⁾ demonstrated no differences in the levels of synovial cytokines and growth factors between two and four sessions of IA PRP injection. A single large-dose injection was administered without discontinuation of routine medication. No major adverse events were observed.

These findings highlight that a favorable treatment response is strongly associated with persistently lower WOMAC scores over the long term, underscoring the potential predictive value of an early response for sustained clinical improvement. (Figure 2) The Good Response group

showed a continuous increase in Difference WOMAC scores from baseline to 12 months after PRGF injection, indicating a sustained treatment effect. In contrast, the short-response group showed minimal early improvement, followed by a marked long-term decline, suggesting a limited response. (Table 4)

Logistic regression analyses for individual WOMAC sub-scores were not performed separately. Given the sample size and number of predictors included in the multivariate model, additional domain-specific analyses could increase the risk of model overfitting and multiple testing bias. Some confounding factors that may affect WOMAC scores were difficult to control over a long follow-up period. Future well-planned research will be useful in WOMAC subscore analysis for the detailed prediction of PRGF results.

Age, local knee tenderness, and radiographic score of the affected joint could predict the response three months after IA steroid injection therapy⁽²⁶⁾. Furthermore, older age was associated with good outcomes with IA HA injection, whereas sex, BMI, and race were not⁽²⁷⁾. Higher BMI and higher scores on the KL system were significant negative predictive factors for PRP injection^(12,21,28). Disease factors including late-stage KOA and meniscal problems⁽²⁹⁾ also negatively affect the clinical outcomes of IA PRP treatment.

Radiographic severity emerged as an important determinant of treatment response in this study. Although a higher proportion of patients with advanced KOA (KL 3–4) was observed in the short-response group, multivariate analysis revealed that this negative association was not uniform across all severity levels. After combining KL grades 1 and 2 as the reference group due to the limited number of KL grade 1 cases, only KL grade 4 remained independently associated with a significantly lower likelihood of achieving favorable clinical outcomes. In contrast, KL grade 3 was not statistically significant after adjustment. These findings suggest that the relationship between radiographic severity and treatment response may not follow a simple linear progression across the KL grades. Instead, a threshold effect appeared to emerge for KL grade 4.

This observation is clinically relevant, as it indicates that PRGF treatment may be effective in moderate-to-advanced KOA (KL 3), while outcomes become significantly less favorable in severe KOA (KL 4).

An *in vitro* study revealed that double-spin PRP from young (18-35 years) donors induced a more youthful chondrocyte phenotype than that from donors older than 65 years, as evidenced by increased type II collagen and SOX-9 expression in mice⁽³⁰⁾. Filardo et al.⁽³¹⁾ reported better results in younger patients with a lower degree of cartilage degeneration in single- and double-spin PRP groups. Age may affect the outcome of PRGF owing to the number and division ability of mesenchymal stem, and the concentration of growth factors decreases with age. In this study, 26.51% of the participants were older than 70 years of age, and statistical analysis showed no significant effect on the response to PRGF.

Previous studies^(11,12) reported that BMI > 25 kg/m² and KL grade > 2 are independent primary risk factors for autologous PRP injection failure. However, in the present study, BMI was not associated with clinical response to IA PRGF injection. 9.3% of participants had BMI \geq 30 kg/m². Clinical improvements in male and female patients were not significantly different. Previous studies have also concluded that sex does not affect the clinical results of either autologous PRP injections or IA HA injections.

The KOA stage is one of the factors affecting IA PRGF. In this study, after a single IA PRGF injection was administered, most participants showed a good response for the first 6 months without significant differences among the severities of KOA. Twelve months after the injection, the number of participants with a good response had decreased to 72.56%. Among the short responses, KL4 patients were 3.49 times more than the other groups according to the odds ratio.

DM is characterized by chronic hyperglycemia and chronic inflammation, which induce damage to endothelial cells, fibroblasts, and other critical cellular constituents implicated in regenerative processes. Karina et al. reported that Diabetic PRP had lower mean total protein but higher vascular endothelial growth factor (VEGF)

concentrations than non-DM PRP. This may be because lysed platelets from diabetic donors release more VEGF than those from non-diabetic donors⁽³²⁾. Differences in biology may affect the expression of other cytokines, exosomes, or other processes. An *in vitro* study by Vlasova et al. showed that human dermal fibroblasts had a pro-apoptotic effect from the PRP of DM donors, but there were some differences in DM type I and II⁽³³⁾. In this study, no statistical significance was found for good responses.

In our study, HT was a statistically significant negative factor of IA-PRGF treatment. Previous study⁽³⁴⁾ showed a relationship between HT and the platelet pathway. Although the levels of angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and angiopoietin-1 (Ang-1), were increased in PRP from patients with HT the levels decreased after antihypertensive drugs were started⁽³⁴⁾. HT is an influencing factor of KOA in terms of progression and severity^(35,36,37). Endothelial dysfunction, impaired microcirculation, chronic low-grade systemic inflammation, and platelet dysfunction are all possible pathophysiological mechanisms. Some antihypertensive drugs, such as Amlodipine⁽³⁸⁾ and Losartan,⁽³⁹⁾ may negatively affect IA-PRGF outcomes. Further studies on the severity and treatment of HT affecting IA PRGF outcomes should be conducted to explain the relationship and the conclusive mechanism. Other chronic inflammatory diseases may also affect the outcome; therefore, further studies are recommended to predict the clinical result⁽⁴⁰⁾.

The physical activity level is another factor that should be considered. Moderate-to-high activity levels are usually related to a good response to PRGF in athletes, while in KOA patients with high activity, pain, and inflammation usually result in a poor response. In real life, some KOA patients require high activity levels for daily life and jobs, and a special PRGF treatment protocol may be required for a good response in these patients. If this highly active group can return to its expected function, it will be beneficial and more cost-effective than medication or surgical treatments. Nevertheless, the cost of the PRGF

treatment course should not exceed 2,500 USD (THB 80,000), which is the cost of a total knee joint replacement in Thailand^(41,42). The PRGF protocol, using a commercial set of certified technicians under well-controlled time, temperature, and sterile techniques, may contribute to similar demographic populations with predictably good responses. Multicenter studies could provide more information regarding the generalizability of the findings.

Despite the significant findings of this study, it had several limitations that must be acknowledged. First, the specific mechanism by which hypertension negatively impacts PRGF efficacy remains unclear, particularly whether it is a result of systemic inflammatory markers or impaired localized vascularity. Detailed data on HT, including severity, disease control, and medications, are limited. Second, while a 'threshold effect' was observed at KL grade 4, the precise biological transition from Grade 3 to Grade 4, which diminished PRGF effectiveness, warrants further histological or molecular investigation.

Additionally, this study utilized a composite WOMAC score; a domain-specific analysis of pain, stiffness, and function might provide a more nuanced understanding of the treatment response. Furthermore, the timing for evaluating the clinical outcome of a single IA PRGF is 12 months; therefore, scheduled repeated doses of IA PRGF may affect the outcome. The lack of a control group to evaluate the placebo effect and cost-effectiveness analysis is also a limitation of this study.

Finally, the intrinsic biological variability of growth factor concentrations in autologous blood was not measured, which may partially explain the lack of response in 27.44% of the patients. Future research that incorporates standardized growth factor quantification and systemic health markers is required to address these variables.

CONCLUSIONS

A Single IA PRGF injection resulted in significant improvement in pain and physical function in all KOA patients, from mild to severe, one month after injection. Age over 70 years, female

sex and excessive BMI were not associated with the good clinical outcome to the treatment. The underlying HT negatively affects good responses. KOA severity was another statistically significant negative factor for good outcomes at 12 months after a single injection. Repeated PRGF injections at six months may improve the response rate; however, further studies are required to confirm this.

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