Original Article

Factors Associated with the Good Outcome after a Single Injection of Platelet-Rich Plasma in Patients with Osteoarthritic Knee: A Prospective Cohort Study

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ABSTRACT

Objectives: To determine the associated factors with the good outcome of a single dose intraarticular platelet-rich plasma (IA PRP) injection on pain reduction in patients with knee osteoarthritis.

Study design: A prospective cohort study.

Setting: Outpatient Department of Rehabilitation Medicine at Phramongkutklao Hospital.

Subjects: Patients with mild to severe knee osteoarthritis

Methods: Patients with knee osteoarthritis who received a single IA PRP injection were eligible to participate in this study. The visual analog scale (VAS) score as a primary outcome and the dimension of physical function as measured by the SF-36 questionnaire were determined at baseline and at week four after the injection. A good outcome was defined as a ≥30% reduction from baseline VAS at week four. Logistic regression was performed to determine factors associated with good outcomes of a single injection of IA PRP.

Results: Fifty-eight patients with knee osteoarthritis participated in this study. The mean difference in VAS scores between baseline and week 4 was -1.58 (2.11) with a $p < 0.001$. However, only 41.34% of the participants had a good outcome. Multivariable analysis found no significant factors associated with good outcomes.

Conclusions: Less than half the participants had clinically significant improvement in VAS four weeks after a single injection of IA PRP. However, the present study did not have sufficient statistical power to determine associated factors for a good outcome, possibly due to the small sample size.

Keywords: knee osteoarthritis, platelet-rich plasma, intra-articular injection, cohort study

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Introduction

Knee osteoarthritis is the most common degenerative joint disease, occurring most frequently in older and female patients.[1] Patients may suffer from pain and inflammation in the knee which can limit their activities. In the advanced stage, knee deformities such as severe genu varus can be found that lead to disability and poor quality of life.[2, 3]

Non-pharmacological knee osteoarthritis treatments include education, weight reduction, exercises, physical modalities, knee braces, and walking aids. Pharmacological treatment usually aims to pain and inflammation in the early stage of knee osteoarthritis and on maintaining the quality of life of patients using oral paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs).[4] Most analgesics have only short-term effects on control of symptoms; physicians must be aware of their efficacy and potential adverse reactions.[5]

Intra-articular (IA) injection is another effective treatment option for knee osteoarthritis. Platelet-rich plasma (PRP) injection is one form of intraarticular knee management which is prepared from the patient's own blood.[6] It is plasma with a high platelet concentration which can repair damaged tissue. PRP also provides some autologous growth factors and cytokines that act as anti-inflammatory agents and improve tissue regeneration.[7,8] IA PRP injection can reduce pain and improve quality of life among patients with knee osteoarthritis.[9]

Several previous studies comparing IA PRP and IA hyaluronic acid (HA) injections have reported that PRP is safe, easy to use, and acceptable to patients.[10] According to previous studies, clinical outcomes measured with instruments such as the visual analog scale and the Western Ontario and McMaster University (WOMAC) osteoarthritis index are better in the PRP group than in the HA group.[11,12] Furthermore, unlike HA, IA PRP is suitable for all stages of OA treatment. Adverse effects in the two groups were not significantly different.[13,14]

Several methods of PRP preparation and injection regimens have been described,[15,16] e.g., PRP can involve several injections or a single dose. A previous study reported that multiple injections of PRP had better results than a single dose.[17] However, clinical outcomes have been reported to improve considerably with only a single injection of PRP.[18,19]

Many factors are involved in the prediction of clinical outcomes of IA knee injection. Age, local knee tenderness, and

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radiographic score of the affected joint can predict response after three months of IA steroid injection therapy.[20] Furthermore, older age are associated with good outcomes with IA HA injection, while gender, body mass index (BMI), and race are not significantly associated.[21] However, a previous study showed that higher BMI and higher scores with the Kellgren and Lawrence (KL) system are significant predictive factors of failure of PRP injection.[22] In summary, it can be concluded that the ability to consistently predict the clinical outcome of IA knee injections for osteoarthritis is limited due to the varying influence of different factors.

Currently, there is little clinical evidence regarding predictors of good outcomes with a single IA PRP injection. The present study aimed to determine the factors associated with good outcomes from a single injection of IA PRP on pain reduction in patients with knee osteoarthritis.

Methods

Study design and participants

This prospective cohort study was a conducted in an outpatient clinic of the Department of Rehabilitation Medicine, Phramongkutklao Hospital, Bangkok, from August 2021 to December 2022. Adult patients aged 40 years or older with mild to severe osteoarthritis of the knee (KL grade 2 to 4) who experienced knee pain with a visual analog scale (VAS) score of at least 30 mm and who had received conservative treatment for at least three months were eligible to participate in the study. Patients with a history of knee surgery, secondary knee osteoarthritis, hematologic diseases, current users of anticoagulant/antiplatelet drugs, or those with a planned knee arthroplasty within eight weeks after the injection were excluded. All participants provided written informed consent before participating in the study. The Institutional Review Board, Royal Thai Army Medical Department gave ethical approval for this study (IRB number R085h/64).

Outcome measures

At enrolment, demographic and clinical characteristics of all participants were collected, including factors suspected of potentially being able to influence results after an injection. These factors included age, sex, BMI, duration of knee osteoarthritis, KL classification, and laxity of the collateral ligament.

The current study used the VAS score as the primary outcome of pain assessment. The participants were instructed to indicate their current pain intensity by placing a mark on a line extending from 0-100 mm. An interview was used to complete the short form-36 (SF-36) questionnaire in Thai.[23] There are eight dimensions in the SF-36 questionnaire; however, this study only focused on the items related to physical functioning (PF). There are ten questions about physical functioning, and the range of possible answers is 0 (worst) to 100 (best). Data were collected before and four weeks after IA PRP injection.

In this study, clinically significant difference (CID) in VAS was used to categorize the patient's results into two groups: good and poor outcomes. A good outcome was defined as a reduction in VAS from baseline of at least 30% at week four.

PRP preparation

The Arthrex Autologous Conditioned Plasma system (ACP®) was used to prepare the PRP. The process began with a trained technician collecting approximately 10 mL of venous blood from the median antecubital vein using a sterilized 20-gauge needle. The blood sample was then placed in a single centrifuge and spun at 1,500 rpm for 5 minutes. After cooling for approximately 3 minutes, the layer containing concentrated platelets was carefully extracted using a double syringe technique. The desired outcome was to obtain 5-7 mL of PRP.

Injection technique

The patient was supine with the knee flexed approximately 60-70 degrees. After an allergy check, the skin was prepared with povidine solution using a sterile technique. Subsequently, 5 mL of 1% Xylocaine without adrenaline was injected through the skin using a 22-gauge needle at the soft anterolateral spot adjacent to the patellar tendon. Finally, the physician injected a single syringe of the prepared PRP through the joint capsule at the same area as the Xylocaine injection. A cold pack was applied to the injection site for 10 minutes after the injection.

Patient safety

Patients were provided standard recommendations for post-injection care, including a period of rest for 1-2 days, avoidance of non-steroidal anti-inflammatory drugs for seven days, minimizing knee stretches until the pain subsides, and maintenance of normal range of motion in the knee joint. If necessary, paracetamol was administered for pain treatment. To ensure patient safety, all participants underwent a comprehensive screening for side effects immediately after the injection and during the 4-week follow-up period. Additionally, participants were informed that they could visit the clinic before the 4-week follow-up if they experienced any serious adverse effects such as fever or worsening arthritis. This process allowed identification and monitoring of potential adverse effects or complications that may have arisen due to the procedure.

Statistical analysis

The necessary sample size for this study was calculated using the logistic regression analysis events per variable (EPV) procedure.[24] Four to five variables, e.g., age, sex, obesity, the severity of knee OA, and the duration of symptoms, were intended to be analyzed using binary logistic regression. The number of EPV was set at 15, so the event (good outcome of PRP injection) was 75. A study by Tavassoli et al. found

Table 1. VAS and PF at baseline and at week 4 after a single injection of IA PRP

Outcome	Pre-injection Mean (SD)	Post injection Mean (SD)	Mean difference (Post - Pre)	*p*-value
VAS	5.93 (1.53)	4.36 (2.07)	-1.58 (2.11)	< 0.001
PF	35.78 (22.26)	44.74 (25.86)	8.97 (24.99)	0.008

VAS, visual analog scale; PF, physical function dimension of SF-36 questionnaire; SD, standard deviation, IA PRP, intra-articular platelet-rich plasma

that a single dose of PRP injection had a good result record in 86% of cases.[25] Based on that, the estimated sample size was determined to be approximately 88 patients (75/0.86).

In the descriptive analysis, frequency and percentage were used for categorical data, while mean and standard deviation were used for continuous data. A chi-square test or Fisher's exact test was used to assess the significant difference between proportions. Factors associated with a good outcome at week four after injection were identified using multiple logistic regression. The paired T-test was used to compare the results before and after IA PRP injection. The results were analyzed using STATA statistical software.

Results

A total of 58 outpatients with knee osteoarthritis were eligible to participate in this study. Most were over 65 years of age (62.07%), were women (86.21%), and had moderate to severe knee osteoarthritis (KL level 3 to 4) (84.48%). As shown in Table 1, VAS scores before and after injections had mean and standard deviation (SD) values of 5.93 (1.53) and 4.36 (2.07), respectively, with a mean difference (SD) of -1.58 (2.11) and $p < 0.001$. The PF scores were higher at week 4 after injection (mean=35.78, SD=22.26) than at pre-injection (mean=44.74, SD=25.86), t (57) = -2.73, p= 0.008. The percentage of patients with good outcomes was 41.34%. Pain at the injection site persisting for more than three days was the most common side effect (13.79%), as shown in Table 2. The univariable analysis found no associated factors for good VAS responders (Table 3). Additionally, no associated

Table 2. Side effects reported or observed at week 4 after a single injection of IA PRP

Side effects	Frequency	Percentage
Pain at injected site > 3 days	8	13.79
Knee swelling > 3 days	3	5.17
Subcutaneous hemorrhage	1	1.72
Knee joint Effusion	0	0.00
Arthritis	0	0.00

IA PRP, intra-articular platelet-rich plasma

Table 3. Univariable analysis of factors associated with a good response to a single injection of IA PRP

Variables	Overall	VAS Response		Odds ratio	*p*-value
		Good	Poor		
Age					
≤ 65	22 (37.93)	12 (54.55)	10 (45.45)	2.4	0.111[a]
> 65	36 (62.07)	12 (33.33)	24 (66.67)		
Sex					
Female	50 (86.21)	22 (44)	28 (56)	2.35	0.449[b]
Male	8 (13.79)	2 (25)	6 (75)		
BMI (kg/m^2)					
≤ 25	25 (43.10)	11 (44)	14 (56)	1.21	0.724[a]
> 25	33 (56.90)	13 (39.39)	20 (60.61)		
Duration					
< 5 years	35 (60.34)	17 (48.57)	18 (51.43)	2.16	0.17[a]
≥ 5 years	23 (39.66)	7 (30.43)	16 (69.57)		
KL level					
2	9 (15.52)	4 (44.44)	5 (55.56)	1.16	1[b]
3-4	49 (84.48)	20 (40.82)	29 (59.62)		
MCL laxity					
No	36 (63.16)	14 (38.89)	22 (61.11)	0.85	0.768[a]
Yes	21 (36.84)	9 (42.86)	12 (57.14)		
LCL laxity					
No	48 (84.21)	20 (41.67)	28 (58.33)	1.43	0.726[b]
Yes	9 (15.79)	3 (33.33)	6 (66.67)		

Values are reported as number (percentage); [a]Chi-square test, [b]Fisher exact test

BMI, Body Mass Index; KL, Kellgren-Lawrence classification; MCL, Medial collateral ligament; LCL, Lateral collateral ligament; IA PRP, intra-articular platelet-rich plasma

Table 4. Logistic regression analysis to determine associated factors for good response of a single injection of IA PRP

Variables	Adjusted odds ratio	95% CI		*p*-value
		Lower	Upper	
Age: ≤ 65	2.63	0.81	8.33	0.111
Sex: female	3.69	0.57	23.66	0.168
BMI: ≤ 25 kg/m^2	1.22	0.34	4.55	0.769
Duration: < 5 years	2.56	0.72	9.09	0.145
KL level: 2	1.26	0.21	7.53	0.8
Constant	0.21	0.13	3.15	0.257

BMI, body mass index; KL, Kellgren Lawrence classification;
CI, confidence interval; IA PRP, intra-articular platelet-rich plasma

factors for good outcomes were found in a multivariable analysis (Table 4).

Discussion

Knee osteoarthritis is a destructive degenerative disease which causes joint cartilage and the underlying bone to gradually degenerate over time. Higher levels of cartilage-degrading enzymes are expressed in knee osteoarthritis,[26] an indication that attempts to treat knee osteoarthritis have been unsuccessful.

This study aimed to determine the factors associated with a good outcome, i.e., pain reduction, after a single injection of IA PRP in patients with knee osteoarthritis. The main findings revealed that VAS at week 4 was lower than at baseline (mean difference = -1.58 (2.11) with $p < 0.001$). However, only 24 of 58 participants (41.4%) experienced a reduction of at least 30% in pain intensity, the indication of a good outcome. No demographic or clinical factors were found to have a statistically significant association with a good outcome. However, there is a possibility that participants who were female (adjusted odds ratio [OR] = 3.69, $p = 0.168$), aged ≤ 65 years (adjusted OR = 2.63, $p = 0.111$), and had a duration of knee osteoarthritis < 5 years (adjusted OR = 2.56, $p = 0.145$) had a greater chance of experiencing a good outcome. These three associations had low p-values that could potentially reach statistical significance ($p < 0.05$) with a larger number of participants.

In that regard, a study by Mazzola M and colleagues found that people over 60 had an autologous PRP injection failure rate similar to this study.[22] In this study, there was no statistically significant correlation between age and good response ($p = 0.111$), possibly due to the small sample size. More research is needed to evaluate the relationship of age and good outcomes.

More female patients had significant clinical improvement than males in this study. However, previous studies have reported finding no significant impact of gender on the clinical results of either autologous PRP injection or IA Hyaluronic injection.[21, 22] That 86% of the individuals in our study were women may have been a factor in the overall greater positive reaction to PRP injection in this study, i.e., there may have been a reduction in generalizability due to the small number of male participants. The upshot is that it is not possible to definitively state that sex has an impact on the outcome of IA PRP injection based on these results.

The chronic osteoarthritic knee symptoms of patients may be associated with central sensitization which plays an essential role in pain signaling in the central nervous system, resulting in increased pain sensitivity, duration of pain, and areas affected.[27,28] A study by Fatimah et al. reported that no association between response and duration of symptoms could be identified based on regression and correlation statistics of intraarticular steroid injection.[20] However, it is difficult to establish whether the duration of a symptom is a contributing factor due to the numerous factors that impact knee osteoarthritis over time.[2] In practice, patients with persistent symptoms are usually encouraged to combine many treatment modalities to manage their pain. In this study, a single injection of IA PRP generally had a poor response among participants with longer periods of symptoms of knee osteoarthritis.

BMI > 25 kg/m^2 and KL grade > 2 were found to be primary independent risk factors for autologous PRP injection failure in a study by Alessio-Mazzola et al.[22] However, in the present study, BMI ≤ 25 kg/m^2 and KL grade 2 were not associated with good responses to IA PRP injection. Again, this result might be due to the limited population size in this study.

Previous research has demonstrated that PRP injections significantly improve physical function compared to HA injections.[7,10] In the present study, four weeks after the IA PRP injection, there was an improvement in the physical function of the patients. That positive response of physical function to a single injection and short duration of IA PRP treatment support those previous reports.

This study has several limitations. First, the sample size did not reach the target due to the impact of the COVID-19 situation. Consequently, the statistical power of regression analysis to determine associated factors was compromised. Second, approximately 90% of the participants were female, so it was not possible to generalize the study results to the general population. Finally, this study had a relatively follow-up short period. Nevertheless, focusing on factors related to positive outcomes and on the short-term effects of a single dosage of PRP are issues important enough to warrant further investigation.[29]

Conclusions

A single injection of IA PRP can result in significant improvements in pain and physical function in patients with knee osteoarthritis after at four weeks. Age over 65 years, female gender, and duration of symptoms less than five years are factors that tend to be related to a good pain reduction response to treatment. However, the associations of these three factors were not demonstrated to be statistically significant. A larger number of participants will be required for further studies.

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