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original article

Factors affecting the therapeutic effects of multiple intra-articular injections of platelet-rich-plasma for knee osteoarthritis

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ABSTRACT

Background: Platelet-rich-plasma (PRP) is rapidly spreading as a conservative treatment option for knee osteoarthritis (KOA), however, its therapeutic efficacy is controversial. This study aimed to investigate the factors affecting the therapeutic effect of intra-articular PRP therapy for KOA in patients who received multiple PRP injections (PRP-I).

Methods: This is a historical cohort study included 1057 knees of 701 patients who received PRP-I during KOA treatment from 2018 to 2020. The difference in visual analog scale (VAS) scores before and after PRP-I was defined as the amount of change in VAS (ΔVAS). A linear mixed-effects model was employed with ΔVAS as a random effect and age, sex, BMI, KL classification, pre-treatment VAS, treatment duration, and the number of PRP injections as fixed effects. Evaluations using the Kellgren-Lawrence (KL) classification were added.

Results: Age, KL grade, and VAS score before treatment and after three, four, and five PRP-I were significantly associated with ΔVAS score. According to KL grade, age was significantly associated with ΔVAS score in the KL grade 4 group. VAS score before treatment was significantly associated with ΔVAS score, regardless of KL grade. Three-time PRP-I were significantly associated with ΔVAS in the KL-grade 1 and 2 groups. For KL grade 4, two or more PRP-I were significantly associated with the high efficacy.

Conclusions: Age, pain before treatment, KL grade and number of injections were associated with pain reduction after intra-articular PRP-I for KOA treatment. Pain reduction can be expected after PRP-I when patients are younger or experience severe pain before treatment. Three-time PRP-I are recommended to reduce pain in early-stage KOA and more than three times in advanced-stage KOA.

Trial registration: Retrospectively registration.

1. Introduction

Knee osteoarthritis (KOA) is one of the leading causes of joint dysfunction and disability in middle-aged and elderly people.[1,2] The pathogenesis of osteoarthritis (OA) involves wear and degeneration of articular cartilage, which in turn leads to joint inflammation. Many patients with KOA are treated conservatively with rehabilitation, anti-inflammatory medications, and intraarticular injections of hyaluronic acid (HA) or steroids.[2] Patients with advanced knee osteoarthritis who are resistant to conservative treatment are commonly considered for surgical treatment such as total knee arthroplasty or high tibial osteotomy.[3]

Recently, cell-based regenerative medicine using platelet-rich plasma (PRP) and mesenchymal stem cells (MSC) has emerged as a new conservative treatment option for KOA.[4] In particular, PRP therapy has been spreading widely in recent years, especially in the field of sports medicine, because of its relative simplicity and less invasive preparation, and reports of the therapeutic effects of intra-articular injections of PRP for KOA have also been increasing.[5–11] In the treatment of KOA, anti-inflammation, inhibition of cartilage catabolism, and chondrogenesis have been suggested as possible mechanisms for the beneficial effects of intra-articular PRP injections.[12–15]

Despite many reports on the beneficial effects of intra-articular PRP injection, several studies have reported conflicting results regarding its therapeutic effects,[7,16,17] and the efficacy and indications for PRP treatment in KOA remain controversial. Possible reasons for this

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inconsistency include wide variations in patient background, such as age, OA grade, and treatment protocol, including the number of injections and intervals[6,7,9,10,18,19]. In addition, the response to treatment appears to vary among patients. In clinical settings, PRP is often injected alone or repeatedly without following a specific protocol, depending on the severity of the patient's symptoms. Although it is important to predict treatment efficacy and strategy, the factors associated with treatment efficacy have not yet been fully clarified.

Therefore, the primary aim of this study was to investigate factors associated with pain reduction in a large cohort of patients with KOA. The secondary aim was to evaluate the differences among the patient groups divided according to OA grade. The hypotheses were that age and pain before treatment would be factors associated with the therapeutic effects of intra-articular PRP injection and that the response would differ depending on the OA grade.

2. Materials and methods

2.1. Patient selection

The study protocol conformed to the Declaration of Helsinki and was approved by the appropriate Ethics Committee. All patients provided informed consent before participation. We retrospectively reviewed consecutive patients who received intra-articular PRP injections for the treatment of KOA at our clinic. The indication criteria for the PRP injections were as follows: (1) patients diagnosed with KOA who received intra-articular PRP injections at any age, (2) patients complaining of pain and loss of function, and (3) patients resistant to conservative treatment, such as rehabilitation, medication, and HA injections. Inclusion criteria for this study were (1) patients who had at least one PRP injection for KOA at our clinic in approximately 3 years from 2018 to 2020, and (2) patients who were able to be followed up after the injection. The exclusion criteria for this study were (1) previous knee injury requiring surgery, (2) active or previous knee joint infection, (3) poorly controlled diabetes, and (4) serious medical history such as systemic inflammatory disease, hematologic disease, or malignancy. All patients were instructed to perform home exercises on their own, in addition to regular rehabilitation, by a physical therapist at the clinic during and after PRP treatment. All patients did not receive intra-articular steroid injections during the treatment period at our clinic. In this study, the number of treatment sessions was not predetermined and the number of PRP injections was arbitrarily determined depending on the symptoms. Multiple PRP intra-articular injections were administered approximately every 3 months, with an interval of at least 1 month. Details of the PRP administration intervals are shown in Table 1.

2.2. PRP treatment procedures

PRP was prepared using a Condensia system (KYOCERA Corporation, Kyoto, Japan) following the manufacturer's instructions provided by the company. First, 20 mL of whole blood was collected from a vein in the upper arm followed by twice centrifugation: the 1st centrifugation at 600×*g* for 7 min and the 2nd centrifugation at 2000×*g* for 5 min. After the first centrifugation, up to 2 mL of the plasma layer without leukocytes was collected from the erythrocyte layer. After the second centrifugation, 2 mL of leukocyte-poor PRP (LP-PRP) was collected by removing the platelet-poor plasma and was used for intra-articular injection without activation. The PRP obtained using this method is classified as P2-Bβ PRP (leukocyte-poor (LP)-PRP) based on the PAW classification system.[20] Purified PRP was injected into the suprapatellar bursa under ultrasound guidance by a well-trained physician. During the procedure, the patient's knee was kept in slight flexion, and the injection was performed under sterile conditions using a 23G needle with a lateral suprapatellar approach.

Table 1
Details on PRP administration intervals.

	PRP administration intervals			
	1st to 2nd	2nd to 3rd	3rd to 4th	4th to 5th
PRP 2 times	79.4 ± 34.7			
PRP 3 times	93.0 ± 29.9	104.9 ± 57.1		
PRP 4 times	99.8 ± 31.2	100.6 ± 27.6	106.0 ± 30.7	
PRP 5 times	97.3 ± 22.9	93.4 ± 25.9	94.7 ± 26.9	99.5 ± 28.0

Values are presented as mean (days) ± SD.

2.3. Data collection and outcomes

Patient background and demographic data were obtained from electronic medical records, and a visual analog scale (VAS; maximum 100 points) was obtained from pre- and post-treatment questionnaires. The VAS scores before and after PRP treatment were obtained, and the difference between them was defined as the change in the VAS score (ΔVAS). Each VAS after PRP treatment was obtained approximately 2 months after PRP injection, and each VAS before treatment was obtained just before the PRP injection. Patient demographic data included sex, age, body mass index (BMI), and platelet count. The number of PRP injections was also assessed. Radiological KOA grade was assessed using the Kellgren-Lawrence (KL) classification system[21] using standing anteroposterior radiographs taken before treatment. Grading of the KL classification was performed by two examiners independently under the results blinded ($\kappa = 0.88$; 95 % CI, 0.84–0.92). In inconsistent cases, the two examiners discussed the results and determined their grades.

2.4. Statistical analysis

All analyses were performed on the unit of the knees. Even when the same patient received PRP treatment for OA in both knees, each knee was analyzed as an individual knee. The absolute VAS score after each PRP injections and ΔVAS were evaluated using One-way analysis of variance (ANOVA) and Tukey test for post-hoc multiple comparison analysis (Figs. 1 and 2). The factors affecting ΔVAS in the treatment of a series of PRP intra-articular injections were examined using a linear mixed-effects model with subjects as the variable effect, because data from both knees of the same patient were used separately and because multiple measurements were obtained from the same knee. A linear mixed-effects model was employed with ΔVAS as a random effect and age, sex, BMI, KL classification, pre-treatment VAS, treatment duration, and the number of PRP injections as fixed effects (Table 3). The effect of each parameter on ΔVAS was presented as estimates, 95 % confidence intervals, t-values and p-values. To address missing values in BMI, multiple imputation was performed with 20 iterations. The patients were also divided into three groups according to KL grading, and the same model was evaluated for each KL group. Differences in demographic data among the groups were evaluated using the chi-square test for categorical variables or one-way ANOVA and post-hoc Dunnet test for continuous variables (Table 4). In each of the KL classification groups, the analyses were performed with a linear mixed-effects model, same as above. All statistical analyses were performed using the SPSS software (version 23.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

3. Results

3.1. Study characteristics

A total of 1057 knees from 701 patients (137 males, 564 females) were examined. The patients' demographic data are shown in Table 2. The mean patient age was 69.4 ± 10.0 years old. The mean BMI was 25.2 ± 4.2 (kg/m^2). The mean platelet count was 23.6 ± 5.9 (× 10^4/μL). The mean VAS at the start of treatment was 50.6 ± 24.3 points, and the mean PRP treatment interval was 96.9 ± 31.5 days. Most patients

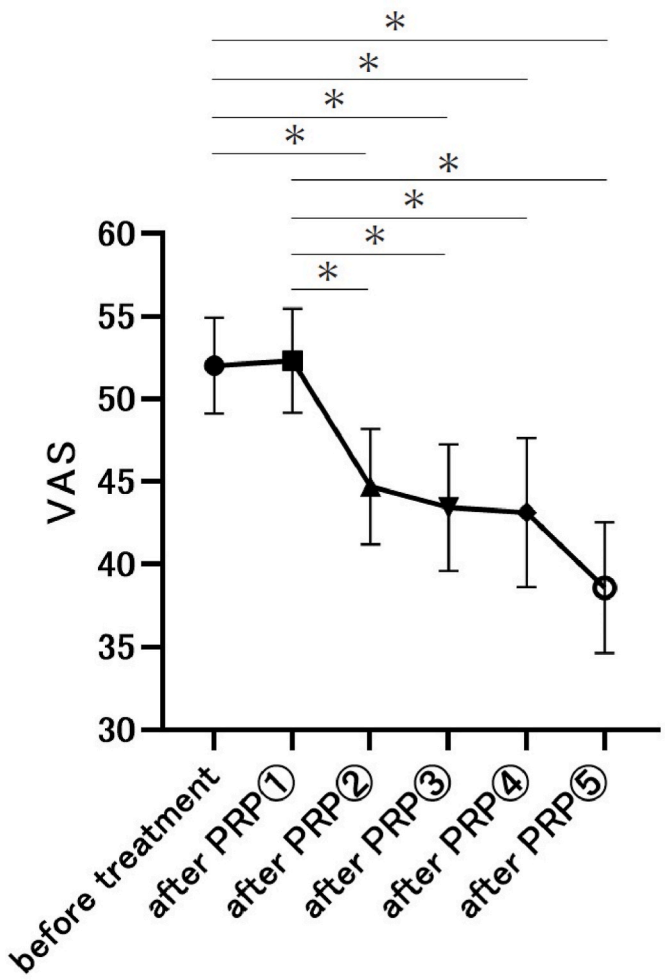

Fig. 1. The absolute VAS score before treatment and after each PRP injection
*: Significant difference ($P < 0.05$).

had advanced KOA with KL grades 3 and/or 4.

3.2. VAS score after each PRP injection

The absolute VAS scores before treatment and after each PRP injection are shown in Fig. 1. VAS scores after the second, third, fourth, and fifth PRP injections were significantly lower than the VAS before treatment and after the first PRP injection.

3.3. ΔVAS values of each PRP injection

ΔVAS values of each PRP injection are shown in Fig. 2. ΔVAS of the third and fourth PRP injection were significantly larger than ΔVAS of the first PRP injection.

3.4. The effect of each parameter on ΔVAS

A summary of the results of the analysis of the effect of each parameter on ΔVAS is shown in Table 3. Age, KL grade and VAS score before treatment were significantly associated with ΔVAS. Three, four, and five PRP injections were significantly associated ΔVAS.

3.5. Characteristics by KL classification

A summary of the demographic data and number of PRP injections according to the KL classification is presented in Table 4. There were

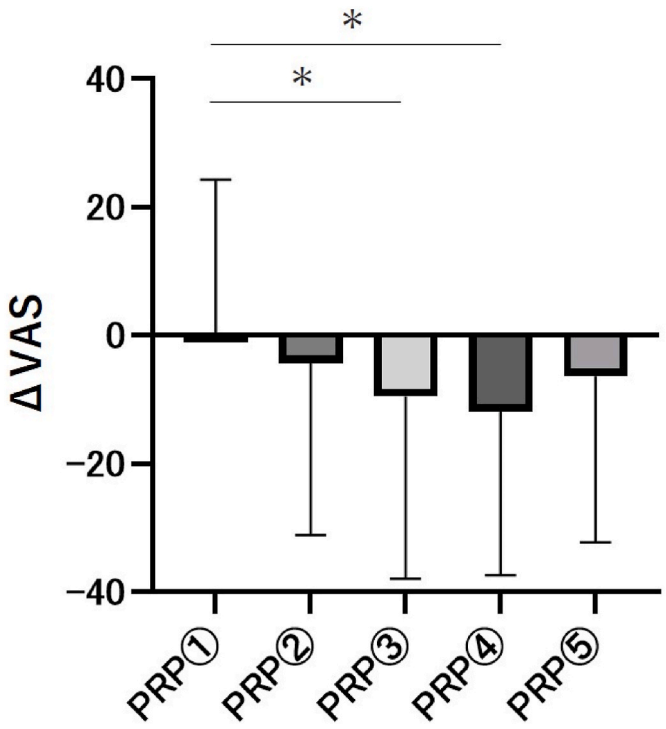

Fig. 2. The ΔVAS value of each PRP injection
*: Significant difference ($P < 0.05$).

Table 2
Summary of characteristic data of included patients.

Characteristics	
Total numbers of patients (cases, knees)	701, 1057
Gender (cases)	male 137, female 564
Age (years)	69.4 ± 10.0
Body mass index (kg/m^2)	25.2 ± 4.2
Platelet count (× 10^4/μL)	23.6 ± 5.9
VAS at the start of treatment (points)	50.6 ± 24.3
PRP administration interval (days)	96.9 ± 31.5
Kellgren - Lawrence classification (knees)	
Grade 1	17 (1.6 %)
Grade 2	127 (12 %)
Grade 3	281 (26.6 %)
Grade 4	632 (59.8 %)

Values are presented as mean ± SD.

Table 3
Summary of the results in the analysis of the effect of each parameter on ΔVAS.

	Estimate	95 % CI	t-value	P-value
Age (per 1 year)	0.33	0.15–0.52	3.5	<0.001
Gender (Female)	1.37	−2.32–5.05	0.7	0.467
BMI [per 1 (kg/m2)]	−0.28	−0.73–0.16	−1.2	0.216
KL grade (per 1)	4.19	2.12–6.27	4.0	<0.001
PRP injections intervals (per 1 day)	0.00	−0.02–0.01	−0.7	0.514
VAS at the start of treatment (per 1 point)	−0.58	−0.64–−0.52	−18.5	<0.001
The number of PRP injections				
1	reference			
2	−4.61	−9.65–0.42	−1.8	0.072
3	−8.37	−14.00–−2.74	−2.9	0.004
4	−9.89	−16.69–−3.09	−2.9	0.004
5	−8.04	−15.91–−0.17	−2	0.045

Table 4
Summary of demographic data and number of PRP injections by KL classification.

	KL classification				P-value
	1	2	3	4	
Case (knees)	17	127	281	632	
Gender					<0.001
Male	9 (52.9 %)	49 (38.6 %)	88 (31.3 %)	151 (23.9 %)	
Female	8 (47.1 %)	78 (61.4 %)	193 (68.7 %)	481 (76.1 %)	
Age	60.5 ± 11.8	61.4 ± 10.7	68.4 ± 9.4	72.2 ± 8.4	<0.001
BMI	23.2 ± 3.3	24.2 ± 3.5	24.7 ± 3.8	25.6 ± 4.5	<0.01
VAS at the start of treatment (points)	44.1 ± 25.1	37.6 ± 23.4	48.3 ± 24.9	54.4 ± 23.1	<0.001
Platelet count (× 10^4/μL)	25.3 ± 6.2	24.8 ± 6.8	23.5 ± 6.0	23.4 ± 5.9	0.065
The number of PRP injections					
1	10 (58.8 %)	40 (31.5 %)	74 (26.3 %)	159 (25.2 %)	
2	2 (11.8 %)	30 (23.6 %)	71 (25.3 %)	132 (20.9 %)	
3	2 (11.8 %)	24 (18.9 %)	54 (19.2 %)	138 (21.8 %)	
4	2 (11.8 %)	10 (7.9 %)	34 (12.1 %)	94 (14.9 %)	
5	1 (5.9 %)	23 (18.1 %)	48 (17.1 %)	109 (17.2 %)	
mean number of PRP injections	1.9 ± 1.3	2.6 ± 1.5	2.7 ± 1.4	2.8 ± 1.4	0.051

n (%), mean ± SD.

significant differences in sex, age, BMI, and the VAS before treatment between the KL groups. There was a tendency for more women, older patients, and patients with a higher BMI as the KL grade advanced. The VAS before treatment in KL grade 3 and 4 were significantly higher than that in KL grade 2. There was no significant difference between the platelet count and the KL grade. Although no statistically significant differences were found, there was a trend toward an increase in the number of PRP injections as the KL grade advanced.

3.6. The effect of each parameter on ΔVAS by KL classification

A summary of the results of the analysis of the effect of each parameter on ΔVAS by KL classification is presented in Table 5. KL grades 1 and 2 were evaluated together as early-stage KOA because of the small number of patients. Age was significantly associated with ΔVAS in KL grade 4 patients. The VAS scores before treatment were significantly associated with ΔVAS in all KL grade groups. Regarding the number of PRP injections, only three PRP injections was significantly associated with ΔVAS for KL grades 1–2. For KL grades 3, two, three, and five PRP injections were significantly associated with ΔVAS. For KL grades 4, two, three, four and five PRP injections were significantly associated with ΔVAS.

4. Discussion

The most important finding of this study was that patient age, pain before treatment, and number of injections (three, four, and five) were significantly associated with pain reduction after intra-articular PRP injection for the treatment of KOA. In the subgroup analysis by KL grade, only 3-time injections were significantly associated with pain reduction in patients in the KL grade 1–2 group. However, more than 2-time injections had the highest efficacy after four injections in the KL grade 4 group. These results suggest that younger patients and those with more severe pain before treatment tend to respond to intra-articular injection of PRP. To reduce pain, the number of injections can be modified according to the KL-grade.

In recent years, numerous studies have reported favorable results of intra-articular PRP injection for KOA, mostly in relatively young patients under the age of 60 years old.[5,7–11] Filardo et al. reported a negative correlation between age and IKDC score, with better clinical improvement in younger patients with mild cartilage degeneration after intra-articular PRP injection.[16] Kon et al. compared the clinical results of intra-articular injections of PRP, high-molecular weight (HW) HA, and low-molecular weight (LW) HA and reported that symptoms improved more in the PRP group than in the LW HA and HW HA groups at 6 months in patients age 50.[22] These results support the findings of the present study that younger patients are more likely to respond to intra-articular PRP injections.

Regarding the influence of OA grade, the therapeutic effects of intra-articular PRP injections for the treatment of advanced KOA has been recently reported.[18,19,23,24] Saita et al. reported that KL grade 4 OA with severe varus alignment of the FTA >190° was associated with a lower improvement after multiple intra-articular PRP injections,.[18] Jubert et al. reported that a single intra-articular PRP injection showed therapeutic effects comparable to those of a single corticosteroid injection in patients with advanced KOA, including pain reduction, improvement in activities of daily living, and quality of life.[19] In the present study, pain reduced after multiple intra-articular PRP injections in patients with advanced KOA. These results suggest that intra-articular PRP injections can improve intra-articular conditions, possibly by suppressing

Table 5
Summary of the results in the analysis of the effect of each parameter on ΔVAS by KL classification.

	KL grade 1-2				KL grade 3				KL grade 4			
	Estimate	95 % CI	t-value	P-value	Estimate	95 % CI	t-value	P-value	Estimate	95 % CI	t-value	P-value
Age (per 1 year)	0.16	−0.29–0.61	0.7	0.489	0.25	−0.07–0.56	1.5	0.123	0.53	−0.27–0.80	3.9	<0.001
Gender (Female)	9.44	−0.71–19.60	0.8	0.068	−5.09	−11.29–1.11	−1.6	0.107	1.36	−3.56–6.28	0.5	0.587
BMI [per 1 (kg/m2)]	0.83	−0.69–2.36	1.1	0.281	−0.60	−1.43–0.23	−1.4	0.158	−0.22	−0.76–0.31	−0.8	0.414
PRP injections intervals (per 1 day)	−0.01	−0.04–0.02	−0.7	0.478	−0.02	−0.05–0.01	−1.2	0.236	0.00	−0.02–0.03	0.4	0.658
VAS at the start of treatment (per 1 point)	−0.80	−0.94–−0.67	−11.9	<0.001	−0.52	−0.63–−0.40	−8.7	<0.001	−0.57	−0.65–−0.49	−13.9	<0.001
The number of PRP injections												
1	reference				reference				reference			
2	−6.08	−19.26–7.11	−0.9	0.363	−8.41	−16.38–−0.45	−2.1	0.039	−7.98	−14.41–−1.55	−2.4	0.015
3	−17.27	−31.44–−3.10	−2.4	0.017	−8.88	−17.60–−0.16	−2.0	0.046	−9.96	−17.36–−2.56	−2.6	0.008
4	−4.13	−24.37–16.11	−0.4	0.687	−9.15	−19.67–1.38	−1.7	0.088	−13.61	−22.57–−4.65	−3.0	0.003
5	−3.49	−19.12–12.14	−0.4	0.658	−13.81	−22.96–−4.66	−3.0	0.003	−11.44	−22.02–−0.85	−2.1	0.034

intra-articular inflammation.

In the present study, the number of injections (3, 4, and 5) was significantly associated with pain reduction after intra-articular PRP injections. According to recent systematic reviews, multiple injections at intervals of 1 week to 1 month appear to be commonly used as administration protocols for intra-articular PRP injections in the treatment of KOA.[8,25–27] However, no definitive protocol has been established that includes the number of injections or intervals. It has been reported that even a single injection PRP improves symptoms and the effects last for average 6–12 months.[28–31] Patel et al. reported that a single injection of PRP was as effective as two injections at 3-week intervals at a 6-month follow-up.[10] Meanwhile, a recent systematic review by Kim et al. reported that intra-articular PRP injections can improve pain and function in patients with KOA for up to 12 months compared with HA, regardless of the number of injections.[32] The superiority of three PRP injections over a single injection in the sustainability of the anti-inflammatory effect was suggested in an animal study.[33] Chouhan et al. compared the effects of multiple and single PRP administrations in a guinea pig OA model and reported that articular cartilage scores at 3 months and synovial scores at 6 months were significantly higher in the 3 injections group than in the single-injection or control groups.[33] Görmeli et al. conducted a randomized controlled trial and reported that the VAS and IKDC subjective scores in the three injection groups were better than those in the 1 injection group at the 6-months follow-up.[34] A systematic review of clinical studies comparing single and multiple injections reported that similar effects on pain improvement were observed in both groups, while clinical outcomes, including the assessment of joint function, were significantly better after multiple injections than after a single injection.[11] Interestingly, the results of this study showed that patients with advanced KOA showed pain relief even after multiple injections, whereas patients with early-stage KOA showed significant pain relief only after three injections These reports suggesting that multiple injections may be desirable or required to obtain better treatment effects, although appropriate intervals according to KOA progression need to be determined.

This study has the following limitations. First, this study included no control group, and the efficacy of the PRP injections over other treatments may be biased. In addition, the possible bias of placebo effect cannot be ruled out. However, all patients received conservative treatment before the PRP injection. Therefore, this study reflects the effects of PPR injections in patients who do not respond to traditional conservative treatments. Second, only the VAS was used to assess outcomes, and other functional and radiographic assessments were not performed. The standard deviations in VAS were large because of its characteristic. Therefore, the outcomes could differ if other outcome parameters were used, we plan to investigate the efficacy of PRP injections with other patient-reported outcomes in the future. Third, other treatments, including analgesics and HA injections, were not restricted since the PRP injection was used as a treatment option and it was impractical to restrict all other treatments in clinical setting. Therefore, the effect of other treatments on pain reduction could not be excluded. However, as noted above, patients received conservative treatments including analgesics, HA injections, and rehabilitation for several months before PRP injection. Therefore, the results of this study reflect the effects of the PRP injections on patients who did not respond to conventional conservative treatments. Fourth, physical activities levels of included patients were not evaluated, which could potentially affect the VAS value. Finally, this study was a retrospective study, which may have introduced selection bias because patients were able to choose the repeat of the PRP treatment. Future prospective studies with a treatment protocol and control group would be desirable.

5. Conclusions

Patient age, pain before treatment, and the number of injections were associated with pain reduction after intra-articular PRP injections for KOA treatment. Pain reduction can be expected after PRP injection when patients are younger or experience severe pain before treatment. Multiple intra-articular injections are recommended to reduce pain. Injecting three times for patients with early-stage OA and injecting more than three times for patients with advanced-stage OA was revealed to be most effective.

Ethical approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Sobajima clinic (protocol code SC-003M and date of approval November 19, 2020).

Informed consent was obtained from all subjects involved in the study.

Consent of publication

Not Applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Conflicts of interests

The authors have no conflicts of interest relevant to this article.

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Authors' contribution

All authors have made substantial contributions to (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be submitted. The specific contributions of the authors are as follows: (1) Conception and design of the study: TaM, SS, RK. (2) Analysis and interpretation of the data: all authors, Drafting of the article: KK, TaM, SS. (3) Final approval: all authors.

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