PODCAST 5-in-5

Clinical Efficacy of Platelet-Rich Plasma Injection and Its Association With Growth Factors in the Treatment of Mild to Moderate Knee Osteoarthritis

A Randomized Double-Blind Controlled Clinical Trial As Compared With Hyaluronic Acid

Yong-Beom Park,* MD, PhD, Jun-Ho Kim,† MD, Chul-Won Ha,‡§||¶ MD, PhD, and Dong-Hyun Lee,# MD
Investigation performed at Samsung Medical Center, Seoul, Republic of Korea

Background: Although platelet-rich plasma (PRP) has potential as a regenerative treatment for knee osteoarthritis, its efficacy varies. Compositional differences among types of PRP could affect clinical outcomes, but the biological characterization of PRP is lacking.

Purpose: To assess the efficacy of intra-articular PRP injection in knee osteoarthritis as compared with hyaluronic acid (HA) injection and to determine whether the clinical efficacy of PRP is associated with its biological characteristics.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: A total of 110 patients with symptomatic knee osteoarthritis received a single injection of leukocyte-rich PRP (1 commercial kit) or HA. Clinical data were assessed at baseline and at 6 weeks and 3 and 6 months after injection. The primary endpoint was an improvement in the International Knee Documentation Committee (IKDC) subjective score at 6 months, and the secondary endpoints were improvements in scores based on the Patient Global Assessment, the visual analog scale (VAS) for pain, the Western Ontario and McMaster Universities Osteoarthritis Index, and the Samsung Medical Center patellofemoral score. Cell counts and concentrations of growth factors and cytokines in the injected PRP were assessed to determine their association with clinical outcomes.

Results: PRP showed significantly improvement in IKDC subjective scores at 6 months (11.5 in the PRP group vs 6.3 in the HA group; $P = .029$). There were no significant differences between groups in other clinical outcomes. The Patient Global Assessment score at 6 months was better in the PRP group ($P = .035$). The proportion of patients who scored above the minimal clinically important difference (MCID) for VAS at 6 months was significantly higher in the PRP group ($P = .044$). Within the PRP group, the concentrations of platelet-derived growth factors were high in patients with a score above the MCID for VAS at 6 months. The incidence of adverse events did not differ between the groups ($P > .05$).

Conclusion: PRP had better clinical efficacy than HA. High concentrations of growth factors were observed in patients who scored above the MCID for clinical outcomes in the PRP group. These findings indicate that concentration of growth factors needs to be taken into consideration for future investigations of PRP in knee osteoarthritis.

Registration: NCT02211521 (ClinicalTrials.gov identifier).

Keywords: osteoarthritis; platelet-rich plasma; hyaluronic acid; growth factor; cytokine

Osteoarthritis (OA) of the knee is a multifactorial chronic disease characterized by pathological changes in all parts of the knee joint, including articular cartilage and synovium,[38] and results in pain, functional limitations, and disability.[41] In treating knee OA, the goals are to relieve pain, improve function and quality of life, and limit disability. Palliative interventions, including exercise, anti-inflammatory drugs, and analgesics, have been used as early to intermediate OA care.[7,34] In cases where palliative interventions are insufficient, intra-articular injections of hyaluronic acid (HA) or corticosteroids are

The American Journal of Sports Medicine
2021;49(2):487–496
DOI: 10.1177/0363546520986867

administered before resorting to surgical interventions. However, as the efficacy of intra-articular HA injection as a treatment for knee OA is controversial,[6,21,46] the need for a new treatment option has become evident.

Platelet-rich plasma (PRP) has been investigated in regenerative medicine.[14,27,35,39] PRP contains many growth factors that enhance anabolic processes and improve healing by stimulating cell proliferation, angiogenesis, and cell migration[23,30,33] and by facilitating the biosynthesis of cartilage.[5,15,25,29] In addition, PRP has been shown to inhibit catabolic processes by exerting anti-inflammatory and analgesic effects.[2,4,48] Accordingly, many clinical studies have evaluated the efficacy of PRP in the treatment of knee OA. Despite the growing evidence regarding PRP and its use in knee OA, the efficacy of PRP remains inconclusive.[8,16,39,43] While it is possible that the various growth factors and catabolic cytokines contained in PRP are involved in its anabolic and anticatabolic effects,[19,36,49] the majority of previous studies did not provide a precise biological characterization of its various components.

Accordingly, our objective was to compare the efficacy of intra-articular PRP injection with that of HA injection in patients with knee OA. We hypothesized that PRP would be clinically superior to HA in providing pain relief and function improvement in mild to moderate cases of knee OA. In addition, we investigated the association of the PRP composition with clinical efficacy by performing a precise biological characterization of the injected PRP, including cell count and quantification of various growth factors and catabolic cytokines.

METHODS

Study Design

This prospective randomized double-blind controlled clinical trial was conducted at a single institution from November 2014 to October 2015. This study was approved by the institutional review board before enrollment of the first patient (Samsung Medical Center Institutional Review Board, No. 2013-12-056). Informed consent was obtained from each participant. The study was registered in Clinical Trials.gov (NCT02211521).

Patients and Randomization

Patients aged >40 years with knee OA (Kellgren-Lawrence grade 1-3) per the criteria[1] of the American College of Rheumatology were included. Inclusion and exclusion criteria are detailed in Table 1.

TABLE 1
Inclusion and Exclusion Criteria

Inclusion criteria
Age ≥40 y
Osteoarthritis of the knee, according to the criteria of the American College of Rheumatology[1]
Kellgren-Lawrence grade 1-3
Visual analog scale for pain >40 mm at screening and baseline
Exclusion criteria
Hemoglobin <10 g/dL
Platelet <100,000/μL
Presence or history of autoimmune disease
Recent (within 2 wk) fever or serious illness
Local infection at the site of the procedure
Corticosteroid injection at the site of the procedure in the past 1 mo
Systemic use of corticosteroids in the past 2 wk
Female patients who are pregnant, lactating, or planning pregnancy
Use of immunosuppressants in the past 6 wk
Enrollment in any other clinical trial in the past 4 wk
Participants considered inappropriate in the clinical trial by principal investigator (eg, cognitive dysfunction, lack of will)

After their enrollment in the study, patients were randomized to receive PRP or HA in a 1:1 ratio according to a schedule that was based on a stratified random permuted block design with a block size of 4 to 6. After the eligibility assessment by the clinician (C.W.H.), the research coordinator (T.H.S.) introduced the study to the patients using a standardized script. Patients who qualified to participate in the study, per the inclusion and exclusion criteria, were assigned a randomized identification number and allocated to the PRP group or the HA group.

PRP Preparation

Approximately 54 mL of peripheral venous blood was drawn from each patient, using a 60-mL syringe prefilled with 6 mL of acid citrate dextrose. All blood draws were performed at the same time of the day (approximately 1 PM) to minimize the potential variability associated with the time of blood draw. Blood samples were transferred to a commercial PRP separation system (GPS III Platelet Concentration System; Zimmer Biomet) and centrifuged at 3200

¶Address correspondence to Chul-Won Ha, MD, PhD, Department of Orthopedic Surgery, Samsung Medical Center, School of Medicine, Sungkyunkwan University, 81 Irwon-ro, Gangnam-gu, Seoul, 06351, Republic of Korea (emails: chulwon.ha@gmail.com or hacw@skku.edu).
*Department of Orthopedic Surgery, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Republic of Korea.
†Department of Orthopedic Surgery, Seoul Medical Center, Seoul, Republic of Korea.
‡Department of Orthopedic Surgery, Samsung Medical Center, Seoul, Republic of Korea.
§Stem Cell and Regenerative Medicine Institute, Samsung Medical Center, Seoul, Republic of Korea.
‖Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University, Seoul, Republic of Korea.
#Department of Orthopedic Surgery, Himchan Hospital, Busan, Republic of Korea.
Y.B.P. and J.H.K. contributed equally to this work.
Submitted May 6, 2020; accepted September 1, 2020.
One or more of the authors has declared the following potential conflict of interest or source of funding: This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea (grant HI14C3484). AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating thereto.

rpm for 15 minutes, according to the manufacturer's protocols. Subsequently, approximately 6 mL of the PRP (the buffy coat portion) was drawn by a syringe and used for intra-articular injection (3 mL) and for analyses of the sample for growth factors, cytokines, and cell count (3 mL).

Evaluation of Cell Count, Growth Factors, and Cytokines in the PRP

One milliliter each of PRP and whole blood was used for complete blood counts (red blood cells, leukocytes, and platelets). PRP was activated using thrombin, as described previously,[20] and placed in a freezer. The following were quantified in the PRP by an enzyme-linked immunosorbent assay, using the appropriate Quantikine Human Immunoassay Kit (R&D Systems): platelet-derived growth factor (PDGF) AA, BB, and AB; transforming growth factor β1 (TGF-β1); vascular endothelial growth factor (VEGF); epidermal growth factor (EGF); basic fibroblast growth factor (bFGF); insulin-like growth factor 1 (IGF-1); catabolic cytokines, including interleukin 1β (IL-1β) and metalloproteinase 13 (MMP-13); and the catabolic blocker of IL-1 receptor antagonist (IL-1ra).

The optical densities of the PRP were measured in microplate wells using a microplate reader (EL × 800G; BioTek Instruments) at 450 nm. The data were analyzed using KC Junior Software (Power Wave XS UV-Biotek, KC Junior Software). Sample concentrations were measured in duplicates and determined by interpolating from a standard curve.

Blinding and Intervention

To keep the participants blinded to their assigned treatments, blood draws and PRP preparation were completed before injections in all patients, irrespective of their group assignment. At 30 minutes after blood draw in all patients, intra-articular injections of 3 mL of PRP or HA (30 mg/3 mL, molecular weight >10,000 kDa, LBSA0103, Synovian; LG Life Sciences) were performed aseptically, using a supralateral approach and following the same standardized procedure for both treatments. Blindfolds were applied to the patients during the injection to ensure that they were blinded to the treatment. After the injection, patients were instructed to limit the use of the affected leg for at least 24 hours and use cold icing for discomfort.

Outcome Measurement

The primary outcome was improvement in the International Knee Documentation Committee (IKDC) subjective knee score[22] at 6 months, and the secondary outcomes were the Patient Global Assessment and the improvement in scores using the 100-mm visual analog scale (VAS) for pain, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),[3] and the Samsung Medical Center patellofemoral scoring system.[26] Patients were assessed at baseline and at 6 weeks and 3 and 6 months after the injection. As the trial followed a double-blind design, all clinical evaluations were performed by an independent physician (C.W.H.), and the clinical research coordinator was blinded to the treatment as well.

Evaluation of Factors Affecting Clinical Outcomes in the PRP Group

Subgroup analysis was performed to identify the variables that may be associated with the improvement of clinical outcomes in patients treated with PRP. Patients receiving PRP were divided into 2 groups—above and below the minimal clinically important difference (MCID)—for the IKDC subjective scores,[18] VAS scores,[47] and WOMAC scores.[42] Age, sex, body mass index, degree of OA, cell counts in whole blood and in PRP, and levels of growth factors and cytokines in PRP were assessed for association with the MCID subgroup.

Statistical Analysis

Sample Size Calculation. To determine the adequate sample size, a power analysis was performed, using the G*Power free software (Version 3.1). A minimum sample size of 49 knees per group was calculated to be required based on 80% power, a false-positive rate of 5%, and an effect size of 0.15. Accordingly, the study was designed to include 55 knees per group to account for a potential dropout rate of approximately 10%.

Statistics. The continuous data are expressed as mean and SD, and the categorical data are expressed as frequency and percentages. The Kolmogorov-Smirnov test was applied to the continuous data to determine if they followed a normal distribution. Baseline demographic characteristics and the mean improvement from baseline in each clinical outcome at each follow-up visit were assessed for each patient. The 2 study cohorts were compared using the Student *t* test (for continuous data that were normally distributed), the Mann-Whitney *U* test (for continuous data that were not normally distributed), or the Pearson chi-square test (for categorical variables). Subgroups were based on the achievement of MCID as an outcome, and the proportion of scores that achieved the MCID was compared between the PRP and HA groups using the Pearson chi-square test. Subgroup analysis (above or below MCID) in the PRP group was performed to determine the difference in demographics, cell counts in whole blood and PRP, and biochemical markers in PRP, using the statistical tests described earlier according to the data type. Data were analyzed using SAS software (Version 9.4; SAS Institute). A P value $<.05$ was considered statistically significant.

RESULTS

In this clinical trial, 128 patients were screened, of which 18 were excluded after screening. Accordingly, 110 patients were enrolled in the study and randomized to the PRP group (n = 55) or the HA group (n = 55) (Figure 1). The 2 groups were similar at baseline with respect to age, sex, body mass index, Kellgren-Lawrence grade for OA, IKDC subjective scores, and Samsung Medical Center

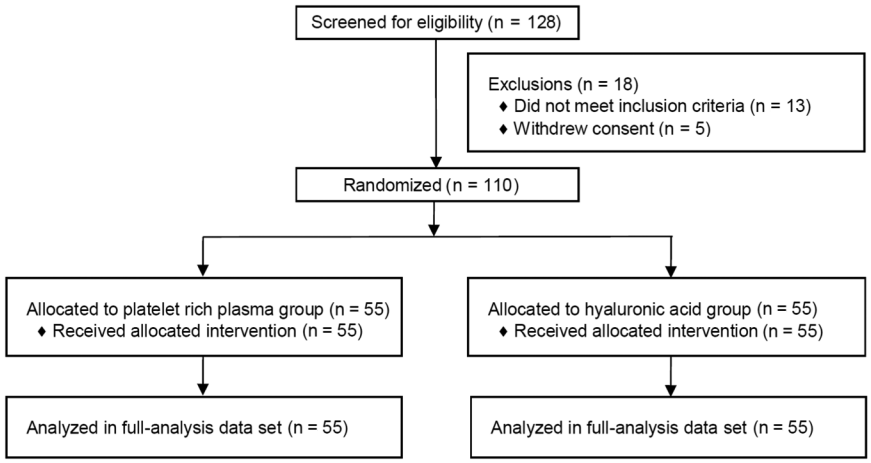

Figure 1. Flow diagram of screening, randomization, and sample size for analysis.

patellofemoral scores but not in the 100-mm VAS scores for pain and WOMAC scores (Table 2).

Clinical Outcomes

The improvement in the primary outcome—the IKDC subjective score 6 months after the injection—was significantly higher in the PRP group than the HA group (11.5 vs 6.3; $P = .029$). In addition, all the secondary clinical outcomes showed an improvement from baseline in both groups at the 6-month visit (Table 3; Appendix Table A1, available in the online version of this article). At 6 weeks, an improvement from baseline was noted in the WOMAC scores for function and stiffness. Moreover, the total WOMAC scores were higher in the PRP group than the HA group (Table 3). Absolute values of all scores are presented in Appendix Table A2 (available online). In addition, the Patient Global Assessment scores were higher in the PRP group than the HA group at all 3 time points; however, this difference was statistically significant at only the 6-month time point (Figure 2). The proportion of patients whose scores were above the MCID for the total WOMAC scores and for the VAS scores was significantly higher in the PRP group than the HA group at 6 weeks and 6 months, respectively (Figure 3).

Cell Count

The platelet count in the PRP was significantly higher than in the whole blood by approximately 3 times (976,000/μL vs 234,000/μL; $P < .001$). The leukocyte count in the PRP was also significantly higher than that in the whole blood (29,400/μL vs 6350/μL; $P < .001$). Conversely, the red blood cell count was significantly lower in the PRP than in the whole blood (900,000/μL vs 4,356,000/μL; $P < .001$). There were no significant differences between the groups in the number of platelets, leukocytes, and red blood cells in either the PRP or the whole blood ($P > .05$ in all comparisons) (Appendix Table A3, available online).

Quantification of Growth Factors and Cytokines

Growth factors and cytokines were obtained from 51 patients in the PRP group and 54 in the HA group. The mean ± SD concentrations in the PRP were as follows: PDGF-AA, 1651.9 ± 881.9 pg/mL; PDGF-BB, 3801.6 ± 2109.2 pg/mL; PDGF-AB, 10,712.5 ± 5678.6 pg/mL; TGF-β1, 10,821.0 ± 5167.3 pg/mL; VEGF, 204.3 ± 221.0 pg/mL; EGF, 131.6 ± 91.8 pg/mL; bFGF, 20.4 ± 23.9 pg/mL; IGF-1, 59,181.4 ± 17,054.2 pg/mL; IL-1β, 0.14 ± 0.12 pg/mL; MMP-13, 15.5 ± 23.7 pg/mL; and IL-1ra, 232.4 ± 126.9 pg/mL. The distribution of growth factors and cytokines is shown in Figure 4.

There was no statistically significant difference in the concentrations of growth factors, catabolic cytokines, and IL-1ra levels between the treatment groups, except for bFGF ($P > .05$ in all comparisons) (Appendix Table A4, available online).

Factors Affecting the Clinical Outcomes of PRP Treatment

There was no significant difference in the demographics, degree of OA, and cell counts in whole blood and PRP samples between patients who scored below and above the MCID for VAS scores for pain, IKDC subjective scores, and WOMAC total scores (Table 4). Of the growth factors and cytokines, only PDGF-BB and PDGF-AB showed significant differences between patients who scored above and below the MCID for the VAS ($P = .019$ and $P = .041$, respectively). Although levels of most growth factors did not significantly differ between the groups, they were generally higher in patients who scored above the MCID than in those who scored below, irrespective of the clinical outcome, with the exception of IGF-1.

TABLE 2
Patient Demographics and Baseline Characteristics: Full Analysis Data Set[a]

	PRP (n = 55)	HA (n = 55)	*P* Value
Age, y	60.6 ± 8.2	62.3 ± 9.6	.320[b]
Sex, male:female	16:39	8:47	.065[c]
Body mass index	25.5 ± 2.2	25.9 ± 2.8	.410[b]
Kellgren-Lawrence grade			
1	10	9	.945[c]
2	11	12	
3	34	34	
100-mm VAS score for pain	59.0 ± 9.9	55.2 ± 9.5	.017[d,e]
IKDC subjective scores	40.6 ± 11.9	42.1 ± 10.9	.502[b]
WOMAC scores			
Pain	7.8 ± 3.6	6.5 ± 2.8	.039[b,e]
Function	27.6 ± 11.3	23.7 ± 8.2	.038[b,e]
Stiffness	3.2 ± 1.6	2.9 ± 1.4	.241[d]
Total	38.6 ± 15.4	33.0 ± 11.8	.037[b,e]
SMC patellofemoral scores			
Pain	45.9 ± 14.6	43.1 ±12.2	.151[d]
Function	43.0 ± 16.6	42.4 ± 14.7	.822[d]

[a]Values are presented as mean ± SD or No. HA, hyaluronic acid; IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma; SMC, Samsung Medical Center; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
[b]Student *t* test.
[c]Pearson chi-square test.
[d]Mann-Whitney *U* test.
[e]$P < .05$.

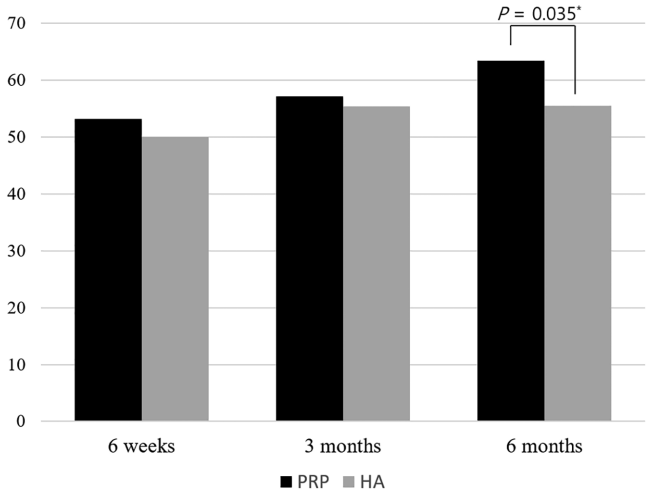

Figure 2. Patient Global Assessment scores for the PRP and HA treatment groups. The scores at 6 months were higher in the PRP group than the HA group. HA, hyaluronic acid; PRP, platelet-rich plasma.

TABLE 3
Improvement in Study Endpoints From Baseline at Each Follow-up Visit: Full Analysis Data Set[a]

Score[b]	PRP	HA	*P* Value
IKDC subjective			
6 wk	7.4 ± 10.8	5.5 ± 9.7	.524[c]
3 mo	8.1 ± 11.4	5.2 ± 12.7	.227[d]
6 mo	11.5 ± 12.8	6.3 ± 11.0	.029[d,e]
100-mm VAS for pain			
6 wk	18.7 ± 17.3	13.5 ± 16.8	.114[d]
3 mo	14.5 ± 19.7	10.5 ± 19.9	.299[d]
6 mo	20.9 ± 19.8	13.6 ± 18.6	.058[d]
WOMAC			
Pain			
6 wk	2.2 ± 2.8	1.5 ± 3.1	.132[c]
3 mo	1.6 ± 3.2	0.3 ± 5.5	.260[c]
6 mo	1.9 ± 3.2	1.7 ± 2.9	.691[d]
Function			
6 wk	6.6 ± 8.4	3.4 ± 8.2	.043[c,e]
3 mo	4.7 ± 11.0	1.9 ± 9.1	.219[c]
6 mo	4.0 ± 13.4	4.4 ± 8.6	.802[c]
Stiffness			
6 wk	0.9 ± 1.6	0.2 ± 1.6	.007[c,e]
3 mo	0.5 ± 1.9	0.1 ± 1.5	.202[c]
6 mo	0.5 ± 1.8	0.4 ± 1.7	.918[c]
Total			
6 wk	9.7 ± 10.9	5.1 ± 11.5	.013[c,e]
3 mo	6.8 ± 14.7	2.3 ± 13.7	.162[c]
6 mo	6.4 ± 16.4	6.5 ± 11.5	.967[d]
SMC patellofemoral			
Pain			
6 wk	5.4 ± 11.2	3.0 ± 12.9	.645[c]
3 mo	7.2 ± 14.3	2.1 ± 13.5	.100[d]
6 mo	8.7 ± 15.3	4.6 ± 13.8	.211[d]
Function			
6 wk	7.0 ± 12.9	5.5 ± 12.1	.711[c]
3 mo	6.1 ± 13.8	3.7 ± 15.0	.838[c]
6 mo	7.4 ± 13.4	3.8 ± 15.5	.258[d]

[a]Values are presented as mean ± SD. HA, hyaluronic acid; IKDC, International Knee Documentation Committee; PRP, platelet-rich plasma; SMC, Samsung Medical Center; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
[b]Sample size per visit: 6 weeks, PRP (n = 54) and HA (n = 55); 3 months, PRP (n = 52) and HA (n = 53); 6 months, PRP (n = 52) and HA (n = 50).
[c]Mann-Whitney *U* test.
[d]Student *t* test.
[e]$P < .05$.

Safety

The frequency of adverse events did not significantly differ between the treatment groups (Table 5). There were no serious adverse events in either group. All adverse events were mild or moderate. Two patients in the PRP group reported pain during the injection procedure, and 1 patient in this group reported swelling of the knee joint immediately after receiving the injection. During the follow-up period, mild swelling of the knee joint and a few cases of mild tenderness were observed in both groups (Figure 5).

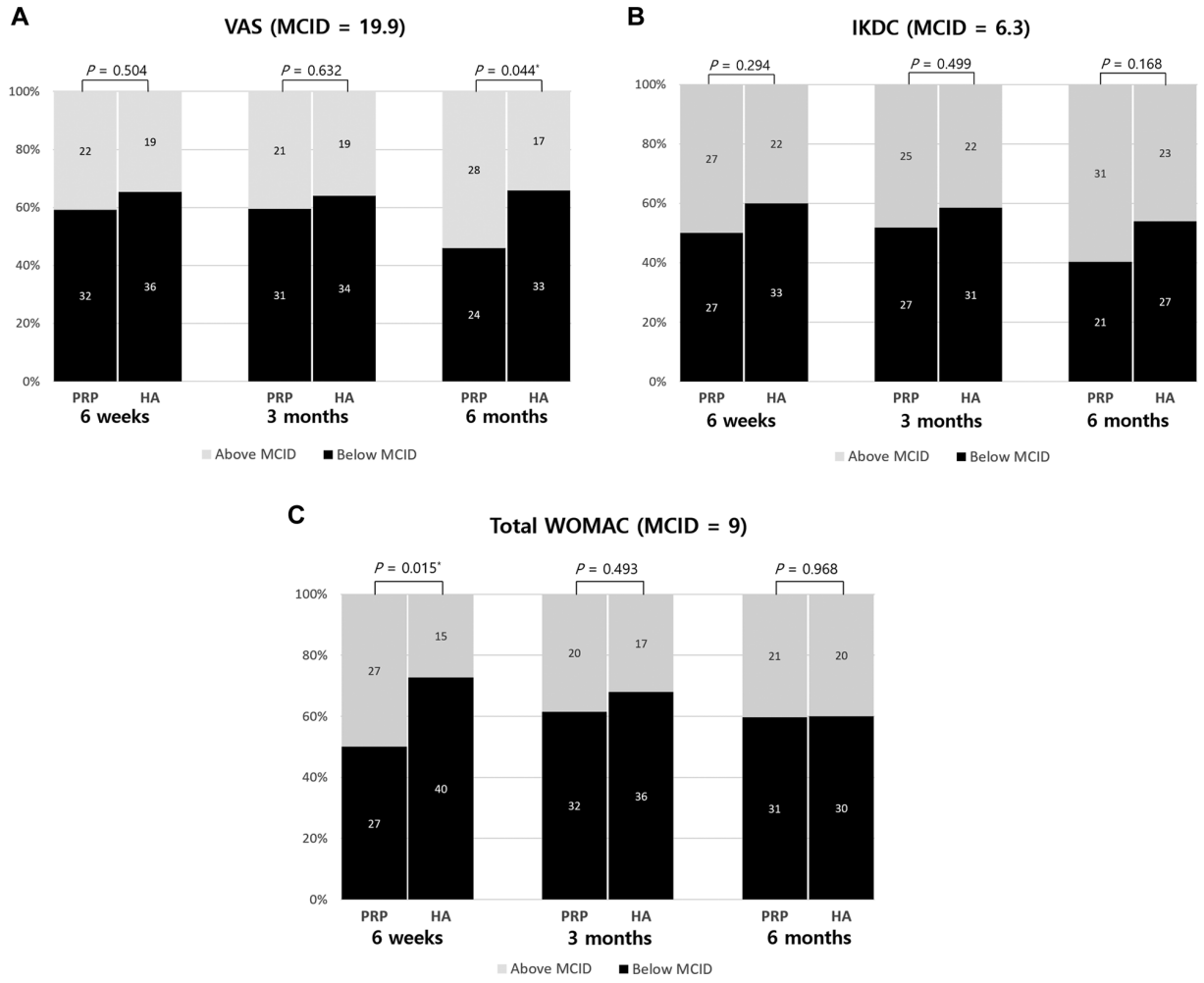

Figure 3. The proportions of patients treated with PRP and HA with scores above and below the MCID for the (A) VAS for pain, (B) IKDC, and (C) WOMAC. The proportion of patients whose scores were above the MCID was higher in the PRP group than the HA group in the majority of the assessments; however, only the VAS scores at the 6-month visit and the total WOMAC scores at the 6-week visit were statistically different. HA, hyaluronic acid; IKDC, International Knee Documentation Committee; MCID, minimal clinically important difference; PRP, platelet-rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

DISCUSSION

In this study, both PRP and HA provided significant clinical improvement in terms of knee function and alleviation of pain. While most secondary outcome measures did not show statistically significant differences between the treatment groups, the primary outcome measure—an improvement in IKDC subjective score at 6 months—was significantly higher in the PRP group than the HA group. In addition, the concentrations of some growth factors in patients receiving PRP whose scores were above the MCID for some clinical outcome measures at 6 months were higher than in patients receiving PRP whose scores were below the MCID for these outcome measures. Specifically, the levels of PDGF-BB and PDGF-AB were significantly higher in patients scoring above the MCID for the VAS. These findings may improve our understanding of the variability observed in clinical outcomes of PRP and support the development of guidelines for clinical applications of PRP in knee OA.

In this study, PRP was shown to improve the clinical outcomes of knee OA and the patient's perception of satisfaction. Six months after the procedure, the IKDC subjective scores and the Patient Global Assessment showed significantly higher improvement in patients treated with PRP than in those treated with HA. Similarly, recent meta-analyses reported pain relief and function improvement 1 year after PRP injection in patients with symptomatic knee OA,[8,12] although a recent randomized clinical trial comparing PRP with HA reported no significant difference in patient-reported WOMAC pain scores,[11] which was inconsistent with our findings. We believe that the potential differences in the PRP separation methods, the follow-up period, and the degree of the OA may affect the different

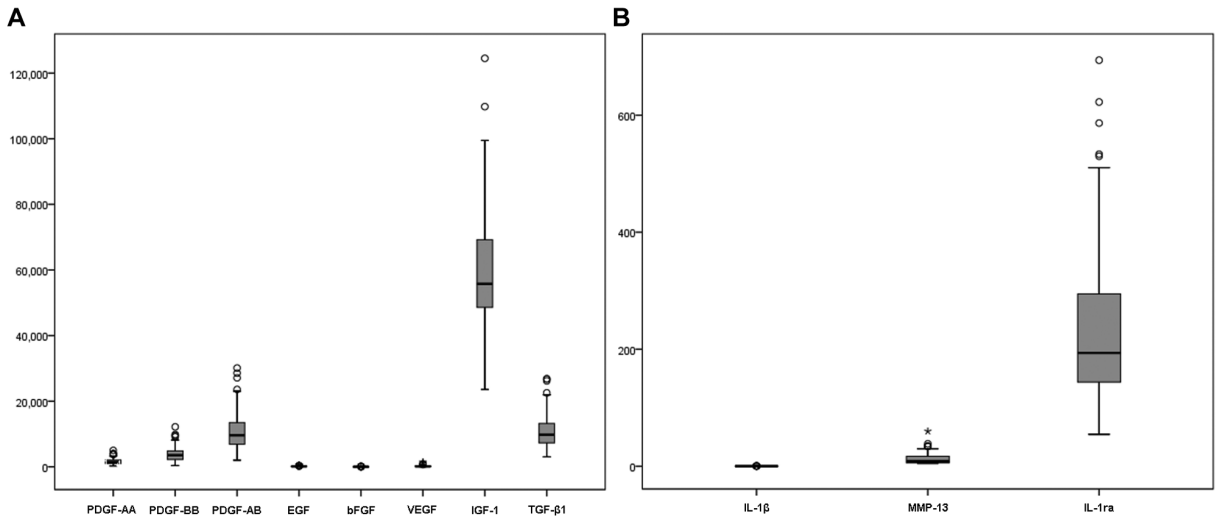

Figure 4. The distribution of the concentrations of (A) growth factors and (B) catabolic cytokines and IL-1 receptor antagonist. Among the growth factors, IGF-1 showed the highest concentrations. Among the catabolic cytokines and the antagonist, IL-1ra showed the highest concentrations. The horizontal line indicates the median; the box extends from the 25th to the 75th percentile; the bars indicate the lowest and highest observed value. The circles indicate outliers. For abbreviations, see Methods section.

TABLE 4
Subgroup Analysis of Patients Who Scored Above or Below the MCID for VAS, IKDC, and WOMAC in the PRP Group[a]

	VAS (MCID = 19.9)			IKDC (MCID = 6.3)			WOMAC (MCID = 9)		
	Above (n = 28)	Below (n = 24)	*P* Value	Above (n = 30)	Below (n = 22)	*P* Value	Above (n = 21)	Below (n = 31)	*P* Value
Age, y	60.2 ± 8.3	61.8 ± 8.2	.506	61.3 ± 8.6	61.3 ± 7.7	.795	63.2 ± 8.0	59.4 ± 8.1	.094
Sex, male:female	9:19	7:17	.817	10:20	6:16	.640	6:15	10:21	.777
Body mass index	24.9 ± 2.2	25.9 ± 2.0	.098	25.4 ± 2.2	25.3 ± 2.2	.918	24.9 ± 2.5	25.7 ± 1.9	.239
K-L grade			.781			.860			.340
1	6	4		5	5		3	7	
2	6	4		6	4		6	4	
3	16	16		19	13		12	20	
Whole blood, $10^3/\mu L$									
WBC	6.4 ± 1.3	6.1 ± 1.3	.428	6.2 ± 1.2	6.3 ± 1.5	.800	6.1 ± 1.3	6.4 ± 1.3	.523
RBC	4428.9 ± 591.6	4403.3 ± 370.2	.855	4493.7 ± 337.2	4312.7 ± 650.9	.198	4394.8 ± 355.6	4432.3 ± 579.2	.793
PLT	220.7 ± 45.1	248.4 ± 59.9	.063	226.0 ± 49.3	243.7 ± 58.9	.244	899.4 ± 305.4	937.7 ± 396.8	.085
PRP, $\times 10^3/\mu L$									
WBC	30.7 ± 8.9	27.8 ± 7.8	.213	30.0 ± 9.1	28.6 ± 7.6	.556	28.3 ± 10.2	30.1 ± 7.1	.452
RBC	917.1 ± 700.0	976.7 ± 624.9	.747	902.7 ± 704.0	1001.8 ± 607.2	.589	882.4 ± 789.1	986.8 ± 567.2	.581
PLT	915.4 ± 320.3	930.3 ± 408.3	.884	905.4 ± 325.5	945.2 ± 409.0	.698	899.4 ± 305.4	937.7 ± 396.8	.710
Growth factors and cytokines, $\times 10^3/\mu L$[b]									
PDGF-AA	1707.2 ± 900.2	1417.0 ± 760.5	.235	1615.2 ± 959.5	1525.8 ± 681.3	.718	1698.4 ± 970.0	1499.9 ± 762.1	.429
PDGF-BB	4299.8 ± 2446.8	2809.9 ± 1646.7	.019[c]	3766.0 ± 2448.5	3450.6 ± 1955.2	.619	3974.9 ± 2809.4	3413.0 ± 1798.2	.397
PDGF-AB	11,940.2 ± 6444.7	8522.4 ± 4535.9	.041[c]	11,028.4 ± 6597.5	9575.5 ± 4759.3	.397	11,750.7 ± 7189.3	9553.9 ± 4796.1	.205
EGF	132.3 ± 105.5	104.2 ± 60.1	.272	121.9 ± 103.8	116.6 ± 64.5	.838	132.4 ± 120.3	111.6 ± 61.3	.492
bFGF	19.8 ± 26.2	8.8 ± 9.0	.050	17.2 ± 25.7	11.8 ± 11.7	.329	20.5 ± 30.1	11.3 ± 11.3	.211
VEGF	234.6 ± 204.5	198.0 ± 282.9	.602	237.8 ± 218.3	191.9 ± 271.3	.515	303.1 ± 328.4	164.3 ± 146.2	.096
IGF-1	59,382.4 ± 15,265.7	59,377.6 ± 23,756.3	.999	61,424.3 ± 19,031.1	56,654.8 ± 19,822.7	.398	58,348.5 ± 14,094.1	60,033.7 ± 22,207.5	.770
TGF-B1	10,777.8 ± 5038.1	10,332.8 ± 6142.1	.782	10,488.7 ± 6067.0	10,697.1 ± 4797.0	.897	10,736.6 ± 5944.8	10,477.6 ± 5309.9	.874
IL-1β	0.1 ± 0.1	0.1 ± 0.1	.415	0.1 ± 0.1	0.1 ± 0.1	.328	0.1 ± 0.1	0.1 ± 0.1	.375
MMP-13	15.9 ± 16.8	10.8 ± 4.8	.140	12.5 ± 9.8	15.1 ± 16.6	.502	11.9 ± 7.9	14.7 ± 15.5	.471
IL-1RA	251.9 ± 129.0	238.5 ± 92.5	.685	244.2 ± 112.1	248.0 ± 117.2	.909	263.6 ± 116.1	234.6 ± 111.7	.387

[a]Values are presented as mean ± SD or No. IKDC, International Knee Documentation Committee; K-L, Kellgren-Lawrence; MCID, minimal clinically important difference; PLT, platelets; PRP, platelet-rich plasma; RBC, red blood cells; VAS, visual analog scale; WBC, white blood cells; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[b]For abbreviations, see Methods.

[c]$P < .05$.

results between the current study and the previous one.[11] Another recent randomized clinical trial with 5 years of follow-up reported that PRP provided overall superior clinical improvement to that seen with HA in both symptom and function.[13] In that study, while there was no significant difference between PRP and HA at the final evaluation, only

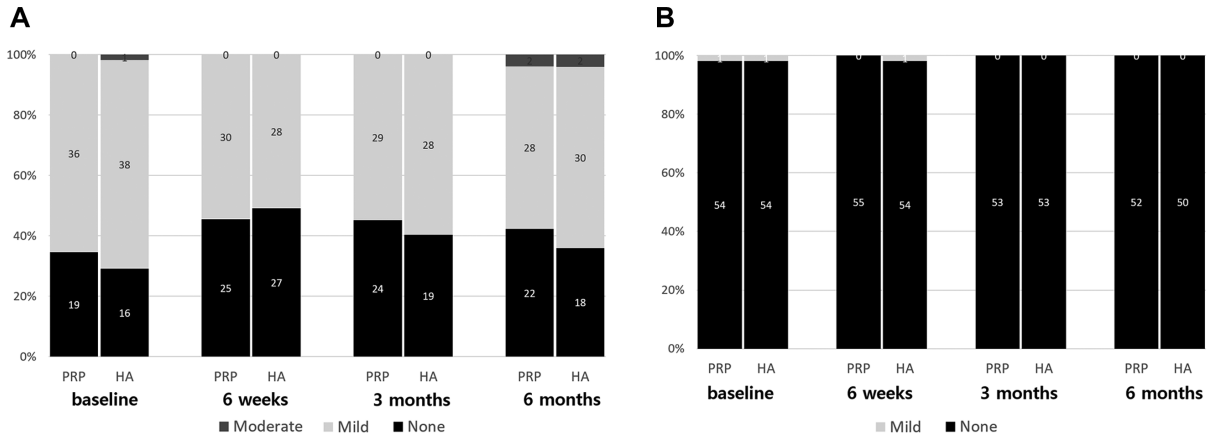

Figure 5. The proportion of patients who experienced (A) swelling or (B) tenderness of the knee joint during each study visit. No significant differences were observed between the groups for either adverse event at any visit. HA, hyaluronic acid; PRP, platelet-rich plasma.

TABLE 5
Patients Experiencing Adverse Events at the System Organ Class Level[a]

	PRP	HA
System organ class	6 (10.9)	8 (10.9)
Gastrointestinal disorders	1	0
General disorders and administration site conditions	3	0
Injury, poisoning, and procedural complications	0	2
Musculoskeletal and connective tissue disorders	1	5
Nervous system disorders	0	1
Constipation	1	0
Preferred term[b]		
Injection site pain	2	0
Injection site swelling	1	0
Nasopharyngitis	1	2
Musculoskeletal pain	1	3
Backache	0	2
Headache	0	1

[a]Values are presented as No. (%). HA, hyaluronic acid; PRP, platelet-rich plasma.

[b]According to the Medical Dictionary for Regulatory Activities (MedDRA).

the PRP treatment showed values that were significantly higher than the baseline values. A recent systematic review of 10 studies reported that 6 months after the injection, patients treated with PRP were more satisfied than those receiving normal saline.[24] Similarly, in our study, patient satisfaction at 6 months after treatment, as assessed by the Patient Global Assessment, was significantly higher in the PRP group than the HA group. Taking these findings together, we believe that PRP could provide clinical improvement in pain and function in patients with knee OA.

In this study, PRP injection resulted in clinically meaningful differences in various clinical outcomes. The absolute value of the change from baseline in the IKDC subjective score at 6 months (11.5 points) was higher than the reported MCID value, which is an absolute change of 6.3 points 24 weeks after treatment.[18] In addition, the proportion of patients above the MCID in VAS scores at 6 months was significantly higher in the PRP group than the HA group, and the improvement in VAS scores at 6 months in this group (20.9 points) was higher than the absolute value of the MCID (19.9 points).[47]

The MCID in VAS scores, as reported from different studies, was variable, ranging from a change of 7 to 37 points from the baseline score.[44] In the current study, the baseline VAS scores were 59.0 and 55.2 in the PRP and HA groups, respectively. According to a previous review article,[44] the MCID for the VAS was between 19 and 27 points when the baseline scores were between 50 and 65 points, suggesting that assigning an MCID value of 19.9 was appropriate for our study. Unlike the IKDC and VAS scores, WOMAC scores did not achieve the MCID in this study. Only a few studies have reported the MCID for WOMAC scores, despite the fact that WOMAC is a commonly used assessment tool in knee OA.[18,42] In addition, a baseline score for WOMAC was not reported for any of those studies. Accordingly, additional studies are required to assess the MCID for the WOMAC in terms of the baseline score and assessment procedures. Taken together, these findings suggest that PRP could be a therapeutic option for pain reduction and functional improvement in knee OA.

Interestingly, our results suggest that there may be an association between some of the measured growth factors and the improvement in clinical outcomes in patients treated with PRP. Several previous studies reported high variability in growth factors and catabolic cytokines in PRP samples.[9,10,19,31,32,37] Although some studies reported an association of growth factors and cytokines with cell count in PRP,[10,19,45] to the best of our knowledge, only 1 study evaluated the association between growth factors and clinical outcomes in knee OA.[28] In that study, the levels of

PDGF-AB and TGF- β1 were significantly correlated with a change in the WOMAC score at 3 months. These findings are inconsistent with the results of the current study, in which the concentrations of most growth factors were high in patients who scored above the MCID, irrespective of the clinical outcome measure. Of the growth factors, the concentrations of PDGF-BB and PDGF-AB were significantly higher in patients who scored above the MCID for the VAS. It is difficult to directly compare the results of the current study with those of previous studies because the potential differences in the methods of PRP separation, sample sizes, and degree of OA may affect the results. Nevertheless, the results of the current study suggest that the concentrations of growth factors need to be considered in future investigations of the use of PRP in the treatment of knee OA in a clinical setting.

Some limitations of this study need to be addressed. First, this study did not include a negative control (placebo) group. However, HA is commonly used as a positive control in studies of knee OA, and the MCID for the different clinical outcome measures was compared with that of the positive control and can therefore be considered to reflect the real clinical benefits of PRP treatment. Second, only 1 commercial PRP preparation kit was used in this study. Several previous studies reported that the use of different kits or separation methods could result in different concentrations of cellular components, growth factors, and catabolic cytokines.[9,31,32,37] However, the use of 1 type of commercial PRP preparation kit was important in determining the association between the levels of growth factors or cytokines and the clinical outcomes. Third, leukocyte-rich PRP was used in our study. While leukocyte concentrations can theoretically affect clinical outcomes, a previous report showed no significant difference in clinical outcomes between treatment with leukocyte-rich PRP and leukocyte-poor PRP.[40] Fourth, a single injection of PRP was selected. One study reported that multiple injections of PRP were effective as compared with a single injection of PRP.[17] However, the efficacy of PRP in knee OA is controversial, which should be determined before injection count. In addition, a single injection was more feasible owing to the study design of double blinding. Fifth, radiological evaluation was not included in our study. Although PRP has the potential to enhance the anabolic process, there is a paucity in evidence of disease-modifying effect, including structural change. Therefore, our study focused on the association of clinical outcomes with biological characteristics of injected PRP. Sixth, several subgroup analyses were conducted in this study, which could increase the chance of false-positive results. To minimize this error, comparisons of clinical outcome were based on their MCIDs. Finally, the potential variability in the composition of the different types of PRP might have affected the results of this study. Apart from the inevitable interindividual variability, we attempted to minimize the variability in the composition of the PRP samples by drawing venous blood from all patients at the same time of the day and by performing the PRP separation procedure using a single commercial kit.[32,37]

In conclusion, PRP treatment of knee OA has better clinical efficacy than treatment with HA and was associated with a good safety profile. In addition, PRP treatment resulted in improved patient satisfaction. The concentration of specific growth factors (PDGF-BB and PDGF-AB) was significantly higher in patients with a score above the MCID for the VAS. Based on these findings, this study suggests that PRP could be a reliable therapeutic option in knee OA in short-term follow-up and that the concentrations of growth factors need to be taken into consideration in future studies of PRP for the treatment of knee OA.

ACKNOWLEDGMENT

The authors thank Tae-Hee Seo for her effort in collecting clinical data and ensuring the accuracy and completeness of the data.

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