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Efficacy and Safety of a Single Intra-articular Injection of Platelet-rich Plasma on Pain and Physical Function in Patients With Ankle Osteoarthritis—A Prospective Study

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ABSTRACT

Ankle osteoarthritis (OA) can cause disabling symptoms, and some patients prefer to be treated with minimally invasive procedures. The aim was to evaluate the efficacy and safety of a single intraarticular injection of platelet-rich plasma (PRP) for patients with ankle OA. In a prospective study done in a university-affiliated tertiary care medical center, 44 patients with symptomatic ankle OA for at least 6 months were recruited. Patients received a single injection of PRP (3 mL) into symptomatic ankles. The primary outcome was the change from baseline in the visual analog scale (VAS) pain (0-10 cm) at 6 months. Secondary outcomes included the Ankle Osteoarthritis Scale (AOS) score, American Orthopedic Foot and Ankle Society (AOFAS) hindfoot-ankle score, single-leg stance test (SLS), rescue analgesics consumption and patient satisfaction. Thirty-nine participants (88.64%) completed the study. Significantly improvement in the VAS and AOS was noted at 1-, 3-, and 6-month follow-ups ($p < .001$). The mean VAS pain decreased significantly from 4.1 ± 1.7 at baseline to 2.2 ± 1.9, 1.7 ± 1.5, and 1.8 ± 1.6 at 1, 3, and 6 months ($p < .001$). The mean total AOS score reduced by 1.5, 2.2, and 2.1 from baseline respectively postinjection ($p < .001$). The mean AOFAS hindfoot-ankle score improved from 80.3 points at baseline to 87.2, 91.6, and 89.7 points at 1, 3, and 6 months ($p < .001$). SLS tests improved significantly ($p < .001$) at each follow-up. Acetaminophen consumption dropped significantly ($p < .001$) and no serious adverse events occurred. The study showed promise for a single intraarticular injection of PRP in the treatment of ankle OA.

Ankle osteoarthritis (OA) can cause pain and functional limitations. Approximately 6% to 13% of all cases of OA involve the ankle joint (1,2). Treatment options include analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), weight reduction, physical therapy, activity modification, orthotic devices, intra-articular injections, and surgery. Although some cases can be treated successfully with surgery, many patients are either not good candidates for surgery or prefer not to have surgery. Therefore, a treatment that reduces joint pain and improves function yet avoids the toxic effects of medications and the morbidity and mortality risks of surgery is needed. One promising option may be the intra-articular injection of platelet-rich plasma (PRP) (3-5).

PRP is an autologous blood product that mainly contains concentrated platelets and growth factors. The growth factors serve to promote local angiogenesis, modulate inflammation, inhibit catabolic enzymes and cytokines, recruit local stem cells and fibroblasts to sites of damage, and induce healthy nearby cells to manufacture greater numbers of growth factors (6). Local use of PRP directly at the site of cartilage injury is thought to stimulate a natural healing cascade and accelerate cartilage repair (7-10). Several systematic reviews and meta-analysis have concluded that PRP was safe and effective for the

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The trial was registered at ClinicalTrials.gov (Registry number NCT04022928).

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treatment of knee OA (10-13). Whether the efficacy may be generalized to ankle OA remains debatable. To date, there were only limited studies supporting its use in ankle OA (3-5,14,15).

Despite the favorable outcomes reported with intraarticular injections of PRP, the optimal number and frequency of its use remains inconclusive. A range of single to multiple injections with weekly to every 3- or 4-week schedules had been reported for knee OA (16,17). Several recent research studies had shown that a single intraarticular injection of PRP is safe and effective for the treatment of knee OA (17-20). The single-injection regimen is attractive, as it may be more convenient and has less adverse events than multiple injections. It may possibly represent a cost-saving strategy. The purpose of this study was to investigate the efficacy and safety of a single intraarticular injection of PRP in patients with ankle OA.

Patients and Methods

Study Design and Participants

This prospective study was conducted in the outpatient rehabilitation department at a university-affiliated tertiary-care medical center between July 2018 and May 2019. Patients were referred from our outpatient orthopedic department with the diagnosis of ankle OA. Consecutive patients fulfilled the following inclusion criteria: (1) aged 20 years or older; (2) reported ankle pain for at least 6 months, despite conservative treatment (rest, physical therapy, orthoses or pain medications, etc.) or inability to tolerate the side effects of medications; (3) ankle radiographs taken within 6 months (reviewed by the senior author Y.J.C.) were equivalent to grades 1 to 4 ankle OA by the Kellgren-Lawrence grading system (21); (4) average ankle pain of at least 3 cm on a 10-cm visual analog scale (VAS); (5) were normally active, not bedridden or confined to a wheelchair, able to walk 30 m without the aid of a walker, crutches, or cane; (6) were willing to discontinue all NSAIDs or other analgesic medication (except for rescue medication) during the study; (7) no use of physical therapy or changes in shoes or orthotic devices during the study period; and (8) radiological evidence of bilateral ankle OA was accepted if global pain VAS in the contralateral ankle was less than 3 cm. Exclusion criteria included pregnant and lactating women, lower leg trauma other than within the ankle, previous orthopedic surgery on the spine, hip or knee, presence of active joint infections of foot or ankle, previous surgery or arthroscopy on the affected ankle within 12 months, intra-articular steroid or hyaluronate injection in the treated ankle within the past 6 months, treatment with anticoagulants or immunosuppressives, history of rheumatoid arthritis, gout, or any other inflammatory arthropathy, presence of other comorbidity (neoplasm, diabetes mellitus, paresis, recent trauma, hematologic disease, etc.), visual, vestibular impairments or poor health status that would interfere with the clinical assessments during the study.

The study was approved by the institutional review board for human investigation. All patients provided signed informed consent for participation in the study.

The study consisted of a screening visit, a baseline visit-during which intraarticular injection of PRP into the ankle joints was done, and follow-up visits at 1, 3, and 6 months postinjection. Potential study participants returned for a baseline visit after a 1-week washout period for NSAIDs and analgesics.

For PRP preparation, specialized platelet concentrate separator containing acid citrate dextrose as anticoagulant and a specific separator gel that harvest platelets and plasma, preventing contamination of red blood cells and leukocytes were used. Approximately 7 mL of venous blood was drawn from each patient and was collected into a PLTenus PLUS Platelet Concentrate Separator (TCM Biotech International Corp., Taiwan). The collected blood was centrifuged at a speed of 500 to 1200 rpm for 8 minutes, then 3-mL leukocyte-poor PRP were harvested. The platelet concentration obtained is approximately 2.4 times greater than the baseline platelet concentration, which is considered to be moderately elevated. The moderately elevated platelet concentration seems to induce optimal biologic benefit, with lower platelet concentrations leading to suboptimal effects and higher platelet concentrations to inhibitory effects (22-25).

The injections were performed by the same experienced physician (S.F.S.), who took no part in the clinical assessment or in the data analysis. No analgesics, glucosamine or chondroitin, or NSAIDs for the ankle were permitted during the study. Acetaminophen (500 mg, maximum dose of 4 g/d) was the only rescue medication allowed for ankle pain. Acetaminophen was not permitted within 24 hours before any visit.

The clinical assessment was documented by a single investigator (S.Y.W.) for each patient prior to the injection and at 1, 3, and 6 months after the injection.

Outcome Measures

The primary outcome was the change from baseline in the VAS pain score (0-10 cm) at 6 months (Appendix) (26). The secondary outcome measures included the Ankle Osteoarthritis Scale (AOS) score, American Orthopedic Foot and Ankle Society (AOFAS) hindfoot-ankle score, the single-leg stance (SLS) test, use of analgesic medication and patient satisfaction (Appendix) (27-30).

Safety evaluations were monitored by recording the occurrence of systemic and local adverse events on a diary card during the study.

Statistical Analyses

Based on the G*Power 3.0 and the statistical method used for the study purpose, repeated measures 1-way analysis of variance (ANOVA), the required sample size was 36 participants (power = 0.85; alpha = 0.05; R^2 of covariate in medium level 0.09; effect size in medium level 0.25, number of groups = 2, number of measures = 4, correlation among repeated measures = 0.3, nonsphericity correction $\varepsilon = 1$). Assuming a 20% dropout rate, the number of participants was increased to 44.

All statistical procedures were conducted with SPSS software (version 20.0). Change of primary and secondary outcome measures among baseline, 1, 3, and 6-month follow-ups were assessed using repeated measures 1-way ANOVA and Bonferroni post hoc test. *p*values of <.05 were considered statistically significant.

Subgroup Analyses

We divided patients by radiographic severity and by disease duration. We compared the outcome scores at various time points to determine whether radiographic severity and disease duration would influence the treatment response. Between-subgroup differences were assessed using independent-samples *t* tests for satisfaction, independent samples 1-way analysis of covariance (baseline data as covariate) or Johnson-Neyman techniques for the other outcome measures. Within-subgroup differences were assessed using repeated-measures 1-way ANOVAs. *p*values of <.05 were considered statistically significant.

Results

Forty-eight potential participants were assessed for eligibility, of whom 4 (8.33%) were excluded, and 44 participants satisfied our inclusion and exclusion criteria and consented to take part in the study. Five patients (11.36%) withdrew during the study period, 1 (2.27%) that withdrew consent prior to receiving the injection, 3 (6.82%) that did not return for follow-up visits, and 1 (2.27%) that moved to another city. Thirty-nine patients (88.64%) completed the study. Demographic data and disease characteristics of the patients are presented in Table 1.

Primary and Secondary Outcomes

The mean VAS improved by 1.9, 2.4, and 2.3 from baseline at 1-, 3-, and 6-month follow-ups, respectively ($p < .001$ for each score compared with baseline; Table 2).

Significant reduction in AOS (including total scores, pain, and disability subscores) from baseline was noted at 1, 3, and 6 months postinjection ($p < .001$ for each score compared with baseline; Table 2). The mean AOFAS hindfoot-ankle score improved from 80.3 ± 8.9 points at

Table 1
Demographic characteristics of the participants

Characteristic	Ankle OA (N = 39)	Range
Age*	55.5 ± 8.8	36-69
Sex (F/M)†	22/17	
Weight (kg)*	67.7 ± 11.1	47-84.8
Height (cm)*	163.0 ± 9.0	150-182
Body mass index (kg/m^2)*	25.5 ± 3.9	19.5-34.6
Employment status (light/heavy labor)†	28/11	
Ankle injection side (left/right)†	16/23	
Kellgren-Lawrence grade, n (%)†		
Grades 1 and 2	28 (71.79%)	
Grades 3 and 4	11 (28.21%)	
Disease duration (years)†	2.6 ± 1.1	0.1-15
≤1 year	11 (28.21%)	
>1 year	28 (71.79%)	

Abbreviations: OA, osteoarthritis.
* The values are given as the mean ± standard deviation.
† The values are given as number of patients with the percentage in parentheses.

Table 2
The outcome measures before and after treatment

OA Ankle (N = 39)	Baseline	1 Month	3 Months	6 Months	*p* Value	Post Hoc Test
VAS[§]	4.1 ± 1.7	2.2 ± 1.9	1.7 ± 1.5	1.8 ± 1.6	<.001[‡]	AB[‡] AC[‡] AD[‡]
Total AOS[§]	4.3 ± 1.7	2.6 ± 2.0	2.1 ± 1.7	2.2 ± 1.7	<.001[‡]	AB[‡] AC[‡] AD[‡] BC[*]
Pain subscale[§]	4.1 ± 1.6	2.5 ± 1.9	1.9 ± 1.6	2.0 ± 1.5	<.001[‡]	AB[‡] AC[‡] AD[‡] BC[*]
Disability subscale[§]	4.6 ± 2.0	2.8 ± 2.3	2.2 ± 1.8	2.4 ± 2.1	<.001[‡]	AB[‡] AC[‡] AD[‡] BC[*]
AOFAS	80.3 ± 8.9	87.2 ± 10.3	91.6 ± 9.1	89.7 ± 10.0	<.001[‡]	AB[‡] AC[‡] AD[‡] BC[†]
SLS	27.5 ± 33.5	41.4 ± 35.8	43.7 ± 35.1	42.8 ± 34.3	<.001[‡]	AB[*] AC[†] AD[†]
Acetaminophen (tablets/wk)	15.1 ± 6.2	6.3 ± 2.5	5.7 ± 2.4	6.5 ± 2.6	<.001[‡]	AB[‡] AC[‡] AD[‡]
Satisfaction		70.9 ± 21.2	71.7 ± 20.1	71.7 ± 21.2	.946	

Abbreviations: VAS, visual analog scale for pain; AOS, Ankle Osteoarthritis Scale; AOFAS, American Orthopedic Foot and Ankle Society; SLS, single-leg stance.
The possible range for the AOS score was 0 to 10; the possible range for the AOFAS score was 0 to 100.
AB is the comparison before and 1 month after the PRP injections; AC is the comparison before and 3month after the PRP injections; and AD is the comparison before and 6 months after the PRP injections; BC is the comparison 1 month and 3 months after the PRP injections.
The values are given as mean ± standard deviation.
[*] $p < .05$.
[†] $p < .01$.
[‡] $p < .001$.
[§] Higher scores represent worse pain or function.

baseline to 87.2 ± 10.3, 91.6 ± 9.1, and 89.7 ± 10.0 points, respectively, at 1, 3, and 6 months ($p < .001$ for each score compared with baseline; Table 2). Significant improvements in AOS ($p < .05$) and AOFAS hindfoot-ankle ($p < .01$) scores from 1 to 3 months were noted also.

All patients demonstrated significant improvements on SLS tests from baseline at each follow-up visit ($p < .001$). Patients used much less analgesics during the study period ($p < .001$; Table 2).Patient satisfaction score (0-100) was rated as 70.9, 71.7, and 71.7 at 1, 3, and 6 months (Table 2). No patients reported dissatisfaction or aggravations of the ankle symptoms compared to preinjection condition throughout the study.

The injections were well tolerated and no serious adverse events were observed. Five patients experienced brief postinjection pain that resolved within 72 hours. The local adverse reaction rate was 12.8% per injection. No patient withdrew from the study because of an adverse event.

Results of Subgroup Analyses

We classified patients into the radiographic mild-moderate group (Kellgren-Lawrence graded 1 and 2, n = 28) and the radiographic-severe group (Kellgren-Lawrence graded 3 and 4, n = 11). Within-group comparison showed that the radiographic mild-moderate group showed significant improvements in VAS, AOS, AOFAS hindfoot-ankle scores, and SLS at each follow-up visit (Table 3). The radiographic-severe group showed significant improvements in AOS and AOFAS hindfoot-ankle scores only, with no significant improvements in VAS, SLS, and satisfaction. Between-group comparison showed significantly greater improvements on the SLS tests in the radiographic mild-moderate group at 1-month follow-up ($p = .043$). The radiographic mild-moderate group also reported significantly higher satisfaction at 3 and 6 months ($p = .027$ and $p = .005$; Table 3). Additional Johnson-Neyman analyses revealed the region of significant between-group differences in the VAS pain scores at 1 month (Table 3, Fig. 1). Among the patients with a baseline VAS of ≤4.2, the radiographic mild-moderate group tended to have a better VAS pain reduction; whereas among the patients with a baseline of VAS≥7.4, the radiographic-severe group tended to have a better VAS pain reduction (Table 3, Fig. 1).

Eleven patients (28.21%) had disease duration ≤1 year and 28 patients (71.79%) had disease duration >1 year. Within-group comparison showed significant improvements in VAS, AOS, AOFAS hindfoot-ankle scores, and SLS at each follow-up in both groups (Table 4). Between-group comparisons showed no differences in the outcomes at any follow-up time point. However, Johnson-Neyman analyses revealed the region of significant between-group differences in VAS pain score at

Table 3
Comparisons between the 2 different radiographic severity groups

	Radiographic Mild-Moderate (n = 28)	Radiographic Severe (n = 11)	*p* Value[*]
VAS baseline	4.1 ± 1.7	4.0 ± 1.6	
1 month	1.8 ± 1.6	3.1 ± 2.3	Baseline ≤4.2 or ≥7.4
3 months	1.4 ± 1.5	2.4 ± 1.4	.168
6 months	1.5 ± 1.5	2.8 ± 1.2	.161
p value[†]	<.001[‖]	.140	
AOS baseline	4.4 ± 1.7	4.1 ± 1.7	
1 month	2.3 ± 2.0	3.4 ± 2.0	.632
3 months	1.9 ± 1.8	2.6 ± 1.4	.547
6 months	1.9 ± 1.7	3.1 ± 1.4	.485
p value[†]	<.001[‖]	.003[§]	
AOS pain baseline	4.3 ± 1.7	3.6 ± 1.5	
1 month	2.2 ± 1.8	3.3 ± 2.1	.533
3 months	1.8 ± 1.7	2.3 ± 1.4	.655
6 months	1.7 ± 1.5	2.8 ± 1.3	.323
p value[†]	<.001[‖]	.004[§]	
AOS disability subscale			
Baseline	4.5 ± 1.9	4.6 ± 2.2	
1 month	2.5 ± 2.2	3.5 ± 2.4	.534
3 months	2.0 ± 1.9	2.8 ± 1.4	.336
6 months	2.1 ± 2.1	3.3 ± 1.7	.560
p value[†]	<.001[‖]	.013[‡]	
AOFAS baseline	81.3 ± 7.6	77.9 ± 11.4	
1 month	88.9 ± 8.5	83.1 ± 13.2	.121
3 months	93.2 ± 7.3	87.6 ± 11.8	.400
6 months	91.5 ± 8.9	85.4 ± 11.5	.359
p value[†]	<.001[‖]	.009[§]	
SLS baseline	29.4 ± 34.2	22.7 ± 32.8	
1 month	46.0 ± 35.0	29.6 ± 36.7	.043[‡]
3 months	47.2 ± 36.5	34.9 ± 31.0	.358
6 months	47.6 ± 35.2	30.6 ± 30.1	.174
p value[†]	.002[§]	.135	
Satisfaction 1 month	74.3 ± 19.9	62.3 ± 22.7	.111[¶]
3 months	76.1 ± 18.0	60.5 ± 21.7	.027[‡,¶]
6 months	77.4 ± 19.1	57.1 ± 20.1	.005[§,¶]
p value[†]	.665	.357	

Abbreviations: VAS, visual analog scale for pain; AOS, Ankle Osteoarthritis Scale; AOFAS, American Orthopedic Foot and Ankle Society; SLS, single-leg stance.
The values are given as the mean ± standard deviation.
[*] Between-group difference determined using independent samples 1-way ANCOVA (baseline data as covariate) or Johnson-Neyman technique.
[†] Within-group difference determined using repeated measures 1-way ANOVA.
[‡] $p < .05$.
[§] $p < .01$.
[‖] $p < .001$.
[¶] Independent samples *t* test

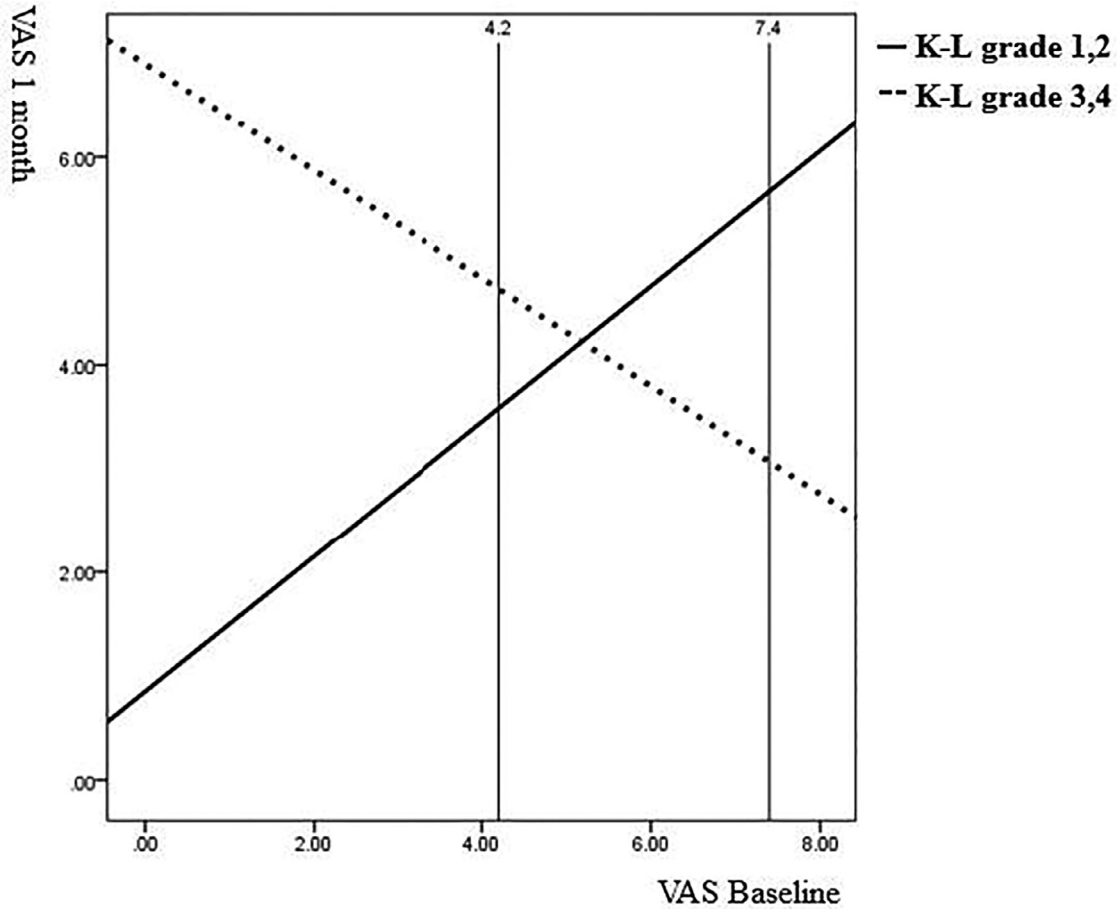

Fig. 1. Graph showing that, among the patients with a baseline VAS ≥7.4, the radiographic severe group had a significantly greater VAS pain reduction at 1 month than the radiographic mild-moderate group. Among the patients with a baseline VAS of ≤4.2, the radiographic mild-moderate group had a significantly greater VAS pain reduction at 1 month than the radiographic severe group. The numbers on both axes of the graph indicate the VAS pain score.

6 months (Table 4, Fig. 2). Among the patients with a baseline of VAS ≥4.2, the group with disease duration ≤1 year tended to have a better VAS pain reduction at 6-month follow-up than those with disease duration >1 year (Table 4, Fig. 2).

Discussion

To our knowledge, this is the first study to investigate the efficacy and safety of a single intra-articular injection of PRP for the treatment of ankle OA. The study showed that a single injection of PRP was well tolerated, provided pain reduction and functional improvement in patients with ankle OA. These effects could last for at least 6 months.

The primary outcome was the VAS pain reduction at 6 months. The mean VAS pain score reduced by 1.9 (46.3%), 2.4 (58.5%), and 2.3 (56.1%) at 1, 3, and 6 months, respectively. In clinical trials of chronic pain treatments, reduction in chronic pain intensity of at least 30% appeared to reflect at least moderate clinically important differences (31). It appeared that the magnitude of pain reductions reached clinical meaningful significance. Martini et al investigated the efficacy of single injection of PRP for patients with Kellgren-Lawrence grade 1 or 2 knee OA. The median VAS score improved from 64.2 mm at baseline to 42.8 mm at 6 months, corresponding to a median reduction of 33.3% from baseline (32). Interestingly, our study showed greater VAS pain reduction (56.1%) after 1 injection of PRP in patients with Kellgren-Lawrence grades 1-4 ankle OA at 6 months postinjection.

In our study, the maximal improvements in VAS, AOS, AOFAS, and SLS occurred at 3 months postinjection. The results were consistent with those of a recent pilot study of 20 patients by Fukawa et al that showed 3 PRP injections at 2-week interval were safe and could improve pain and function in patients with ankle OA for up to 24 weeks (4). Similar to our results, the maximal pain reduction also occurred at 12 weeks. Repetto et al evaluated 20 patients with ankle OA and they found significant improvements in pain and function after 4 weekly PRP injections at an average follow-up of 17.7 months (5). It is noteworthy that 39 patients in our study who received only 1 injection of PRP also demonstrated significant clinical benefits. Since OA is a chronic disease that often requires systemic or local therapies, economic concern is an evolving field worthy of consideration. The one injection regimen may possibly represent a cost-saving strategy. It may decrease patient time expenditure and have less adverse events than multiple injections. This remains an area important and interesting for further investigation.

In this study, the average VAS pain reduced from 4.1 at baseline to 1.8, and the total AOS reduced from 4.3 at baseline to 2.2 at 6 months. We previously published a pilot study using one injection of Botulinum toxin A (100-unit, Allergan) for patients with Kellgren-Lawrence grade 2 ankle OA. The results demonstrated a mean reduction of 2.2 in the VAS pain and a mean reduction of 2.3 in the total AOS score at 6 months after the injections (18). Similar effects were noted in patients receiving one injection of sodium hyaluronate plus rehabilitation exercise. Although similar improvements in pain and disability were

Table 4
Comparisons between the 2 different disease duration groups

	Disease Duration ≤1 Year (n = 11)	Disease Duration >1 Year (n = 28)	*p* Value*
VAS baseline	4.3 ± 1.6	3.9 ± 1.7	
1 month	2.2 ± 1.5	2.2 ± 2.1	.475
3 months	1.5 ± 0.9	1.8 ± 1.7	.125
6 months	1.2 ± 1.3	2.1 ± 1.6	VAS baseline ≥4.2
p value†	<.001§	<.001§	
AOS baseline	4.7 ± 1.6	4.1 ± 1.7	
1 month	2.6 ± 1.5	2.7 ± 2.2	.408
3 months	1.6 ± 1.1	2.3 ± 1.9	.833
6 months	2.2 ± 1.3	2.2 ± 1.8	.287
p value†	<.001§	<.001§	
AOS pain baseline	4.7 ± 1.6	3.8 ± 1.6	
1 month	2.4 ± 1.6	2.5 ± 2.1	.448
3 months	1.5 ± 1.1	2.1 ± 1.8	.765
6 months	1.9 ± 1.2	2.1 ± 1.7	.690
p value†	<.001§	<.001§	
AOS disability			
Baseline	4.9 ± 1.6	4.4 ± 2.1	
1 month	2.7 ± 1.6	2.8 ± 2.5	.738
3 months	1.7 ± 1.2	2.4 ± 2.0	.748
6 months	2.5 ± 2.1	2.4 ± 2.1	.345
p value†	<.001§	<.001§	
AOFAS baseline	78.2 ± 6.5	81.1 ± 9.5	
1 month	83.1 ± 8.2	88.7 ± 10.6	.666
3 months	91.7 ± 7.6	91.5 ± 9.7	.863
6 months	92.7 ± 8.2	88.6 ± 10.5	.425
p value†	<.001§	<.001§	
SLS baseline	28.5 ± 37.4	27.1 ± 32.6	
1 month	40.2 ± 36.1	41.8 ± 36.3	.613
3 months	50.8 ± 40.1	40.9 ± 33.3	.966
6 months	53.3 ± 40.4	38.7 ± 31.5	.753
p value†	<.001§	.016‡	
Satisfaction 1 month	72.3 ± 19.7	70.4 ± 22.0	.803‖
3 months	75.5 ± 13.9	70.2 ± 22.2	.469‖
6 months	73.6 ± 14.3	70.9 ± 23.6	.725‖
p value†	.881	.940	

Abbreviations: VAS, visual analog scale for pain; AOS, Ankle Osteoarthritis Scale; AOFAS, American Orthopedic Foot and Ankle Society; SLS, single-leg stance.
The values are given as mean ± standard deviation.
* Between-group difference determined using independent samples 1-way ANCOVA (baseline data as covariate) or Johnson-Neyman technique.
† Within-group difference determined using repeated measures one-way ANOVA.
‡ $p < .05$.
§ $p < .001$.
‖ Independent samples *t* test.

documented in these studies, direct comparisons were difficult because of different injection formulation and different radiographic severity.

The characteristics of the ideal candidate for PRP injection have yet to be defined. Kon et al showed superior efficacy of PRP in younger patients with earlier degrees of OA (33). Patel et al reported that patients with grade 1 knee OA had far better results than those with grade 2 (17). Previous researches regarding the use of PRP for ankle had considered only early-stage osteochondral lesions and ankle chondropathy (14,15). Different from previous studies, we recruited patients with Kellgren-Lawrence grades 1 to 4 ankle OA. We found that among the patients with a baseline VAS ≥7.4, the radiographic-severe group (Kellgren-Lawrence grades 3 and 4) had a better VAS pain reduction at 1 month postinjection; whereas among the patients with a baseline VAS ≤4.2, the radiographic mild-moderate group (Kellgren-Lawrence grades 1 and 2) had a better VAS pain reduction at 1 month. Another interesting findings were that, among patients with a baseline VAS of ≥4.2, those with disease duration ≤1 year had a significant better VAS pain reduction at 6 months than those with disease duration >1 year. Future studies with larger treatment group sizes should better elucidate the factors associated with a favorable patient response and thus help to identify patients who would benefit the most from PRP in the ankles.

To our knowledge, this is the first study that evaluates SLS after PRP injection in patients with ankle OA. SLS test is an objective clinical test of standing balance. Balance is a fundamental skill for transfer, walking and many activities of daily living. Pain associated with OA frequently leads to a reduced activity level and weakening of muscles with a secondary increase of instability and joint degeneration. Reduced muscle strength and deficits in lower limb proprioception associated with OA could compromise effective and timely motor responses in maintaining balance (34,35). In SLS test, only static, and not dynamic balance is challenged. Thus, SLS may not be adequate test for examining the dynamic balance requirements necessary for ambulation and independent mobility. Although the mechanism by which PRP results in improvement on SLS remained unknown, we thought pain reduction might be one of the major contributing factors. More research on the impact of PRP on balance may allow the mechanism to be elucidated and thus permit more effective management of patients with ankle OA.

In this study, all adverse events were mild and self-limiting. The absence of serious adverse events, noted in previous studies and in the present trial, suggests that PRP represents a safe treatment for patients with ankle OA.

There were several limitations. First, this was a single-center study and we recruited patients with ankle OA only. The result cannot be generalized to all the OA populations. Second, the sample size was small and the 6-month follow-up time was short. It is unclear how long the clinical benefits would have been maintained. Third, because of budget limit, we did not have a control group. Therefore, we were unable to determine what proportion of the improvement may have been due to a placebo effect. There is a strong placebo effect from joint injections, which may cause a nearly 30% pain reduction during the first few weeks (36). The placebo effect would mostly be seen in the early periods, thus the late findings of this study at 3 and 6 months may reflect reliable results for PRP injections. Despite our appreciation of the limitations of this investigation, we believe that the results of this study could be useful in the future development of prospective cohort studies and randomized controlled trials that focus on the use of PRP in patients with ankle OA. Further research including a sham control, corticosteroid or hyaluronate injection group is of great interest. Combined therapies with other treatment options, such as intraarticular steroid injections, or therapeutic exercise may help determine the best treatment plan for patients with ankle OA.

In conclusion, a single intraarticular injection of PRP is safe and effective for patients with ankle OA for 6 months. We recommend additional randomized controlled studies with longer follow-up to help confirm our results.

Author Contributions

SF Sun: study conception and design, drafting and revision of manuscript, obtaining of funding and final approval of the article.

CW Hsu: study conception and design, analysis and interpretation of data, revision of manuscript, and final approval of the article.

GC Lin: statistical expertise who performed the statistical analysis, analysis and interpretation of data, revision of manuscript, and final approval of the article.

HS Lin: statistical expertise who performed the statistical analysis, analysis and interpretation of data, drafting and revision of manuscript, and final approval of the article.

YJ Chou: study conception and design, provision of study participants, data collection and analysis, drafting and revision of manuscript, and final approval of the article.

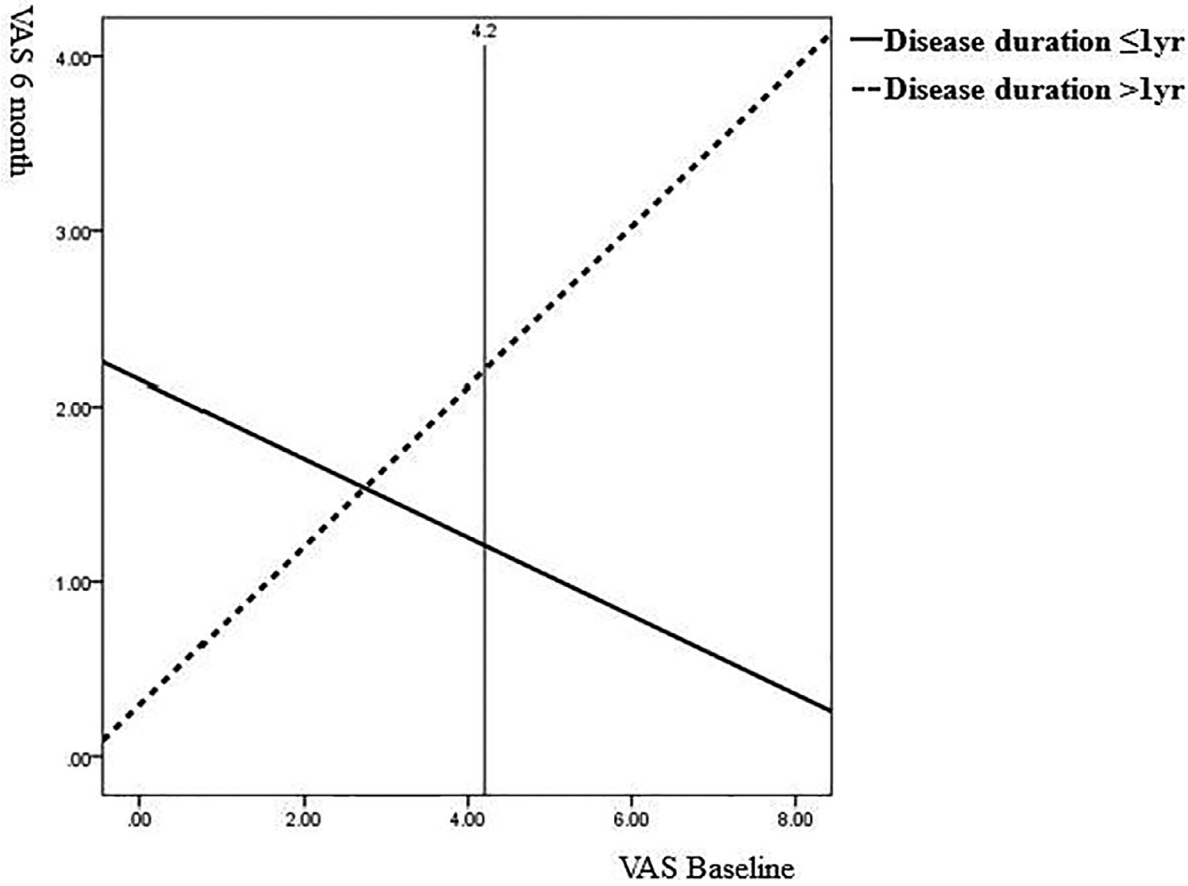

Fig. 2. Graph showing that, among the patients with a baseline VAS of ≥4.2, the group with disease duration ≤1 year had a significantly greater VAS pain reduction at 6 months than the group with disease duration >1 year. The numbers on both axes of the graph indicate the VAS pain score.

SY Wu: study conception and design, collection of data, revision of manuscript, and final approval of the article.

HY Huang: study conception and design, collection of data, revision of manuscript, and final approval of the article.

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Supplementary Materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1053/j.jfas.2020.12.003.

References

1. Thomas RH, Daniels TR. Ankle arthritis. J Bone Joint Surg Am 2003;85:923–936.
2. Saltzman CL, Salamon ML, Blanchard GM, Huff T, Hayes A, Buckwalter JA, Amendola A. Epidemiology of ankle arthritis: report of a consecutive series of 639 patients from a tertiary orthopaedic center. Iowa Orthop J 2005;25:44–46.
3. Vannabouathong C, Del Fabbro G, Sales B, Smith C, Li CS, Yardley D, Bhandari M, Petrisor BA. Intra-articular injections in the treatment of symptoms from ankle arthritis: a systematic review. Foot Ankle Int 2018;39:1141–1150.
4. Fukawa T, Yamaguchi S, Akatsu Y, Yamamoto Y, Akagi R, Sasho T. Safety and efficacy of intra-articular injection of platelet-rich plasma in patients with ankle osteoarthritis. Foot Ankle Int 2017;38:596–604.
5. Repetto I, Biti B, Cerruti P, Trentini R, Felli L. Conservative treatment of ankle osteoarthritis: can platelet-rich plasma effectively postpone surgery? J Foot Ankle Surg 2017;56:362–365.
6. Cugat R, Cusco X, Seijas R, Alvarez P, Steinbacher G, Ares O, Wang-Saegusa A, García-Balletbó M. Biologic enhancement of cartilage repair: the role of platelet-rich plasma and other commercially available growth factors. Arthroscopy 2015;31:777–783.
7. Kabiri A, Esfandiari E, Esmaeili A, Hashemibeni B, Pourazar A, Mardani M. Platelet-rich plasma application in chondrogenesis. Adv Biomed Res 2014;3:138.
8. Sundman EA, Cole BJ, Karas V, Della Valle C, Tetreault MW, Mohammed HO, Fortier LA. The anti-inflammatory and matrix restorative mechanisms of platelet-rich plasma in osteoarthritis. Am J Sports Med 2014;42:35–41.
9. van Buul GM, Koevoet WL, Kops N, Bos PK, Verhaar JA, Weinans H, Bernsen MR, van Osch GJ. Platelet-rich plasma releasate inhibits inflammatory processes in osteoarthritic chondrocytes. Am J Sports Med 2011;39:2362–2370.
10. Khoshbin A, Leroux T, Wasserstein D, Marks P, Theodoropoulos J, Ogilvie-Harris D, Gandhi R, Takhar K, Lum G, Chahal J. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: a systematic review with quantitative synthesis. Arthroscopy 2013;29:2037–2048.
11. Chang KV, Hung CY, Aliwarga F, Wang TG, Han DS, Chen WS. Comparative effectiveness of platelet-rich plasma injections for treating knee joint cartilage degenerative pathology: a systematic review and meta-analysis. Arch Phys Med Rehabil 2014;95:562–575.
12. Laudy AB, Bakker EW, Rekers M, Moen MH. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. Br J Sports Med 2015;49:657–672.
13. Meheux CJ, McCulloch PC, Lintner DM, Varner KE, Harris JD. Efficacy of intra-articular platelet-rich plasma injections in knee osteoarthritis: a systematic review. Arthroscopy 2016;32:495–505.
14. Mei-Dan O, Carmont MR, Laver L, Mann G, Maffulli N, Nyska M. Platelet-rich plasma or hyaluronate in the management of osteochondral lesions of the talus. Am J Sports Med 2012;40:534–541.
15. Angthong C, Khadsongkram A, Angthong W. Outcomes and quality of life after platelet-rich plasma therapy in patients with recalcitrant hindfoot and ankle diseases: a preliminary report of 12 patients. J Foot Ankle Surg 2013;52:475–480.
16. Gormeli G, Gormeli CA, Ataoglu B, Colak C, Aslanturk O, Ertem K. Multiple PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc 2017;25:958–965.

17. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med 2013;41:356–364.
18. Martini LI, Via AG, Fossati C, Randelli F, Randelli P, Cucchi D. Single platelet-rich plasma injection for early stage of osteoarthritis of the knee. Joints 2017;5:2–6.
19. Buendia-Lopez D, Medina-Quiros M, Fernandez-Villacanas Marin MA. Clinical and radiographic comparison of a single LP-PRP injection, a single hyaluronic acid injection and daily NSAID administration with a 52-week follow-up: a randomized controlled trial. J Orthop Traumatol 2018;19:3.
20. Joshi Jubert N, Rodriguez L, Reverte-Vinaixa MM, Navarro A. Platelet-rich plasma injections for advanced knee osteoarthritis: a prospective, randomized, double-blinded clinical trial. Orthop J Sports Med 2017;5:2325967116689386.
21. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
22. Weibrich G, Hansen T, Kleis W, Buch R, Hitzler WE. Effect of platelet concentration in platelet-rich plasma on peri-implant bone regeneration. Bone 2004;34:665–671.
23. Graziani F, Ivanovski S, Cei S, Ducci F, Tonetti M, Gabriele M. The in vitro effect of different PRP concentrations on osteoblasts and fibroblasts. Clin Oral Implants Res 2006;17:212–219.
24. Sampson S, Gerhardt M, Mandelbaum B. Platelet rich plasma injection grafts for musculoskeletal injuries: a review. Curr Rev Musculoskelet Med 2008;1:165–174.
25. Smyth NA, Murawski CD, Fortier LA, Cole BJ, Kennedy JG. Platelet-rich plasma in the pathologic processes of cartilage: review of basic science evidence. Arthroscopy 2013;29:1399–1409.
26. Huskisson EC. Measurement of pain. Lancet 1974;2:1127–1131.
27. Domsic RT, Saltzman CL. Ankle osteoarthritis scale. Foot Ankle Int 1998;19:466–471.
28. Kitaoka HB, Alexander IJ, Adelaar RS, Nunley JA, Myerson MS, Sanders M. Clinical rating systems for the ankle-hindfoot, midfoot, hallux, and lesser toes. Foot Ankle Int 1994;15:349–353.
29. Ibrahim T, Beiri A, Azzabi M, Best AJ, Taylor GJ, Menon DK. Reliability and validity of the subjective component of the American Orthopaedic Foot and Ankle Society clinical rating scales. J Foot Ankle Surg 2007;46:65–74.
30. Berg KO, Wood-Dauphinee SL, Williams JI, Maki B. Measuring balance in the elderly: validation of an instrument. Can J Public Health 1992;83(suppl 2):S7–11.
31. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, von Stein T, White RE, Witter J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–121.
32. Sun SF, Hsu CW, Lin HS, Chou YJ, Chen JY, Wang JL. Efficacy of intraarticular botulinum toxin A and intraarticular hyaluronate plus rehabilitation exercise in patients with unilateral ankle osteoarthritis: a randomized controlled trial. J Foot Ankle Res 2014;7:9.
33. Kon E, Buda R, Filardo G, Di Martino A, Timoncini A, Cenacchi A, Fornasari PM, Giannini S, Marcacci M. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. Knee Surg Sports Traumatol Arthrosc 2010;18:472–479.
34. Hassan BS, Mockett S, Doherty M. Static postural sway, proprioception, and maximal voluntary quadriceps contraction in patients with knee osteoarthritis and normal control subjects. Ann Rheum Dis 2001;60:612–618.
35. Fisher NM, Pendergast DR. Reduced muscle function in patients with osteoarthritis. Scand J Rehabil Med 1997;29:213–221.
36. Kirwan J. Is there a place for intra-articular hyaluronate in osteoarthritis of the knee? Knee 2001;8:93–101.