Allogeneic Platelet-Rich Plasma Versus Corticosteroid Injection for the Treatment of Rotator Cuff Disease

A Randomized Controlled Trial

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Background: The use of platelet-rich plasma (PRP) for the treatment of rotator cuff disease is still controversial. The purpose of the present study was to investigate the safety and efficacy of a fully characterized allogeneic pure PRP injection into the subacromial space of patients with rotator cuff disease in comparison with corticosteroid injection.

Methods: A 2-group, parallel, assessor-blinded, randomized controlled trial was conducted. A total of 60 patients with clinically and structurally diagnosed rotator cuff disease were randomly assigned to receive a subacromial injection of either 4 mL of allogeneic pure PRP or a 4-mL mixture of 1 mL of 40-mg/mL triamcinolone acetonide and 3 mL of 2% lidocaine under ultrasonographic guidance. The primary outcomes were safety and the Constant score at 1 month. The secondary outcomes were pain, range of motion, muscle strength, functional scores, and overall satisfaction and function.

Results: There were no treatment-related adverse events. The Constant score at 1 month did not significantly differ between the PRP and corticosteroid groups. At 6 months, the DASH (Disabilities of the Arm, Shoulder and Hand) score, overall function, and external rotation were significantly better in the PRP group than in the corticosteroid group, and the other clinical outcomes did not show significant differences. All pain measurements, the strength of the supraspinatus and infraspinatus, and 5 functional scores also improved slowly and steadily after injection, becoming significantly better at 6 months compared with those before the injection, whereas those in the corticosteroid group responded promptly but did not further improve.

Conclusions: Allogeneic PRP injections for the treatment of rotator cuff disease are safe but are not definitely superior to corticosteroid injections with respect to pain relief and functional improvement during 6 months. The DASH score, overall function, and external rotation were significantly better in the PRP group than in the steroid group at 6 months. Generally, PRP slowly but steadily reduced pain and improved function of the shoulder until 6 months, whereas corticosteroid did not.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Shoulder pain is very common, with 15 new episodes per 1,000 patients seen in primary care[1]. The prevalence increases over age, with a lifetime prevalence of up to 70%, and peaks in age groups with the highest productivity (40 to 59 years), resulting in a heavy socioeconomic burden[2,3]. Rotator cuff disease is reported to be the most common diagnosis, accounting for up to 70% of shoulder pain[4,5]. Rotator cuff disease includes a spectrum of abnormalities, including

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A **data-sharing statement** is provided with the online version of the article (http://links.lww.com/JBJS/G149).

rotator cuff tendinopathy (or impingement syndrome of the shoulder), partial and full-thickness rotator cuff tears, and cuff tear arthropathy[6]. Whereas there has been considerable controversy among physicians with respect to the optimum treatment of rotator cuff disease, initial treatments would be conservative ones (e.g. exercise, physiotherapy, and anti-inflammatory medicine), even for most patients with a full-thickness tear[7,8]. Among these options, corticosteroid injection into the subacromial space is one of the most preferred treatments[9]. However, recent evidence has shown that it provides only short-term pain relief without modifying the natural course of the disease and could even lead to worsening in the long term[10].

Platelet-rich plasma (PRP) has been a popular alternative for the treatment of various injuries and diseases, including rotator cuff disease, despite the lack of understanding of the exact mechanism[11,12]. This lack of understanding is primarily due to the huge variety of autologous PRPs that have been used in various studies in which an absence of standardization or characterization of the PRP preparations has resulted in different concentrations not only of platelets but also of white blood cells (WBCs), red blood cells (RBCs), fibrinogen, and bioactive materials, including growth factors. Meanwhile, for certain patients with hematological diseases, patients receiving anti-platelet or nonsteroidal anti-inflammatory medications, and older patients with multiple comorbidities, autologous PRP is not an optimum solution[13]. Given these factors, allogeneic PRP prepared with controlled processes and characterized with appropriate information would eliminate problems related to the standardization and characterization of autologous PRP that interfere with the evaluation of its clinical efficacy. Therefore, we conducted a first-in-class clinical trial to assess the safety and efficacy of subacromial injections of a fully characterized allogeneic PRP for patients with rotator cuff disease. Our hypothesis was that allogeneic PRP injections would be safe and as effective as corticosteroid injections in patients with rotator cuff disease.

Materials and Methods

Study Design and Participants

This randomized controlled trial was approved by the institutional review board of our institute and was registered on clinicaltrials.gov (NCT02019537). All participants provided written informed consent. Participants were eligible for inclusion if they were ≥18 years of age and had had unilateral shoulder pain for at least 3 months. Participants had to present with either a Neer or Hawkins impingement sign. In addition, participants were required to have either a painful arc or a positive result on the Jobe test[14,15]. Exclusion criteria included previous subacromial injections within the past 3 months, a history of shoulder trauma, a full-thickness rotator cuff tear as demonstrated with magnetic resonance imaging (MRI) or ultrasonography, and limitation of both active and passive movement of the glenohumeral joint of 25% in at least 2 directions as compared with the contralateral shoulder or with normal values (see Appendix).

Randomization

Enrolled participants were randomly allocated with use of a randomization sequence created with SAS 9.1 statistical software (SAS Institute) on a 1:1 ratio, with block sizes of 4 and 6, to receive either allogeneic PRP (PRP group) or corticosteroid injection (steroid group). The outcome assessor and participants were blinded to the group assignment.

Allogeneic PRP Preparation and Ultrasonography-Guided Injection

Allogeneic PRPs were obtained with use of an automated plateletpheresis system with a leukoreduction set (COBE Spectra LRS Turbo; Caridian BCT) from healthy donors without rotator cuff disease (n = 3), and were characterized as previously described (see Appendix)[13]. For the assessment of the safety of the allogeneic PRP, the venereal disease research laboratory test as well as tests for hepatitis-B virus, hepatitis-C virus, and human immunodeficiency virus were performed and confirmed before application[13]. After activation with calcium gluconate, PRPs were mixed and frozen until use. The mean platelet concentration of the prepared PRP (and standard deviation [SD]) was 988.67 ± 60.10 platelets/mL. The concentrations of 7 growth factors were comparable with those in previous studies that have investigated effects of PRPs on tenocytes from the rotator cuff tendon (Table I)[13,16,17].

Either 4 mL of allogeneic PRP or a 4-mL mixture of 1 mL of 40 mg/mL triamcinolone acetonide and 3 mL of 2% lidocaine was injected under ultrasonographic guidance as previously described (see Appendix)[13,18]. Shoulder and scapular stretching exercises were encouraged 2 times per day for 20 minutes per session after injection (see Appendix). The physician who performed the injections was not involved with outcome assessments of this study.

Outcome Measures

Each participant completed a questionnaire consisting of standardized outcome assessments at baseline, 1 week after injection, and 1, 3, and 6 months after injection. The primary outcomes were safety and the Constant score at 1 month. Safety was assessed on the basis of general symptoms or signs associated with infection and immune response, such as rash, pruritus, fever, chills, urticaria, or dyspnea. Injection sites were examined to identify erythema, swelling, or abnormal discharge after injection and at each visit. Adverse events were categorized with use of the National Cancer Institute Common Terminology Criteria for Adverse Events scale, version 3.0 (CTCAE v3.0). The Constant score is a shoulder-specific outcome measure that is commonly used for the evaluation of treatments for rotator cuff disease[19,20]. The secondary outcomes included pain, range of motion, muscle strength, shoulder function scores (including the Shoulder Pain and Disability Index [SPADI], American Shoulder and Elbow Surgeons [ASES], University of California Los Angeles [UCLA], Simple Shoulder Test [SST], and Disabilities of the Arm, Shoulder and Hand [DASH] questionnaire scores), and overall satisfaction and function (see Appendix, Method 5). (Safety and the secondary outcome measures were not originally registered in the public domain.)

TABLE I Characterization of PRP Used in Present Study: Concentration, Activation, and Method of Application*

Counts of platelets, RBCs, and WBCs, and concentration of fibrinogen	
Platelet count *(x10⁶/μL)*	988.67 ± 60.10
RBC count *(x10⁶/μL)*	0.23 ± 0.04
WBC count *(x10⁶/μL)*	0.01 ± 0.01
Fibrinogen concentration *(mg/dL)*	140.83 ± 0.58
Activation	
Activation status†	3.77% ± 1.76%
Status	Supernatant
Method	Calcium alone
Method of application	
State	Liquid
Volume *(mL)*	4
Number of applications	1
Interval of applications *(day)*	0
Growth factor concentrations	
EGF *(ng/mL)*	2.33 ± 1.10
TGF-β1 *(ng/mL)*	46.65 ± 10.57
VEGF *(ng/mL)*	0.95 ± 0.41
CTGF *(ng/mL)*	52.02 ± 22.43
bFGF *(pg/mL)*	4.35 ± 1.09
PDGF-AB *(ng/mL)*	63.85 ± 6.76
IGF-1 *(ng/mL)*	143.20 ± 38.68

*Data are presented as the mean and the standard deviation unless otherwise specified. RBC = red blood cell, WBC = white blood cell, PRP = platelet-rich plasma, EGF = epidermal growth factor, TGF-β1 = transforming growth factor beta 1, VEGF = vascular endothelial growth factor, CTGF = connective tissue growth factor, bFGF = basic fibroblast growth factor, PDGF-AB = platelet-derived growth factor AB, and IGF-1 = insulin-like growth factor 1. †Activation status was measured with use of flow cytometry with CD61 and CD62P, and the results in each patient were expressed as the percentage of CD62P-positive counts relative to CD61-positive counts.

Statistical Analysis

For the determination of the sample size, an a priori power analysis was performed to provide a statistical power of 80% at a 2-sided significance level of 0.05. A sample size of 30 participants per group was determined to be sufficient in order to detect a 10-point difference in the Constant score between the groups at 1 month after injection based on previous data[21], assuming an SD of 12 and a 20% probability of dropout.

Data were expressed as the mean and the SD or as the median and interquartile range (IQR) or confidence interval (CI) for continuous variables and as frequencies and proportions for categorical variables. The Kolmogorov-Smirnov test was conducted to examine the normality assumption for all scale variables. For group comparisons, the 2-sample t test, chi-square test, or Fisher exact test were used. To determine changes from baseline within or between groups in all variables, a generalized linear mixed-effects model (GLMM) for repeated measurements was performed to account for the correlation from the same subject with adjustment for the baseline value. GLMM uses all available observed data and provides valid results in the presence of missing data under the assumption that missing data are missing at random[22]. Additionally, a complete-case analysis was performed for the sensitivity test. No adjustments were made for multiple comparisons to control the type-I error rate.

All statistical analyses were performed with use of SAS (version 9.4; SAS Institute) and R (version 3.5.1; R Foundation for Statistical Computing). A 2-sided significance level of 0.05 was used for all tests.

Results

Baseline Characteristics of Participants

Between February 2014 and July 2016, 424 participants were screened for eligibility, and 60 were randomized and received ultrasonography-guided subacromial injections of allogeneic PRP or corticosteroid (Fig. 1). There were no significant differences between the 2 groups in terms of baseline characteristics (Table II). Forty-nine (82%) of the 60 participants completed 6 months of follow-up, including 23 (77%) in the PRP group and 26 (87%) in the steroid group.

Safety

Adverse events occurred in 2 participants (7%) in the PRP group and 1 patient (3%) in the steroid group (see Appendix, Table S1). No local or general adverse events related to the allogeneic PRP or steroid injection were observed.

Constant Score

The Constant score was not significantly different between the 2 groups at any time point after the injection (Fig. 2-A) (see Appendix, Table S2-A). In the PRP group, the Constant score gradually improved over time and became significantly higher than the baseline at 6 months, increasing from 65.5 to 74.4 (mean increase, 8.8; 95% CI, 3.3 to 14.3). In the steroid group, the score increased immediately after injection, reached a peak at 1 month, and then deteriorated toward baseline at 6 months, with an overall increase from 64.7 to 68.5 (mean increase, 3.8; 95% CI, −1.4 to 9.1).

Pain

All pain measurements decreased soon after injection (Figs. 2-B through 2-F) (see Appendix S2-A). Generally, all pain measurements slowly but steadily decreased until 6 months in the PRP group whereas those in the steroid group quickly decreased until 1 month and then tended to increase after that until 6 months. However, there were no significant differences between the groups in any of the pain measurements at 6 months. The minimum clinically important difference (MCID) for the visual analog scale (VAS) pain score in patients treated for rotator cuff disease has been reported to be 1.4[23]. At 6 months, the mean pain score in the PRP group decreased by more than the MCID, from 3.7 to 1.8 (mean decrease, −1.8; 95% CI, −2.7 to −0.9) whereas

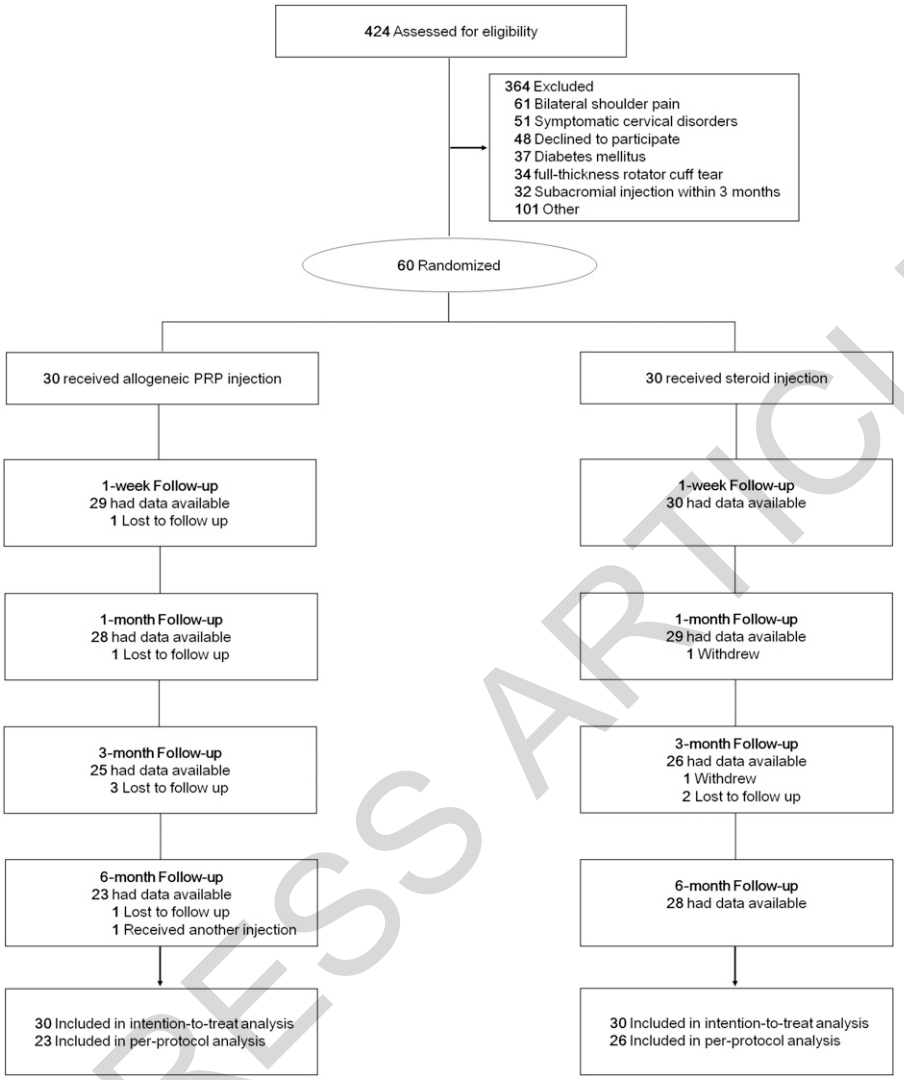

Fig. 1

CONSORT (Consolidated Standards for Reporting Trials) diagram of patients with rotator cuff disease.

that in the steroid group decreased by less than the MCID, from 3.6 to 2.5 (mean decrease, −1.1; 95% CI, −2.0 to −0.3).

Range of Motion

There were no significant differences between the 2 groups in terms of active forward flexion, abduction, or internal rotation at any time point after the injections. However, external rotation with the arm at the side demonstrated significantly greater improvement in the PRP group than in the steroid group (mean difference, 8.0°; 95% CI, 0.7° to 15.2°) (Figs. 3-A through 3-D) (see Appendix Table S2-B).

Strength

The strengths of the supraspinatus, infraspinatus, and subscapularis muscles were not significantly different between the 2 groups at any time point after injection (Figs. 3-E, 3-F, and 3-G) (see Appendix Table S2-C). The strengths of the supraspinatus and infraspinatus in the PRP group became significantly greater at 3 months compared with those before injection, but those in the steroid group showed significant increases at 1 month and then decreased at 3 months. The strength of the subscapularis demonstrated a nonsignificant increase after injection in both groups, except for at 1 month in the steroid group.

Additional Functional Scores

There were no significant differences between the groups in terms of any of the functional scores at 6 months. In the PRP group, the SPADI, ASES, UCLA, SST, and DASH scores improved gradually over time, and each score improved by more than the MCID at 6 months (Figs. 4-A through 4-E) (see Appendix Table S2-D)[24]. The DASH score in the PRP group improved significantly more at 6 months compared with before the injection, from 26.0 to 14.3 (mean decrease, −12.1; 95% CI, −18.8 to −5.4), whereas that in the steroid group did not, decreasing from 23.8 to 20.3 (mean

TABLE II Baseline Characteristics of the Participants*

	Allogeneic PRP (N = 30)	Corticosteroid (N = 30)	P Value
Age *(yr)*	55.3 ± 10.3	52.5 ± 11.2	0.312
Sex *(no. of patients)*			0.584
Male	11 (36.7%)	9 (30.0%)	
Female	19 (63.3%)	21 (70.0%)	
Dominance *(no. of patients)*			0.301
Yes	14 (46.7%)	18 (60.0%)	
No	16 (53.3%)	12 (40.0%)	
Duration of symptoms *(mo)*	11.6 ± 11.4	13.1 ± 15.6	0.655
Previous treatment history† *(no. of patients)*			
Surgery	0 (0%)	0 (0%)	
Pharmaceutical	14 (46.7%)	14 (46.7%)	1.000
Injection	16 (53.3%)	10 (33.3%)	0.118
Physiotherapy	11 (36.7%)	12 (40.0%)	0.791
Acupuncture	11 (36.7%)	6 (20.0%)	0.152
Neer sign *(no. of patients)*			0.766
Positive	22 (73.3%)	23 (76.7%)	
Negative	8 (26.7%)	7 (23.3%)	
Hawkins sign *(no. of patients)*			0.301
Positive	29 (96.7%)	27 (90.0%)	
Negative	1 (3.3%)	3 (10.0%)	
Painful arc sign *(no. of patients)*			1.000
Positive	24 (80.0%)	24 (80.0%)	
Negative	6 (20.0%)	6 (20.0%)	
Jobe test *(no. of patients)*			0.488
Positive	26 (86.7%)	24 (80.0%)	
Negative	4 (13.3%)	6 (20.0%)	
VAS pain score			
At rest	2.3 ± 0.3	2.2 ± 0.3	0.946
On motion	4.1 ± 0.4	4.1 ± 0.3	0.984
At night	4.6 ± 0.5	4.5 ± 0.4	0.804
Mean pain	3.7 ± 0.3	3.6 ± 0.3	0.883
At worst	7.9 ± 0.3	7.0 ± 0.3	0.066
Function score *(points)*			
Constant	65.5 ± 2.1	64.7 ± 1.8	0.790
SPADI	28.5 ± 2.8	33.8 ± 2.0	0.871
ASES	64.7 ± 3.0	64.9 ± 2.0	0.943
UCLA	19.5 ± 0.6	20.8 ± 0.7	0.150
SST	7.5 ± 0.5	7.2 ± 0.4	0.655
DASH	26.0 ± 2.3	23.8 ± 1.8	0.455
Imaging for enrollment *(no. of patients)*			1.000
Ultrasound	21 (70.0%)	21 (70.0%)	
MRI	9 (30.0%)	9 (30.0%)	
Finding with ultrasound or MRI *(no. of patients)*			0.765
Intact	4 (13.3%)	4 (13.3%)	
Fraying or tendinopathy	16 (53.3%)	19 (63.3%)	
Partial-thickness tear	10 (33.3%)	7 (23.3%)	
Full-thickness tear	0 (0%)	0 (0%)	

*Values are expressed as the mean and the standard deviation unless otherwise specified. VAS = visual analog scale, , SPADI = Shoulder Pain and Disability Index, ASES = American Shoulder and Elbow Surgeons, UCLA = University of California Los Angeles, SST = Simple Shoulder Test, and DASH = Disabilities of the Arm, Shoulder and Hand. †Each patient was asked whether they received medication, shoulder injection, physical therapy, or acupuncture during the last 3 months (yes or no).

decrease, −3.5; 95% CI, −9.9 to −2.9). In the steroid group, the 5 scores improved more rapidly immediately after the injection, reaching peak improvement at 1 month, and then worsened thereafter. Only the UCLA score improved by more than the MCID at 6 months in the steroid group.

Overall Satisfaction and Function

Willingness to undergo the injection again, willingness to recommend the injection to others, and the ability to work at the same level as they had previously were not significantly different between the 2 groups at any time point after the injection (see Appendix Table S2-E).

Overall function in the PRP group significantly increased at 6 months compared with that before injection, from 47.7% to 70.0% (mean increase, 22.5%; 95% CI, 11.2% to 33.8%), whereas it did not do so in the steroid group, increasing from 53.3% to 59.3% (mean increase, 6.0%; 95% CI, −4.7% to 16.7%) (Fig. 4-F) (see Appendix Table S2-E). There was a significant difference in overall function between the 2 groups at 6 months (mean difference, 17.0%; 95% CI, 2.7% to 31.4%). In the steroid group, overall satisfaction was significantly higher at 1 week as compared with before the injection but no difference was found at 1, 3, and 6 months (Fig. 4-G).

Discussion

Allogeneic PRP did not cause any apparent adverse events. There was no significant difference between the PRP and steroid groups in terms of the Constant score during or up to 6 months. However, the PRP group had significantly better improvements in the DASH score, overall function, and external rotation than the steroid group at 6 months. Furthermore, all pain measurements, the strength of the supraspinatus and infraspinatus, and the other 5 functional scores also improved slowly and steadily after injection in the PRP group, becoming significantly better at 6 months as compared with those before the injection, whereas those in the steroid group improved promptly but soon deteriorated. These results are consistent with those of recent studies on the short-term efficacy of corticosteroids for tendinopathy as well as a study on the potentially long-term efficacy of allogeneic PRP[9,13,25]. Taking those studies into account, together with concerns about harmful effects of corticosteroids and the positive effects of PRP on tenocytes[26,27], allogeneic PRP appears to be a viable option for patients with rotator cuff disease.

Recent experimental evidence points to the detrimental effects of corticosteroids on tendons, including reduced tenocyte viability, proliferation, and collagen synthesis, non-tenogenic

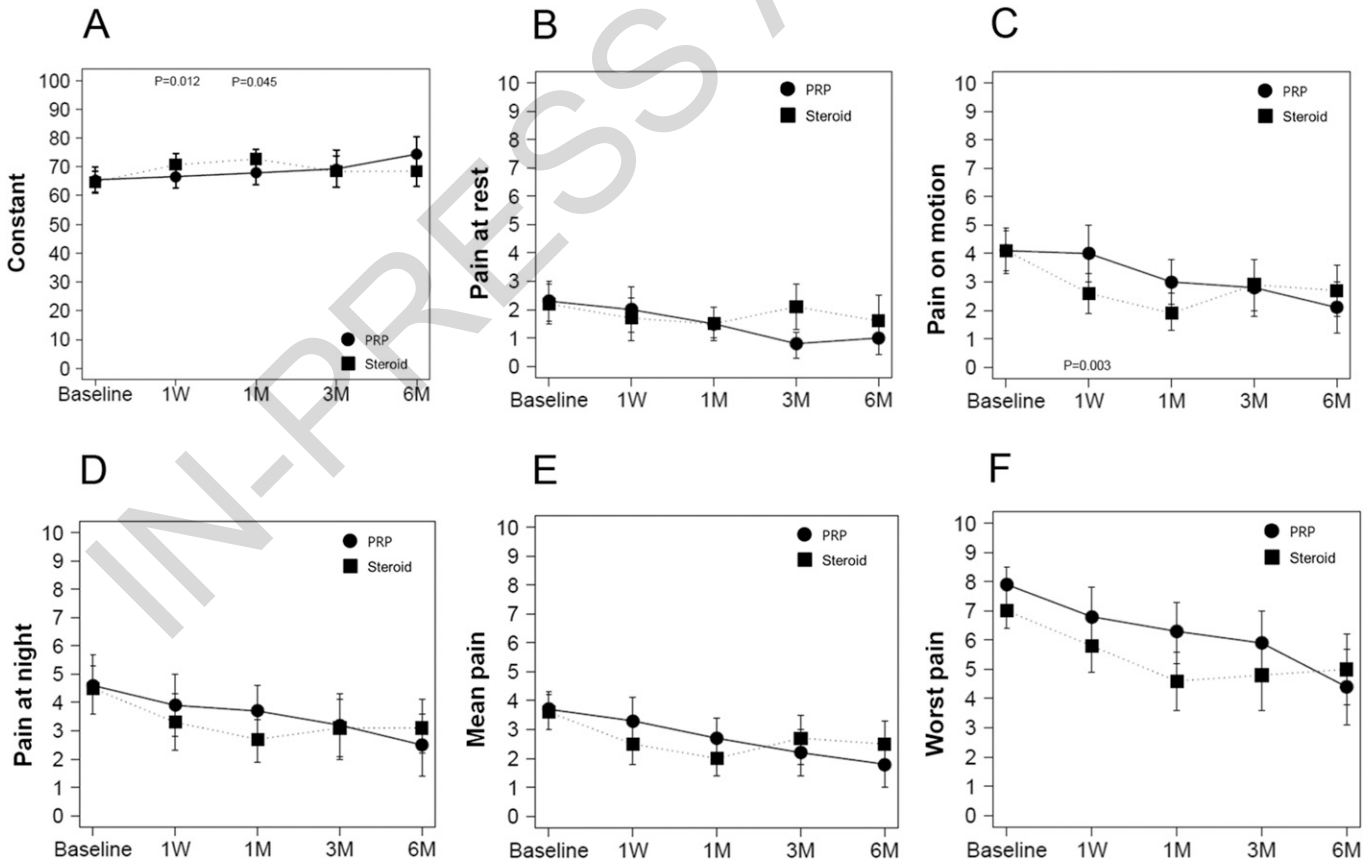

Fig. 2

Figs. 2-A through 2-F Line graphs showing changes in the Constant score (**Fig. 2-A**) and VAS scores for pain (**Figs. 2-B through 2-F**) after PRP and steroid injection. The values are shown as the mean and the standard deviation. W = week, and M = month(s).

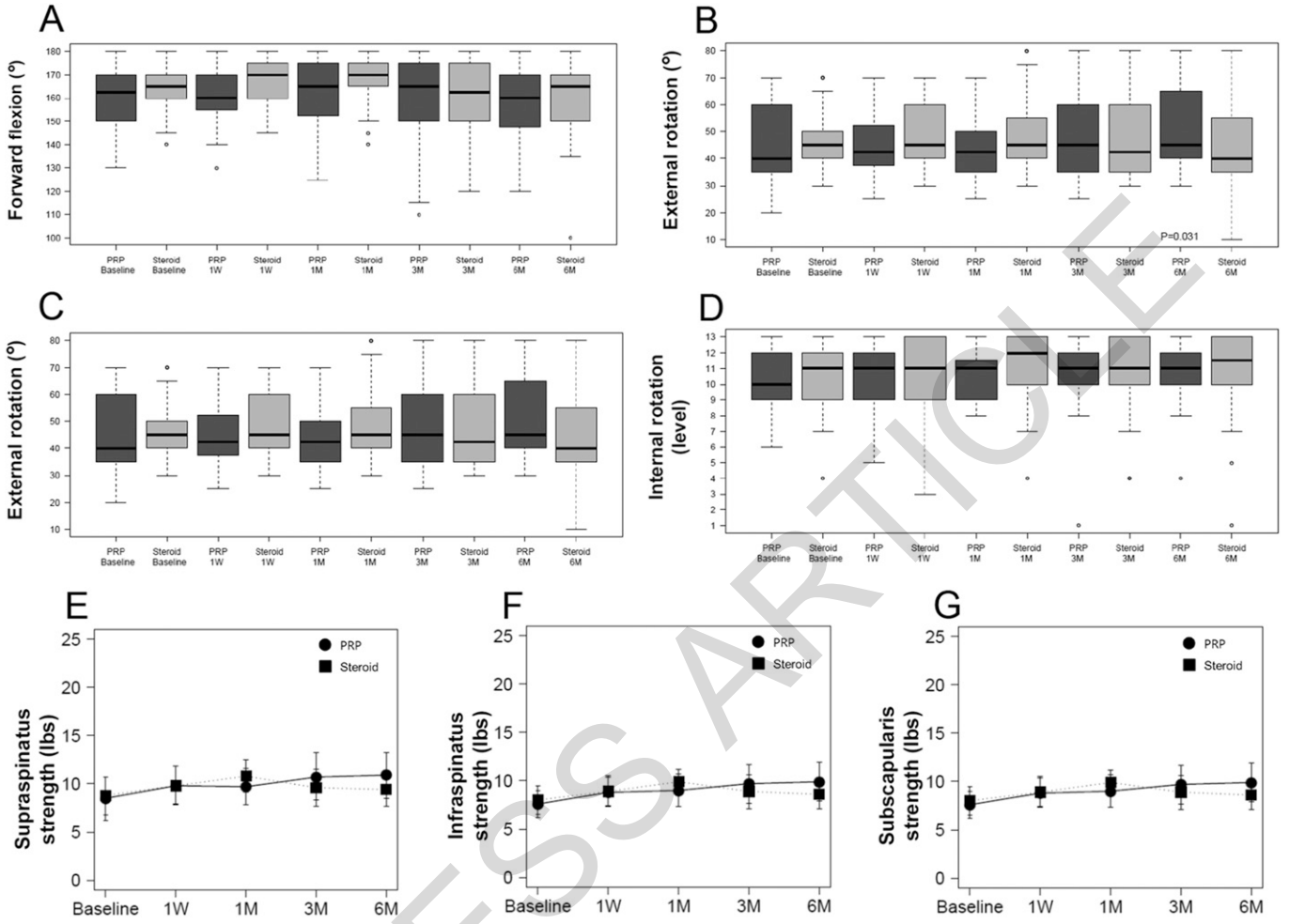

Fig. 3

Figs. 3-A through 3-G Box plots showing changes in range of motion (**Figs. 3-A through 3-D**) and line graphs showing the strength of the rotator cuff muscles (**Figs. 3-E, 3-F, and 3-G**) after PRP and steroid injection. 2.2 lb = 1 kg. The box plots show the median (horizontal lines), minimum and maximum values (whiskers), and outliers (circles). The line graphs show the mean and the standard deviation. W = week, and M = month(s).

differentiation and depletion of tendon stem cells, and disorganization and necrosis of collagen fibers in vivo[28,29]. These findings support those of clinical studies showing that corticosteroids have only short-term benefits[30-32]; alert physicians against the indiscriminate, repeated use of corticosteroids, especially in younger patients with "overuse" types of tendinopathy; and point to the need to seek alternate therapies[33]. As an alternate treatment option, PRP has been extensively investigated in experimental and clinical studies[9,34]. However, the results have been inconclusive, and high-quality randomized controlled trials comparing the efficacy of PRP and corticosteroids are very limited and controversial[11,34,35]. The controversies between studies might be related to differences in the 4 Ds: drug (PRP), delivery (application method), donor (patients), and disease (stage of rotator cuff disease)[13]. In the present study, allogeneic PRP was prepared from healthy donors with an automated plateletpheresis system and then was characterized in terms of the concentrations of the blood cells and growth factors related to rotator cuff healing[36]. In the present study, a single physician with adequate expertise in ultrasonography-guided shoulder injection performed every injection. The diagnosis and stage of rotator cuff disease were established clinically by a shoulder surgeon as well as radiographically by a fellowship-trained musculoskeletal radiologist. This standardization in the 4 Ds of confounding factors could be one of the strengths of this study.

However, the present study had several limitations. First, this study did not include a placebo control, which could cause false-positive results due to the negative effects of corticosteroids[37]. However, several meta-analysis studies showed greater changes with corticosteroids than with saline solution, suggesting use of corticosteroids instead of placebo[38,39]. Second, the duration and rate of follow-up were not adequate to investigate the effects of PRP and corticosteroid injections. However, several systematic reviews have shown that corticosteroids only had a short benefit of up to 2 to 3 months and had no benefit at 6 months[9,28,30,31], suggesting that a trial with a corticosteroid control that follows patients for ≥6 months might be biased or

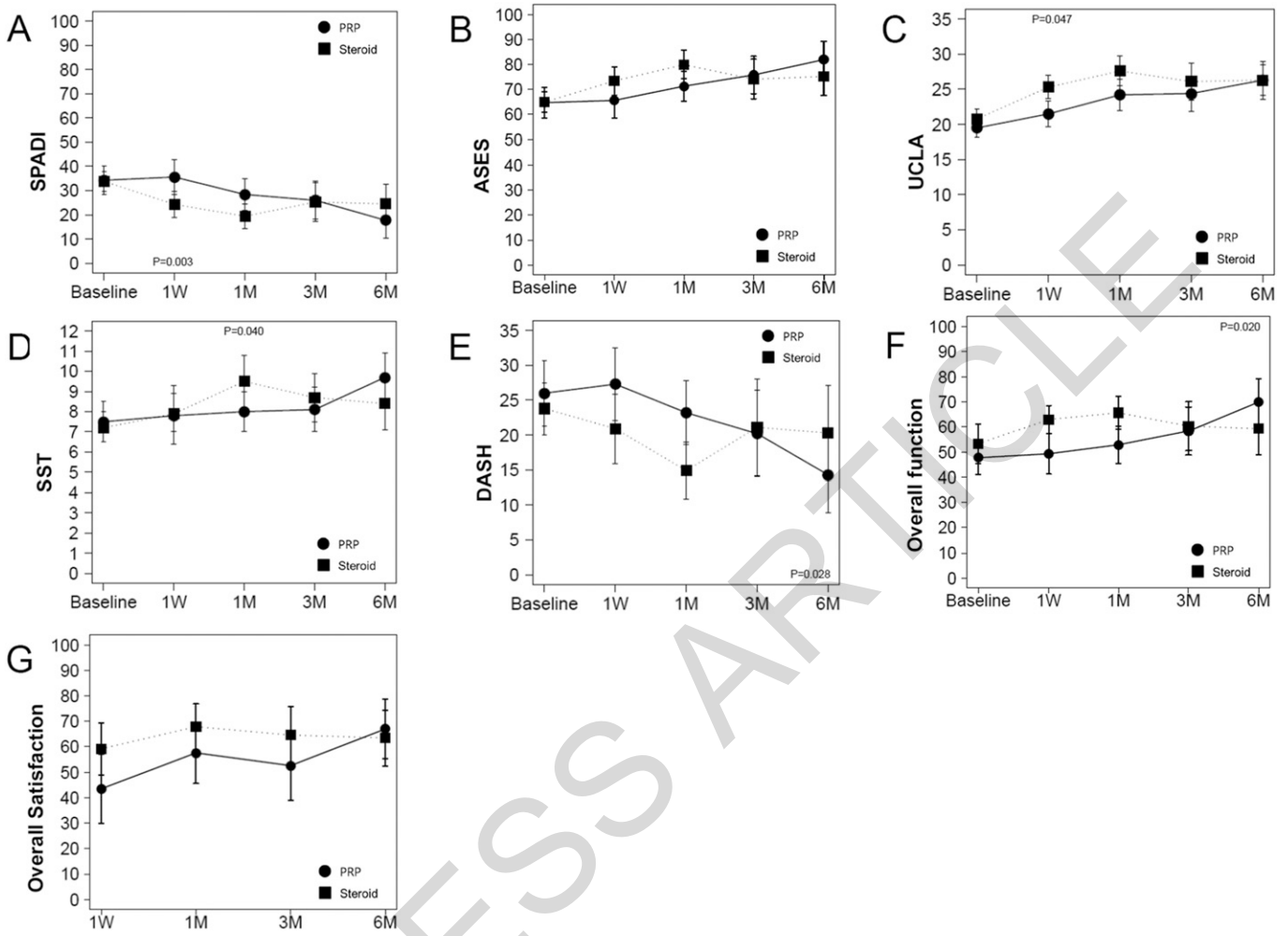

Fig. 4

Figs. 4-A through 4-G Line graphs showing changes in functional scores (**Figs. 4-A through 4-E**), overall function (**Fig. 4-F**), and satisfaction (**Fig. 4-G**) after PRP and steroid injection. SPADI = Shoulder Pain and Disability Index, ASES = American Shoulder and Elbow Surgeons, UCLA = University of California Los Angeles, SST = Simple Shoulder Test, and DASH = Disabilities of the Arm, Shoulder and Hand. The values are shown as the mean and the standard deviation. W = week, and M = month(s).

might not provide useful clinical information even with positive statistical findings. The results of the present study would provide useful information for further studies. Third, structural changes of the subacromial space and rotator cuff tendons that could contain important information were not evaluated. Fourth, the present study involved the use of pure PRP with no blood cells other than platelets. Other kinds of PRPs, especially those containing WBCs, would show different results[38,40,41]. However, the use of pure PRP provides the most fundamental way to clarify platelet-dependent and leukocyte-independent mechanisms of PRP[18]. Fifth, no cost analysis was included in the present study. However, it would be not difficult to expect that the cost of fully characterized allogeneic PRP that could be manufactured in large quantities would be much lower than that of autologous PRP with little or no characterization. Last, safety and secondary outcome measures had not been originally registered in the public domain.

In conclusion, allogeneic PRP injection in patients with rotator cuff disease was safe, but there was no significant difference between the PRP and corticosteroid groups in terms of the Constant score at 6 months. The DASH score, overall function, and external rotation were better in the PRP group at 6 months. Generally, PRP slowly but steadily reduced pain and improved function of the shoulder until 6 months, whereas corticosteroid did not.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/G148). ■

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