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Platelet-Rich Plasma for Arthroscopic Repair of Medium to Large Rotator Cuff Tears

A Randomized Controlled Trial

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Background: Two main questions about the use of platelet-rich plasma (PRP) for regeneration purposes are its effect on the speed of healing and the quality of healing. Despite recent numerous studies, evidence is still lacking in this area, especially in a representative patient population with medium to large rotator cuff tears.

Purpose: To assess the efficacy of PRP augmentation on the speed and quality of healing in patients undergoing arthroscopic repair for medium to large rotator cuff tears.

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

Methods: A total of 74 patients scheduled for arthroscopic repair of medium to large rotator cuff tears were randomly assigned to undergo either PRP-augmented repair (PRP group) or conventional repair (conventional group). In the PRP group, 3 PRP gels (3 × 3 mL) were applied to each patient between the torn end and the greater tuberosity. The primary outcome was the Constant score at 3 months after surgery. Secondary outcome measures included the visual analog scale (VAS) for pain, range of motion (ROM), muscle strength, overall satisfaction and function, functional scores, retear rate, and change in the cross-sectional area (CSA) of the supraspinatus muscle.

Results: There was no difference between the 2 groups in the Constant score at 3 months ($P > .05$). The 2 groups had similar results on the VAS for pain, ROM, muscle strength, overall satisfaction and function, and other functional scores (all $P > .05$) except for the VAS for worst pain ($P = .043$). The retear rate of the PRP group (3.0%) was significantly lower than that of the conventional group (20.0%) ($P = .032$). The change in 1-year postoperative and immediately postoperative CSAs was significantly different between the 2 groups: $-36.76 \pm 45.31 \text{ mm}^2$ in the PRP group versus $-67.47 \pm 47.26 \text{ mm}^2$ in the conventional group ($P = .014$).

Conclusion: Compared with repairs without PRP augmentation, the current PRP preparation and application methods for medium to large rotator cuff repairs significantly improved the quality, as evidenced by a decreased retear rate and increased CSA of the supraspinatus, but not the speed of healing. However, further studies may be needed to investigate the effects of PRP on the speed of healing without risking the quality.

Keywords: platelet-rich plasma; medium to large rotator cuff tear; rotator cuff repair; biological augmentation; retear; integrity

Despite a recent surge of studies about platelet-rich plasma (PRP) in rotator cuff repair, outcomes and mechanisms of PRP should be further elucidated. In contrast to positive potentials of PRP reported in basic research literature,^{9,12,16,20,30} clinical outcomes have been reported as better,^{2,14,23,37} not different,^{1,5,6,11,19,31,43} or even worse.^{3,38} One important reason for these controversies is the

difference in PRPs used in different studies. It includes variation of the concentration, activation, and method of application.²³ It is not practical to standardize the preparation and application of PRP in daily routine practice. However, at least in clinical research, efforts to standardize the process and to provide adequate information that could characterize PRP should be attempted. Another crucial reason is that we still might not identify the proper population of patients who could benefit from PRP. Only a few studies with higher levels of evidence enrolled patients with certain characteristics such as tear size.^{1,6,23} Another possible reason is that many previous studies tend to

observe general outcomes of PRP application rather than trying to find specific effects. The main concept behind the usage of PRP in rotator cuff repair is that it is likely to accelerate the speed of healing at early time points and to improve the quality of healing over time.

Therefore, we tried to evaluate 2 main potentials of PRP on healing after rotator cuff repair: (1) whether it could accelerate the speed of healing measured by the Constant score at 3 months and (2) whether it could improve the quality of healing with assessment of the retear rate at 12 months after repair. We defined eligible patients as those with a medium to large tear because they are the majority of patients undergoing rotator cuff repair and we could avoid potential selection and performance biases that might be encountered if we enrolled patients with a small or massive tear. We adopted a fully automated plateletpheresis system for preparation and calcium-activated gels for the application of PRP to maintain consistency and reproducibility.¹⁸

The purpose of the study was to assess the efficacy of PRP on the speed and quality of healing in patients undergoing arthroscopic repair of medium to large rotator cuff tears. Our hypothesis was that PRP would enhance the speed and quality of healing in this population.

METHODS

Patient Enrollment

This study was a randomized controlled trial in a university hospital enrolling patients with a medium to large rotator cuff tear undergoing arthroscopic rotator cuff repair. The study was approved by our hospital's institutional review board and registered at clinicaltrials.gov (NCT01458665). Patients between 45 and 85 years of age were eligible if they had a medium to large rotator cuff tear (anteroposterior size >10 mm and ≤50 mm) as determined by a clinical examination and magnetic resonance imaging (MRI) before surgery. Patients were excluded if they had a history of shoulder surgery, had acute trauma, had a chronic dislocation or pyogenic infection, had rotator cuff arthropathy with glenohumeral osteoarthritis and superior migration of the humeral head, showed abnormal serological test results or thrombocytopenia (<15,000 platelets/ μ L), had taken anti-platelet medication, had psychiatric problems that precluded informed consent or an inability to read or write, and had other serious issues that precluded participation in the study.

Enrolled patients were randomly allocated in a 1:1 ratio, with block sizes of 4 and 6 using the randomization sequence created with SAS 9.1 statistical software (SAS Institute Inc) to undergo either conventional arthroscopic

rotator cuff repair (conventional group) or arthroscopic rotator cuff repair with PRP (PRP group). PRP was prepared in patients in the PRP group 1 day before surgery. The patients were not blinded and the patients in the conventional group did not have blood drawn.

As confirmative determination of the tear size was conducted during surgery, some patients were identified to have a small or massive tear or were only to be treated with partial repair because of irreparability. These patients were also excluded from the per-protocol analysis of the occurrence of retears but were included in the intention-to-treat analysis of the other outcome measures.

Preparation of PRP

PRP was prepared using a plateletpheresis system with a leukoreduction set (COBE Spectra LRS Turbo; Caridian BCT) and a standard collection program 1 day before surgery as previously described.^{19,23} An aliquot was used for determining complete blood counts with a fully automated analyzer (XE-2100; Sysmex Corp), and the concentration of fibrinogen was determined using an automated coagulation analyzer (CA-7000; Sysmex Corp). The activation status of platelets was also determined using flow cytometry with CD61 and CD62P in 3 patients.¹⁵ For PRP application in rotator cuff repair, platelet counts in PRP were adjusted with saline to 1000×10^3 platelets/ μ L. To produce a gel from prepared PRP, 0.3 mL of 10% calcium gluconate was added to 3 mL of PRP. The dilution and gelling procedure was performed within 1 hour of surgical application.

Surgical Procedures and PRP Application

All arthroscopic surgeries were performed with patients in the lateral decubitus position under general anesthesia as previously described.^{19,24} Briefly, systematic glenohumeral joint and subacromial exploration was performed, and lesions were managed as necessary. In each case, after the frayed and atrophied torn end was removed, the rotator cuff tear was carefully evaluated, and anteroposterior size, mediolateral retraction, number of involved tendons, visual tendon grade,²⁴ excursion, and presence of the subscapularis tear were documented.³⁵ If excursion of the torn end was inadequate, tendon mobilization procedures including superior capsulotomy, coracohumeral ligament release, and medialization of the supraspinatus insertion in the greater tuberosity were performed. Anterior or posterior interval slide was not performed in any patient. The footprint of the greater tuberosity was debrided, and only a minimal layer of cortical bone was removed. Debridement of bursal tissue and subacromial and distal clavicle

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osteophytes was minimally performed. Extensive acromioplasty to flatten a hooked or curved acromion was rarely performed.

Rotator cuff repair was performed to cover the original footprint using a suture bridge technique whenever possible. Suture anchors were inserted through the accessory portal. Generally, 3 to 5 suture anchors were used: 1 or 2 anchors for the medial row and 2 or 3 anchors for the lateral row. Medial-row anchors were inserted first just lateral to the articular surface of the humeral head, and sutures were then threaded through the rotator cuff. After the medial-row sutures were threaded, the 3 PRP gels per patient were applied as previously described.^{18,19} Briefly, a No. 1 PDS II suture (Ethicon) was threaded to the posterior portion of the tear near the footprint of the rotator cuff. One end of the suture was then retrieved through an 8.0-mm cannula in the lateral portal and then through a long 5.5-mm cannula without a diaphragm. Three PRP gels were threaded to the suture per patient and introduced into the long 5.5-mm cannula. With a knot pusher threaded to the suture to back up the PRP gels, the 5.5-mm cannula was introduced into the 8.0-mm cannula, which was aimed at the repair site. As the 5.5-mm cannula reached the repair site, the PRP gels were placed into the site by pulling the suture end in the posterior cannula and by pushing the knot pusher. After the PRP gels were out of the 5.5-mm cannula, the knot pusher was then quickly removed. While the surgeon blocked the outer opening of the 5.5-mm cannula with a finger, a suture retriever was introduced via the anterior portal. The suture was then seized and retrieved through the anterior portal, and the 5.5-mm cannula was removed. With the PRP gels in place, medial-row sutures were tied using the SP knot if necessary.²⁵ The lateral row was then secured using suture anchors, and the PRP gels were interposed at the tendon-bone interface. After repair, greater tuberosity coverage of the repaired tendon was measured to evaluate the repair status as previously described.²⁴

Postoperative Protocol

The shoulder was immobilized for 4 weeks using an abduction brace. Shrugging, protraction, and retraction of shoulder girdles; intermittent exercise of the elbow, wrist, and hand; and external rotation of the arm to neutral with the brace were encouraged as tolerated, usually immediately after surgery. Further passive range of motion (ROM) and active assisted ROM exercises were allowed after the patient was gradually weaned off the abduction brace from 4 to 6 weeks after surgery. Patients began strengthening exercises after 3 months. Light sports activities, such as jogging, were allowed after 3 months, and full return to sports was allowed after 6 to 9 months according to individual recovery.

Outcome Assessments

The primary outcome measure was the Constant score at 3 months after surgery. The secondary outcome measure

includes a variety of clinical and structural outcomes. For the clinical evaluation, each patient completed a questionnaire that consisted of standardized outcome assessments at baseline and at 3, 6, and finally a minimum of 12 months after surgery. Clinical outcomes were assessed according to (1) pain, (2) ROM, (3) muscle strength, (4) overall satisfaction and function, and (5) functional scores. A visual analog scale (VAS) was used to evaluate pain at rest, during motion, and at night. Patients were asked to use a 10-cm scale marked from “no pain” (0) to “unbearable pain” (10). Mean pain scores were calculated and compared. In addition, a score for the worst pain was also recorded. ROM was measured with a goniometer in active forward flexion, abduction, external rotation with the arm at the side, and internal rotation. Internal rotation was measured using vertebral levels, and these were translated into numbers from 1 for the buttocks to 17 for T2. The strength of the supraspinatus, infraspinatus, and subscapularis muscles was measured using a handheld electronic scale (CHS; CAS Corp). To evaluate overall satisfaction and function, 5 questions were asked, with answers of “yes” or “no” to the following: (1) their willingness to undergo surgery again, (2) whether they were prepared to recommend surgery to another, and (3) whether they were able to work as they did before getting sick. Using a 10-cm scale, we also evaluated (4) overall function and satisfaction marked from “I cannot use it” to “I feel normal” for function (the single assessment numeric evaluation [SANE]) and (5) overall satisfaction from “never satisfied” to “very satisfied.” The functional scoring systems used were the American Shoulder and Elbow Surgeons (ASES) score, the Constant score, the University of California, Los Angeles (UCLA) score, the Simple Shoulder Test (SST), and the Shoulder Pain and Disability Index (SPADI). Structural outcomes included the retear rate and change in the cross-sectional area (CSA) of the supraspinatus muscle.^{21,22} The retear rate was measured using MRI. To evaluate the structural integrity, MRI (Achieva 3.0-T; Philips Medical Systems) with a dedicated shoulder coil was performed at a minimum of 9 months after surgery. Retears were evaluated using the Sugaya classification for patients with MRI.³⁹ According to the Sugaya classification, types I, II, and III were considered as healed, and types IV and V were considered as retears. All scans were first reviewed blinded by a fellowship-trained musculoskeletal radiologist and then by an orthopaedic surgeon. When there was a discrepancy in readings, integrity was graded as the worse option. The change in the CSA of the supraspinatus was calculated by subtracting measures of the 2 different time points.^{21,22,44}

Statistical Analysis

To determine the study sample size, an a priori power analysis was performed to provide a statistical power of 80% at an α level of .05. With previous data,^{24,26,29} a sample size of 37 patients per group was determined to be sufficient to detect a 20% or 10-point difference in the Constant score between the groups at 3 months after surgery, assuming

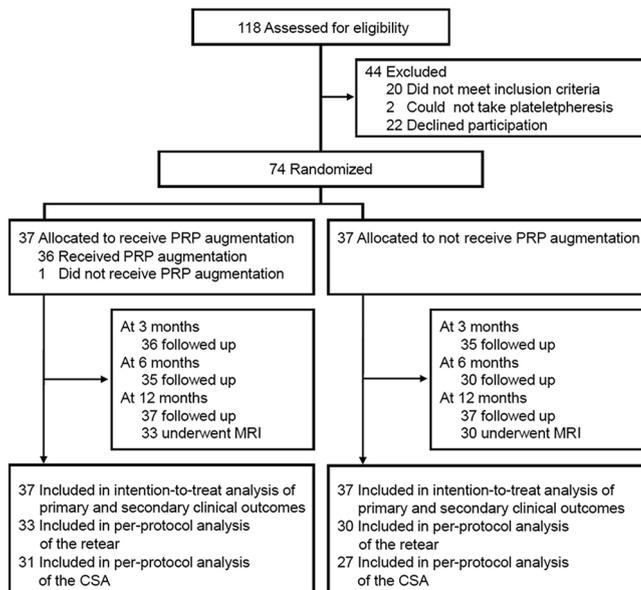


Figure 1. Study flow diagram. CSA, cross-sectional area; MRI, magnetic resonance imaging; PRP, platelet-rich plasma.

an SD of 13.3 and a 20% probability of data loss. Outcome measures except for the retear rate were analyzed based on the intention-to-treat population. Missing data of the patients who dropped out of the study were imputed with the last observation carried forward method. Nominal and ordinal values were compared using the Pearson χ^2 test. The demographic values, overall satisfaction, and change in the CSA were compared using the independent *t* test. The values of VAS, ROM, strength, functional scores, and overall function were analyzed using analysis of covariance and adjusted for preoperative values. Analysis was performed using SPSS version 13.0 (SPSS Inc), and the significance level was set at $P = .05$ throughout.

RESULTS

Patients

Between October 2011 and January 2013, 118 patients were screened for eligibility; 98 were eligible, and 74 patients were randomized and underwent arthroscopic rotator cuff repair either with or without PRP (Figure 1). One patient in the PRP group failed plateletpheresis and underwent rotator cuff repair without PRP. All the participants completed 12 months of follow-up. Postoperative MRI at a minimum of 9 months after surgery for assessing retears was performed in 63 of 74 patients in the study (85.1%): 33 patients (89.2%) in the PRP group and 30 patients (81.1%) in the conventional group. Meanwhile, preoperative, immediately operative, and 1-year postoperative MRI scans to assess the change in the CSA were obtained in 31 patients (83.8%) in the PRP group and in 27 patients (73.0%) in the conventional group (as described in Table 5).

There were no significant differences in baseline patient characteristics of demographics, tear size, representative operative findings and procedures, status of rotator cuff muscles, and follow-up between the 2 groups (Table 1).

Characteristics of PRP Application

The characteristics of PRP application are described with the classification of concentration, activation, and method of application (Table 2). The mean platelet count increased from $172.71 \pm 42.09 \times 10^3$ platelets/ μL in whole blood to $1218.40 \pm 334.69 \times 10^3$ platelets/ μL in PRP, a 7.1-fold increase from baseline ($P < .001$). The mean white and red blood cell count changed from $4.78 \pm 1.78 \times 10^3$ cells/ μL to $0.04 \pm 0.03 \times 10^3$ cells/ μL and from $4.21 \pm 0.55 \times 10^3$ cells/ μL to $0.14 \pm 0.04 \times 10^3$ cells/ μL , respectively, a 0.07-fold and 0.03-fold decrease from baseline, respectively (all $P < .001$). The mean plasma fibrinogen concentration change in PRP was 201.26 ± 29.34 mg/dL. The mean percentage of activated platelets in 3 patients was $14.52\% \pm 1.45\%$.

Constant Score and Other Functional Scores

The Constant score was not significantly different before and at any time point after surgery between the 2 groups (all $P > .05$) (Table 3). The Constant score in the PRP group significantly decreased at 3 months after surgery ($P < .020$), while that in the conventional group did not change ($P < .680$). However, it gradually improved and was significantly higher at 6 months (all $P = .017$) and at final follow-up (all $P < .001$) compared with that before surgery in both groups.

The 2 groups showed similar shoulder function results before and after surgery according to the ASES, UCLA, SST, and SPADI scores (all $P > .05$). At 3 months, the ASES, UCLA, and SPADI scores significantly improved compared with those before surgery in the conventional group ($P = .037$, $.010$, and $.048$, respectively), while those in the PRP group did not. After 6 months, all scores were significantly higher than those before surgery in both groups (all $P < .001$).

Pain

Preoperatively, VAS pain scores at rest, with motion, and at night and mean and worst pain scores were not different in the 2 groups (all $P > .05$) (Table 4). After surgery, all VAS pain measurements decreased over time until final follow-up in both groups. No significant difference between the 2 groups was found for any VAS pain measurement at any time point until final follow-up except for the VAS for worst pain, which was significantly lower in the PRP group (2.49 ± 2.26) than in the conventional group (3.68 ± 2.54) at final follow-up ($P = .043$). At 3 months, VAS pain scores at rest and at night and mean pain scores significantly improved compared with those before surgery in the conventional group ($P = .010$, $.009$, and $.004$, respectively),

TABLE 1
Comparison of Baseline Demographics Between the PRP and Conventional Repair Groups^a

Variable	PRP Repair (n = 37)	Conventional Repair (n = 37)	P Value
Age, y	60.08 ± 4.88	60.92 ± 7.34	.565
Sex (male:female), n	8:29	9:28	.782
Dominance (yes:no), n	28:9	29:8	.782
Duration, mo	30.60 ± 34.15	17.30 ± 26.22	.064
Symptom aggravation, mo	5.89 ± 5.70	4.49 ± 3.76	.365
Size, mm			
Anteroposterior	22.57 ± 8.94	26.84 ± 10.94	.070
Mediolateral	14.65 ± 8.24	15.38 ± 8.07	.701
Cofield type (S:M:L:MSV), n	0:27:10:0	0:25:12:0	.611
Boileau stage (I:II:III:IV), n	19:11:5:2	17:9:10:1	.521
Involved tendons, n	1.59 ± 0.72	1.81 ± 0.74	.208
Tendon grade (A:B:C), ^b n	17:18:2	20:13:4	.856
Excursion (A:B:C), ^c n	25:9:3	26:9:2	.704
Labral tear (yes:no), n	8:29	7:30	.772
Labrum (not done:debride:repair), n	25:12:0	27:10:0	.611
Biceps tear (none:partial:complete), n	21:15:1	19:18:0	.503
Biceps (not done:debride:tenotomy), n	20:4:13	19:0:18	.089
SB grade (0:1:2:3), ^d n	11:14:6:3:3:0	8:16:3:7:3	.452
SB repair (none:debride:repair), n	11:20:6	10:15:12	.251
Anchors, n	3.30 ± 0.66	3.43 ± 0.69	.392
Acromioplasty (yes:no), n	18:19	15:22	.483
GT medialization (yes:no), n	4:33	2:35	.394
GT coverage (grade A:B:C:D), ^e n	27:8:2:0	25:9:2:1	.478
Goutallier grade (grade 0:1:2:3:4), n			
Supraspinatus	1:11:20:5:0	0:9:15:9:4	.133
Infraspinatus	0:24:10:2:1	3:20:11:2:1	.491
Subscapularis	6:22:9:0:0	6:18:10:3:0	.327
Tangent sign (grade 1:2:3), ^f n	27:9:1	23:9:5	.225
Follow-up, mo	13.03 ± 1.79	13.08 ± 1.98	.902
MRI follow-up, mo	9.64 ± 2.09	9.77 ± 1.63	.785

^aValues are expressed as mean ± SD unless otherwise specified. GT, greater tuberosity; MRI, magnetic resonance imaging; PRP, platelet-rich plasma; S:M:L:MSV, small:medium:large:massive; SB, subscapularis.

^bTendon grade assesses rotator cuff quality using 3 gross tendon criteria²⁴: (1) fraying over half of the tendon thickness, (2) delamination of the supraspinatus tendon, and (3) thinning of less than half of the normal thickness. Grading: A = none of these criteria were met; B = fraying or delamination was identified; C = both fraying and delamination or thinning regardless of the other criteria.

^cExcursion evaluates the lateral displacement of the tear end by manual pulling. Grading: A = over the ridge of the greater tuberosity; B = within the original footprint in the greater tuberosity; C = cannot be reduced to the original footprint.

^dSubscapularis tear was graded according to the Nove-Josserand classification in Pfirrmann et al.³⁵ Grading: 0 = normal tendon; 1 = tear less than one-quarter; 2 = tear more than one-quarter but not complete; 3 = complete tear.

^eGT coverage evaluates repair quality. Grading: A = complete coverage of the original footprint; B = incomplete coverage more than half of the footprint; C = incomplete coverage less than half of the footprint; D = presence of defect into the glenohumeral joint.

^fTangent sign assesses muscle atrophy of the supraspinatus. Grading: 1 = negative (the superior border of the supraspinatus was superior to the line tangential to the coracoid and scapular spine); 2 = borderline (the superior border was located about the tangential line); 3 = positive (the superior border was inferior to the tangential line).

while those in the PRP group did not. At 6 months, all scores significantly improved in both groups.

Range of Motion

No significant difference between the 2 groups was found for active forward flexion, abduction, external rotation with the arm at the side, and internal rotation before and at any time point after surgery (see the Appendix, available online at <http://ajsm.sagepub.com/supplemental>). ROM in all planes showed the same tendency over time as previously reported¹⁹; they decreased until 3 months after

surgery and then increased gradually until final follow-up. At final follow-up, forward flexion and abduction in both groups improved significantly. However, external rotation did not improve in both groups.

Strength

Strength of the supraspinatus, infraspinatus, and subscapularis muscles was not significantly different between the 2 groups before and at any time point after surgery (see the Appendix, available online). At 6 months, strength of the infraspinatus and subscapularis significantly

TABLE 2
Characterization of PRP Used
With Respect to Concentration, Activation,
and Method of Application^a

Property	Value
Concentration, mean \pm SD	
Platelets, $\times 10^3/\mu\text{L}$	1218.40 \pm 334.69
WBC, $\times 10^3/\mu\text{L}$	0.04 \pm 0.03
RBC, $\times 10^3/\mu\text{L}$	0.14 \pm 0.04
Fibrinogen, mg/dL	201.26 \pm 29.34
Activation	
Status, ^b mean \pm SD, %	14.52 \pm 1.45
Method	Calcium alone
Method of application	
State	Gel
Volume, mL	3 \times 3
Number	1
Interval, d	0

^aPRP, platelet-rich plasma; RBC, red blood cells; WBC, white blood cells.

^bActivation status was measured using flow cytometry with CD61 and CD62P in 3 patients. Results are expressed as the percentage of CD62P-positive counts over CD61-positive counts.

TABLE 3
Outcome Assessments: Constant, ASES,
UCLA, SST, and SPADI Scores

Variable	PRP Repair (n = 37)	Conventional Repair (n = 37)	P Value
Constant score			
Preoperative	53.76 \pm 17.89	47.17 \pm 20.34	.147
3 mo	45.12 \pm 14.75	45.79 \pm 16.11	.545
6 mo	60.74 \pm 14.53	55.83 \pm 16.24	.471
Final	74.67 \pm 9.17	70.87 \pm 9.76	.169
ASES score			
Preoperative	56.77 \pm 18.83	48.92 \pm 21.91	.105
3 mo	54.89 \pm 17.86	57.97 \pm 20.60	.263
6 mo	73.92 \pm 19.24	68.86 \pm 19.51	.464
Final	87.96 \pm 13.10	83.65 \pm 14.56	.381
UCLA score			
Preoperative	18.28 \pm 4.97	16.08 \pm 5.24	.071
3 mo	21.00 \pm 6.31	18.57 \pm 4.79	.169
6 mo	25.41 \pm 5.96	24.19 \pm 6.56	.931
Final	30.73 \pm 4.15	29.54 \pm 4.86	.454
SST score			
Preoperative	6.39 \pm 2.90	5.03 \pm 3.56	.078
3 mo	5.32 \pm 2.46	5.32 \pm 2.52	.560
6 mo	8.19 \pm 2.84	7.22 \pm 2.68	.478
Final	10.24 \pm 2.14	9.76 \pm 2.27	.790
SPADI score			
Preoperative	42.26 \pm 20.43	52.39 \pm 25.40	.065
3 mo	44.05 \pm 20.27	43.01 \pm 20.05	.613
6 mo	24.35 \pm 18.35	30.73 \pm 21.04	.445
Final	10.98 \pm 12.20	13.80 \pm 11.65	.539

^aValues are expressed as mean \pm SD. ASES, American Shoulder and Elbow Surgeons; PRP, platelet-rich plasma; SPADI, Shoulder Pain and Disability Index; SST, Simple Shoulder Test; UCLA, University of California, Los Angeles.

TABLE 4
Outcome Assessments: VAS Pain Scores^a

Variable	PRP Repair (n = 37)	Conventional Repair (n = 37)	P Value
Pain at rest			
Preoperative	3.17 \pm 2.71	3.24 \pm 2.09	.893
3 mo	3.00 \pm 2.20	2.14 \pm 1.96	.077
6 mo	1.65 \pm 1.53	1.81 \pm 1.81	.672
Final	0.78 \pm 1.23	0.89 \pm 1.61	.758
Pain during motion			
Preoperative	5.27 \pm 2.70	5.78 \pm 2.51	.401
3 mo	4.20 \pm 1.95	4.41 \pm 2.48	.727
6 mo	2.49 \pm 2.11	3.06 \pm 2.33	.369
Final	1.17 \pm 1.44	1.57 \pm 1.82	.299
Pain at night			
Preoperative	5.00 \pm 2.68	5.27 \pm 2.88	.680
3 mo	4.16 \pm 2.68	3.70 \pm 2.69	.395
6 mo	2.43 \pm 2.58	2.59 \pm 2.34	.896
Final	1.22 \pm 1.73	1.97 \pm 2.23	.116
Mean pain			
Preoperative	4.48 \pm 2.25	4.77 \pm 2.03	.568
3 mo	3.82 \pm 2.02	3.41 \pm 2.06	.340
6 mo	2.19 \pm 1.88	2.49 \pm 1.96	.582
Final	1.06 \pm 1.27	1.48 \pm 1.69	.250
Worst pain			
Preoperative	7.42 \pm 2.27	7.89 \pm 2.05	.351
3 mo	6.11 \pm 2.42	6.16 \pm 2.91	.961
6 mo	3.76 \pm 2.54	4.35 \pm 2.92	.476
Final	2.49 \pm 2.26	3.68 \pm 2.54	.043

^aScoring was conducted on a 10-point scale, where 0 = no pain and 10 = unbearable pain. PRP, platelet-rich plasma; VAS, visual analog scale.

TABLE 5
Sugaya Classification and Retear Rate
at 1 Year After Rotator Cuff Repair^a

	PRP Repair (n = 33)	Conventional Repair (n = 30)	P Value
Sugaya classification type			.163
I	5 (15.2)	5 (16.7)	
II	19 (57.6)	10 (33.3)	
III	8 (24.2)	9 (30.0)	
IV	1 (3.0)	4 (13.3)	
V	0 (0.0)	2 (6.7)	
Retears	1 (3.0)	6 (20.0)	.032

^aValues are expressed as n (%). PRP, platelet-rich plasma.

improved in the PRP group, whereas that of the subscapularis only increased in the conventional group. At final follow-up, strength of the supraspinatus, infraspinatus, and subscapularis was significantly greater than preoperative values in both groups (all $P < .001$).

Overall Satisfaction and Function

Patients in the 2 groups showed no significant difference in willingness to undergo surgery again and to recommend

TABLE 6
Change in CSA of the Supraspinatus at 1 Year After Rotator Cuff Repair^a

	PRP Repair (n = 31)	Conventional Repair (n = 27)	P Value
CSA, mm ²			
Preoperative	379.46 ± 96.26	372.84 ± 122.59	.819
Immediately postoperative	450.76 ± 112.27	443.19 ± 109.14	.796
1-year postoperative	414.00 ± 112.39	375.72 ± 118.00	.211
ΔCSA, mm ²			
Immediately postoperative–preoperative	71.31 ± 89.39	70.35 ± 41.73	.960
1-year postoperative–immediately postoperative	–36.76 ± 45.31	–67.47 ± 47.26	.014
1-year postoperative–preoperative	34.55 ± 92.85	2.88 ± 51.34	.121

^aValues are expressed as mean ± SE. CSA, cross-sectional area; PRP, platelet-rich plasma.

surgery to another after surgery (see the Appendix). The rates of patients' ability to work as they did before getting sick and overall function were not different between the 2 groups before and at any time point after surgery. Overall satisfaction was also not different between the 2 groups at any time point after surgery.

Retear Rate

The retear rate of the PRP group (1/33, 3.0%) was significantly lower than that of the conventional group (6/30, 20.0%) ($P = .032$): 1 Sugaya type IV in the PRP group and 4 and 2 Sugaya types IV and V, respectively, in the conventional group (Table 5). More than half of the patients in the PRP group showed Sugaya type II (19/33, 57.6%), whereas only one-third of the patients in the conventional group did (10/30, 33.3%). However, the distribution of Sugaya classification types was not significantly different between the 2 groups ($P = .163$).

Change in CSA of the Supraspinatus

Preoperative, immediately postoperative, and 1-year postoperative CSAs of the supraspinatus muscle were not different between the 2 groups (Table 6). The change between the immediately postoperative and preoperative CSAs was not significantly different between the 2 groups ($P = .960$). The change between the 1-year postoperative and immediately postoperative CSAs was significantly different between the 2 groups: -36.76 ± 45.31 mm² in the PRP group and -67.47 ± 47.26 mm² in the conventional group ($P = .014$). The change between the 1-year postoperative and preoperative CSAs was not significantly different between the 2 groups ($P = .121$).

DISCUSSION

The most important findings of the study are that the application of PRP for rotator cuff repair in patients with medium to large rotator cuff tears improved the quality of healing but did not accelerate the speed of healing. Patients in the PRP group did not show higher Constant scores at 3 months. The only positive clinical finding was

that the PRP group showed lower VAS measures of the worst pain than the conventional group ($P = .043$). Furthermore, ASES, UCLA, and SPADI scores and VAS pain scores at rest and at night and mean pain scores significantly improved only in the conventional group at 3 months after surgery. However, the PRP group showed significant improvement in both structural outcomes compared with the conventional group: a 6-fold lower retear rate (3.0% vs 20.0%, respectively) and a lower decrease in the CSA of the supraspinatus muscle (-36.76 ± 45.31 mm² vs -67.47 ± 47.26 mm², respectively). These results are in line with results of previous studies in different populations.^{19,23} Neither group showed any improvement or differences in clinical outcomes at 3 to 12 months after surgery compared with the control groups, but findings suggested improved structural outcomes at 1 year after repair. Inferior structural outcomes identified at short-term follow-up could lead to longer term deterioration of clinical outcomes and thus would result in higher socioeconomic costs to treat these patients. Therefore, we suggest that the application of PRP for rotator cuff repair is worthwhile, even though it may not provide satisfactory clinical outcomes in the early period.

These results do not necessarily preclude the other potential of PRP: acceleration of healing. In this study, we adopted a more conservative rehabilitation regimen after surgery.^{7,19,23,28} Patients were immobilized in an abduction brace and were not allowed passive ROM exercise for the first 4 weeks. If PRP could improve the quality of healing, a less conservative rehabilitation regimen allowing early passive ROM exercise and possibly active assisted exercises could be adopted without affecting the retear rate. Also, this change in the rehabilitation protocol might result in an acceleration of recovery after repair. However, further studies should be conducted.

We enrolled patients with a medium to large tear in this study. There were several reasons for this decision. First, this patient population is the most common.^{19,34,40} Second, as the retear rate for a small tear with conventional rotator cuff repair without PRP ranges from 0% up to 10%,^{5,34} the application of PRP would not be necessary especially from a cost-benefit perspective. Third, for a massive tear, there might be a large variation in the characteristics of the tear and patients, such as anteroposterior and mediolateral size, excursion, tendon grade, reparability, fatty infiltration and atrophy of rotator cuff muscles, and the presence

of osteoarthritis and pseudoparalysis. All of these variations could be confounding factors for results that would more complicate the analysis process of PRP's effects. Therefore, we needed to confine the study to a patient population that would be the most common with room for improvement with respect to the speed and quality of healing, but without a large variation in characteristics, and we believed that patients with a medium to large tear would best fit this purpose of the study.

Among 5 major components of PRP, that is, platelets, white blood cells, red blood cells, fibrinogen, and plasma, the concentrations of platelets and white blood cells play more critical roles than the others in the effects of PRP, as both of them could release growth factors, cytokines, and proteinases.⁴⁵ While the role of leukocytes in PRP has not been fully elucidated, a few recent studies denoted some progress. Sundman et al⁴¹ described that platelets in PRP increased anabolic signaling such as transforming growth factor- β (TGF- β) and platelet-derived growth factor-AB (PDGF-AB) and that, in contrast, leukocytes increased catabolic signaling molecules such as matrix metalloproteinase-9 (MMP-9) and interleukin-1 β (IL-1 β). McCarrel et al^{32,33} reported a positive correlation between the concentration of white blood cells and the expression of catabolic mediators in an in vitro equine tendon and ligament study, and their more recent work further supported these findings; the treatment of tendon explants with low concentrations of white blood cells and PRP resulted in decreased IL-1 β and tumor necrosis factor- α (TNF- α) gene expression compared with explants treated with high concentrations of white blood cells and PRP. Pifer et al³⁶ showed that the concentrations and activities of MMP-2, -3, and -9 are higher in high-platelet, high-leukocyte PRP than in low-platelet, low-leukocyte PRP. Furthermore, in a rabbit patellar tendon model, Dragoo et al¹⁰ showed that leukocyte-rich PRP caused a greater acute inflammatory response. Besides inflammatory aspects, the effects of leukocytes in PRP on matrix synthesis were reported by some authors. Jo et al²⁰ reported that leukocyte-poor PRP enhanced matrix gene expression and synthesis in degenerative tenocytes from torn rotator cuff tendons. Boswell et al⁴ suggested that minimizing leukocytes in PRP is more important with respect to decreasing inflammation and enhancing matrix gene synthesis. These results from basic research suggest that PRP without leukocytes favors healing without inflammation more than PRP with leukocytes.

During the regeneration process of tendon injuries, leukocytes play their role mostly in the first stage: the inflammatory stage.^{8,13,17} Neutrophils clear debris, microbes, and necrotic tissue to clean the wound and prevent infections, and monocytes mature to become macrophages and further debride the wound. However, we believe that repairs to rotator cuff tears would fail in the second stage of tendon healing (ie, the proliferation stage, where the normally new extracellular matrix is synthesized in the presence of a reduced number of macrophages). In addition, while inducing angiogenesis is a key role of macrophages,⁸ vessel formation is unlikely necessary for tendon regeneration as

it is for cartilage regeneration. Therefore, for the regeneration of chronic degenerative rotator cuff disease or tears, inflammation or angiogenesis is not necessary, and even should be avoided, but matrix synthesis is strongly stimulated. In this sense, we suggest that leukocyte-poor PRP such as the one used in this study would be an optimal preparation for rotator cuff repair. Whereas this short-term study demonstrates better outcomes only regarding the structural integrity, but not in the clinical outcomes, we speculate that improved healing should result in better clinical outcomes at midterm or long-term follow-up.^{27,42}

Limitations of the study are that this (1) was a single-blind study; (2) arbitrarily used PRP in rotator cuff repair (component concentrations; activation method; and application state, number, and method); (3) used a conservative rehabilitation protocol that did not allow immediate passive ROM after surgery (thus, it might not have used an optimized rehabilitation regimen for detecting the effects of PRP on the acceleration of recovery); and (4) had a relatively lower follow-up rate of MRI in the control group.

In conclusion, the results of this study indicate that rotator cuff repair with the current PRP preparation and application method for medium to large rotator cuff repairs significantly improved the quality, as evidenced by a decreased retear rate and increased CSA of the supraspinatus, but not the speed of healing compared with repairs without PRP application. However, further studies may be needed to investigate the effects of PRP on the speed of healing without risking the quality.

REFERENCES

1. Antuna S, Barco R, Martinez Diez JM, Sanchez Marquez JM. Platelet-rich fibrin in arthroscopic repair of massive rotator cuff tears: a prospective randomized pilot clinical trial. *Acta Orthop Belg.* 2013;79(1):25-30.
2. Barber FA, Hrnack SA, Snyder SJ, Hapa O. Rotator cuff repair healing influenced by platelet-rich plasma construct augmentation. *Arthroscopy.* 2011;27(8):1029-1035.
3. Bergeson AG, Tashjian RZ, Greis PE, Crim J, Stoddard GJ, Burks RT. Effects of platelet-rich fibrin matrix on repair integrity of at-risk rotator cuff tears. *Am J Sports Med.* 2012;40(2):286-293.
4. Boswell SG, Schnabel LV, Mohammed HO, Sundman EA, Minas T, Fortier LA. Increasing platelet concentrations in leukocyte-reduced platelet-rich plasma decrease collagen gene synthesis in tendons. *Am J Sports Med.* 2014;42(1):42-49.
5. Castricini R, Longo UG, De Benedetto M, et al. Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: a randomized controlled trial. *Am J Sports Med.* 2011;39(2):258-265.
6. Charousset C, Zaoui A, Bellaiche L, Piterman M. Does autologous leukocyte-platelet-rich plasma improve tendon healing in arthroscopic repair of large or massive rotator cuff tears? *Arthroscopy.* 2014;30(4):428-435.
7. Cuff DJ, Pupello DR. Prospective randomized study of arthroscopic rotator cuff repair using an early versus delayed postoperative physical therapy protocol. *J Shoulder Elbow Surg.* 2012;21(11):1450-1455.
8. Davis VL, Abukabda AB, Radio NM, et al. Platelet-rich preparations to improve healing, part II: platelet activation and enrichment, leukocyte inclusion, and other selection criteria. *J Oral Implantol.* 2014;40(4):511-521.
9. Dolkart O, Chechik O, Zarfati Y, Brosh T, Alhajra F, Maman E. A single dose of platelet-rich plasma improves the organization and

- strength of a surgically repaired rotator cuff tendon in rats. *Arch Orthop Trauma Surg.* 2014;134(9):1271-1277.
10. Dragoo JL, Braun HJ, Durham JL, et al. Comparison of the acute inflammatory response of two commercial platelet-rich plasma systems in healthy rabbit tendons. *Am J Sports Med.* 2012;40(6):1274-1281.
 11. Encalada-Diaz I, Cole BJ, Macgillivray JD, et al. Rotator cuff repair augmentation using a novel polycarbonate polyurethane patch: preliminary results at 12 months' follow-up. *J Shoulder Elbow Surg.* 2011;20(5):788-794.
 12. Ersen A, Demirhan M, Atalar AC, Kapicioglu M, Baysal G. Platelet-rich plasma for enhancing surgical rotator cuff repair: evaluation and comparison of two application methods in a rat model. *Arch Orthop Trauma Surg.* 2014;134(3):405-411.
 13. Gomez M. The physiology and biochemistry of soft tissue healing. In: Griffin LY, ed. *Rehabilitation of the Injured Knee.* St Louis, MO: Mosby Co; 1995:34-44.
 14. Gumina S, Campagna V, Ferrazza G, et al. Use of platelet-leukocyte membrane in arthroscopic repair of large rotator cuff tears: a prospective randomized study. *J Bone Joint Surg Am.* 2012;94(15):1345-1352.
 15. Hagberg IA, Akkok CA, Lyberg T, Kjeldsen-Kragh J. Apheresis-induced platelet activation: comparison of three types of cell separators. *Transfusion.* 2000;40(2):182-192.
 16. Hapa O, Cakici H, Kukner A, Aygun H, Sarkalan N, Baysal G. Effect of platelet-rich plasma on tendon-to-bone healing after rotator cuff repair in rats: an in vivo experimental study. *Acta Orthop Traumatol Turc.* 2012;46(4):301-307.
 17. Hoffmann A, Gross G. Tendon and ligament engineering: from cell biology to in vivo application. *Regen Med.* 2006;1(4):563-574.
 18. Jo CH. Arthroscopic rotator cuff repair with platelet-rich plasma (PRP) gel: a technical note. *Acta Orthop Belg.* 2011;77(5):676-679.
 19. Jo CH, Kim JE, Yoon KS, et al. Does platelet-rich plasma accelerate recovery after rotator cuff repair? A prospective cohort study. *Am J Sports Med.* 2011;39(10):2082-2090.
 20. Jo CH, Kim JE, Yoon KS, Shin S. Platelet-rich plasma stimulates cell proliferation and enhances matrix gene expression and synthesis in tenocytes from human rotator cuff tendons with degenerative tears. *Am J Sports Med.* 2012;40(5):1035-1045.
 21. Jo CH, Shin JS. Changes in appearance of fatty infiltration and muscle atrophy of rotator cuff muscles on magnetic resonance imaging after rotator cuff repair: establishing new time-zero traits. *Arthroscopy.* 2013;29(3):449-458.
 22. Jo CH, Shin JS. Cross-sectional area of the supraspinatus muscle after rotator cuff repair: an anatomic measure of outcome. *J Bone Joint Surg Am.* 2013;95(19):1785-1791.
 23. Jo CH, Shin JS, Lee YG, et al. Platelet-rich plasma for arthroscopic repair of large to massive rotator cuff tears: a randomized, single-blind, parallel-group trial. *Am J Sports Med.* 2013;41(10):2240-2248.
 24. Jo CH, Yoon KS, Lee JH, et al. The effect of multiple channeling on the structural integrity of repaired rotator cuff. *Knee Surg Sports Traumatol Arthrosc.* 2011;19(12):2098-2107.
 25. Jo CH, Yoon KS, Lee JH, Kang SB, Lee MC. The slippage-proof knot: a new, nonstacking, arthroscopic, sliding locking not with a lag bight. *Orthopedics.* 2007;30(5):349-350.
 26. Kleinhenz J, Streitberger K, Windeler J, Gussbacher A, Mavridis G, Martin E. Randomised clinical trial comparing the effects of acupuncture and a newly designed placebo needle in rotator cuff tendinitis. *Pain.* 1999;83(2):235-241.
 27. Kluger R, Bock P, Mittlbock M, Krampla W, Engel A. Long-term survivorship of rotator cuff repairs using ultrasound and magnetic resonance imaging analysis. *Am J Sports Med.* 2011;39(10):2071-2081.
 28. Koo SS, Burkhart SS. Rehabilitation following arthroscopic rotator cuff repair. *Clin Sports Med.* 2010;29(2):203-211, vii.
 29. Kukkonen J, Kauko T, Vahlberg T, Joukainen A, Aarimaa V. Investigating minimal clinically important difference for Constant score in patients undergoing rotator cuff surgery. *J Shoulder Elbow Surg.* 2013;22(12):1650-1655.
 30. Lamplot JD, Angeline M, Angeles J, et al. Distinct effects of platelet-rich plasma and BMP13 on rotator cuff tendon injury healing in a rat model. *Am J Sports Med.* 2014;42(12):2877-2887.
 31. Malavolta EA, Gracitelli ME, Ferreira Neto AA, Assuncao JH, Bordalo-Rodrigues M, de Camargo OP. Platelet-rich plasma in rotator cuff repair: a prospective randomized study. *Am J Sports Med.* 2014;42(10):2446-2454.
 32. McCarrel T, Fortier L. Temporal growth factor release from platelet-rich plasma, trehalose lyophilized platelets, and bone marrow aspirate and their effect on tendon and ligament gene expression. *J Orthop Res.* 2009;27(8):1033-1042.
 33. McCarrel TM, Minas T, Fortier LA. Optimization of leukocyte concentration in platelet-rich plasma for the treatment of tendinopathy. *J Bone Joint Surg Am.* 2012;94(19):e143(141-148).
 34. Park JY, Siti HT, Keum JS, Moon SG, Oh KS. Does an arthroscopic suture bridge technique maintain repair integrity? A serial evaluation by ultrasonography. *Clin Orthop Relat Res.* 2010;468:1578-1587.
 35. Pfirrmann CW, Zanetti M, Weishaupt D, Gerber C, Hodler J. Subscapularis tendon tears: detection and grading at MR arthrography. *Radiology.* 1999;213(3):709-714.
 36. Pifer MA, Maerz T, Baker KC, Anderson K. Matrix metalloproteinase content and activity in low-platelet, low-leukocyte and high-platelet, high-leukocyte platelet rich plasma (PRP) and the biologic response to PRP by human ligament fibroblasts. *Am J Sports Med.* 2014;42(5):1211-1218.
 37. Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up. *J Shoulder Elbow Surg.* 2011;20(4):518-528.
 38. Rodeo SA, Delos D, Williams RJ, Adler RS, Pearle A, Warren RF. The effect of platelet-rich fibrin matrix on rotator cuff tendon healing: a prospective, randomized clinical study. *Am J Sports Med.* 2012;40(6):1234-1241.
 39. Sugaya H, Maeda K, Matsuki K, Moriishi J. Functional and structural outcome after arthroscopic full-thickness rotator cuff repair: single-row versus dual-row fixation. *Arthroscopy.* 2005;21(11):1307-1316.
 40. Sugaya H, Maeda K, Matsuki K, Moriishi J. Repair integrity and functional outcome after arthroscopic double-row rotator cuff repair: a prospective outcome study. *J Bone Joint Surg Am.* 2007;89(5):953-960.
 41. Sundman EA, Cole BJ, Fortier LA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. *Am J Sports Med.* 2011;39(10):2135-2140.
 42. Vastamaki M, Lohman M, Borgmasters N. Rotator cuff integrity correlates with clinical and functional results at a minimum 16 years after open repair. *Clin Orthop Relat Res.* 2013;471(2):554-561.
 43. Weber SC, Kauffman JL, Parise C, Weber SJ, Katz SD. Platelet-rich fibrin matrix in the management of arthroscopic repair of the rotator cuff: a prospective, randomized, double-blinded study. *Am J Sports Med.* 2013;41(2):263-270.
 44. Zanetti M, Gerber C, Hodler J. Quantitative assessment of the muscles of the rotator cuff with magnetic resonance imaging. *Invest Radiol.* 1998;33(3):163-170.
 45. Zimmermann R, Arnold D, Strasser E, et al. Sample preparation technique and white cell content influence the detectable levels of growth factors in platelet concentrates. *Vox Sang.* 2003;85(4):283-289.