# Efficacy of Intraoperative Platelet-Rich Plasma Augmentation and Postoperative Platelet-Rich Plasma Booster Injection for Rotator Cuff Healing

## A Randomized Controlled Clinical Trial

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**Background:** Platelet-rich plasma (PRP) has been applied as an adjuvant treatment for arthroscopic rotator cuff repair (ARCR) to enhance rotator cuff healing. However, it remains debatable whether PRP enhances tendon-to-bone healing.

**Purpose:** To assess the efficacy of intraoperative augmentation and postoperative injection of PRP that was prepared using the double-spin method and calcium activation without thrombin in patients with ARCR.

**Study Design:** Randomized controlled trial; Level of evidence, 1; and cohort study; Level of evidence, 3.

**Methods:** A total of 58 patients underwent ARCR using intraoperative PRP augmentation. Half of the patients were randomly assigned to receive an additional ultrasound-guided PRP injection at the repair site at 2 weeks postoperatively (PRP-booster group); the other half did not receive the booster injection (PRP-only group). A control group that did not receive any PRP treatment was retrospectively matched using propensity score matching. Structural integrity was assessed using magnetic resonance imaging at 1 year postoperatively, and healing rates were compared between patients with tear sizes $\leq$2 cm versus $>$2 cm. Functional outcomes were assessed using the visual analog scale (VAS) for pain; VAS for satisfaction; shoulder range of motion; and Constant, American Shoulder and Elbow Surgeons, and Simple Shoulder Test scores at minimum 2-year follow-up.

**Results:** In patients with tears $>$2 cm, the rate of healing failure at 1-year follow-up was significantly less in the overall PRP group than in the control group (12.9% vs 35.7%, respectively; $P = .040$), however, the PRP-booster group did not present a better healing rate than did the PRP-only group. The overall PRP group had lower VAS for pain scores compared with the control group ($0.5 \pm 1.1$ vs $1.3 \pm 1.8$, respectively; $P = .016$) and higher VAS for satisfaction scores ($9.2 \pm 1.2$ vs $8.6 \pm 1.7$; $P = .023$) at the final follow-up, whereas no statistical difference was found between the PRP-only and PRP-booster groups in functional outcomes.

**Conclusion:** Intraoperative PRP augmentation during ARCR demonstrated superior anatomic healing results in patients with rotator cuff tears $>$2 cm as well as reduced pain and increased subjective satisfaction. PRP booster injection provided no additional benefit to tendon integrity or functional recovery.

**Keywords:** platelet-rich plasma; rotator cuff tear; biological healing of rotator cuff tear; clinical outcome of platelet-rich plasma

Healing failure after arthroscopic rotator cuff repair (ARCR) remains an unsolved problem. Despite the development of operative techniques and surgical devices, healing failure rates between 20% and 94% have been reported.[6,11,36] Furthermore, the rate of healing failure tends to be higher as the tear size increases, and the postoperative functional outcome is generally worse in patients with healing failure.[2,6,7,24] Therefore, achieving anatomic healing of a torn rotator cuff is crucial to enhance long-term outcomes.[6,11,37] Healing failure may be caused by abnormal fibrous regeneration of tissue at the tendon-bone interface.[2,32]

To improve healing after rotator cuff repair, several biologic augmentations, such as growth factors, stem cells, and platelet-rich plasma (PRP), have been attempted.[16,17,26,27,32] Among the various options for biologic augmentation, PRP has been most widely used.[9,39] Several animal studies have reported that PRP may

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enhance the regeneration of tendon tissue[1,22,23,34]; however, mixed results have been reported regarding the use of PRP in human rotator cuff healing.[2,10,34] The lack of standardization of PRP-related factors is the most important reason for these mixed results because PRP application protocols vary from study to study.

No consensus has been established regarding which growth factor in PRP is essential for rotator cuff healing or whether specific preparation methods result in different growth factors and cellular composition. Researchers have used different application methods during surgery, with some surgeons applying the PRP over the repair site or interposing PRP gel between tendon and bone.[10,34] It is uncertain whether a secondary application of PRP after surgery would enhance rotator cuff healing. Furthermore, clinical indications for intraoperative PRP application have not been established, and the literature has reported mixed outcomes regarding whether a large tear is an indication for use of PRP.[5,39]

The purpose of this study was to assess the clinical efficacy of intraoperative PRP augmentation and postoperative PRP booster injection at 2 weeks after surgery, using PRP prepared via the double-spin method and calcium activation without thrombin, in patients undergoing ARCR. We hypothesized that intraoperative PRP augmentation with a booster injection of PRP at postoperative 2 weeks, using PRP prepared via the double-spin method and activated via calcium,[30,33] would enhance rotator cuff healing and improve functional outcomes after ARCR.

## METHODS

### Study Design

This study consisted of 2 parts: (1) a prospective randomized controlled trial to compare the efficacy of intraoperative PRP augmentation with additional ultrasound-guided PRP booster injection around the repair site at 2 weeks after surgery and (2) a comparative cohort study with a control group to assess the efficacy of PRP administration using propensity score matching. Both the clinical trial and the cohort study received institutional review board approval.

A sample size calculation was performed to determine the required number of participants for the prospective randomized controlled trial. According to a previous study,[18] the minimal clinically important difference (MCID) and standard deviation of the Constant score in patients with rotator cuff tears are 10.4 points and 8 points, respectively. With a statistical power of 80% at a significance level of 5%, at least 48 participants (24 in each group) were required to detect an MCID between a PRP-only group and a PRP booster injection group. Assuming a 20% dropout rate, we determined the sample size needed to be 58.

Candidates for the clinical trial were recruited among patients who were planning to undergo ARCR; all patients enrolled in this study had symptomatic chronic shoulder pain or other symptoms related to rotator cuff tendon for >6 months and had full-thickness rotator cuff tear confirmed using magnetic resonance imaging (MRI). The PRP group candidates were enrolled between October 2014 and January 2015, while the control group included patients who underwent ARCR between June 2005 and April 2014 without PRP application. The actual tear size was measured using a probe after debridement during the arthroscopic surgery. Exclusion criteria from the clinical trial were as follows: (1) presence of previous surgical history on the ipsilateral shoulder, (2) active infection and/or rheumatologic or autoimmune disease, (3) rotator cuff tear arthropathy, and (4) preoperative platelet count <150,000/μL. After screening for eligibility, candidate groups were informed about PRP and this clinical trial, and only patients who agreed to participate in the clinical trial via written informed consent were enrolled.

A total of 58 patients were enrolled and were divided into 2 groups randomly using a computer-generated randomization table: 29 patients received only intraoperative PRP augmentation (PRP-only group) and 29 patients received both intraoperative PRP augmentation and a PRP booster injection at 2 weeks postoperatively (PRP-booster group). To allow comparison of the effect of PRP itself, patients who underwent ARCR without any application of PRP were retrospectively enrolled as the control group. Propensity score matching (1:1) was performed retrospectively using variables such as age,[29] sex, osteoporosis, stiffness,[28] and tear size.[2]

Of the 58 randomized participants, 48 (24 patients each in the PRP-only and PRP-booster groups) completed radiologic follow-up at 1 year postoperatively and had a minimum of 2 years of postoperative follow-up data on functional outcomes. The final propensity score-matched control group consisted of 48 patients (Figure 1).

Rotator cuff healing was evaluated using MRI at 1 year postoperatively. A musculoskeletal radiologist with 15 years of experience who was unaware of the present study interpreted the MRI scans and further evaluated rotator cuff healing to the greater tuberosity. According to the

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Ethical approval for this study was obtained from Seoul National University Bundang Hospital (No. E-1405/250-004).

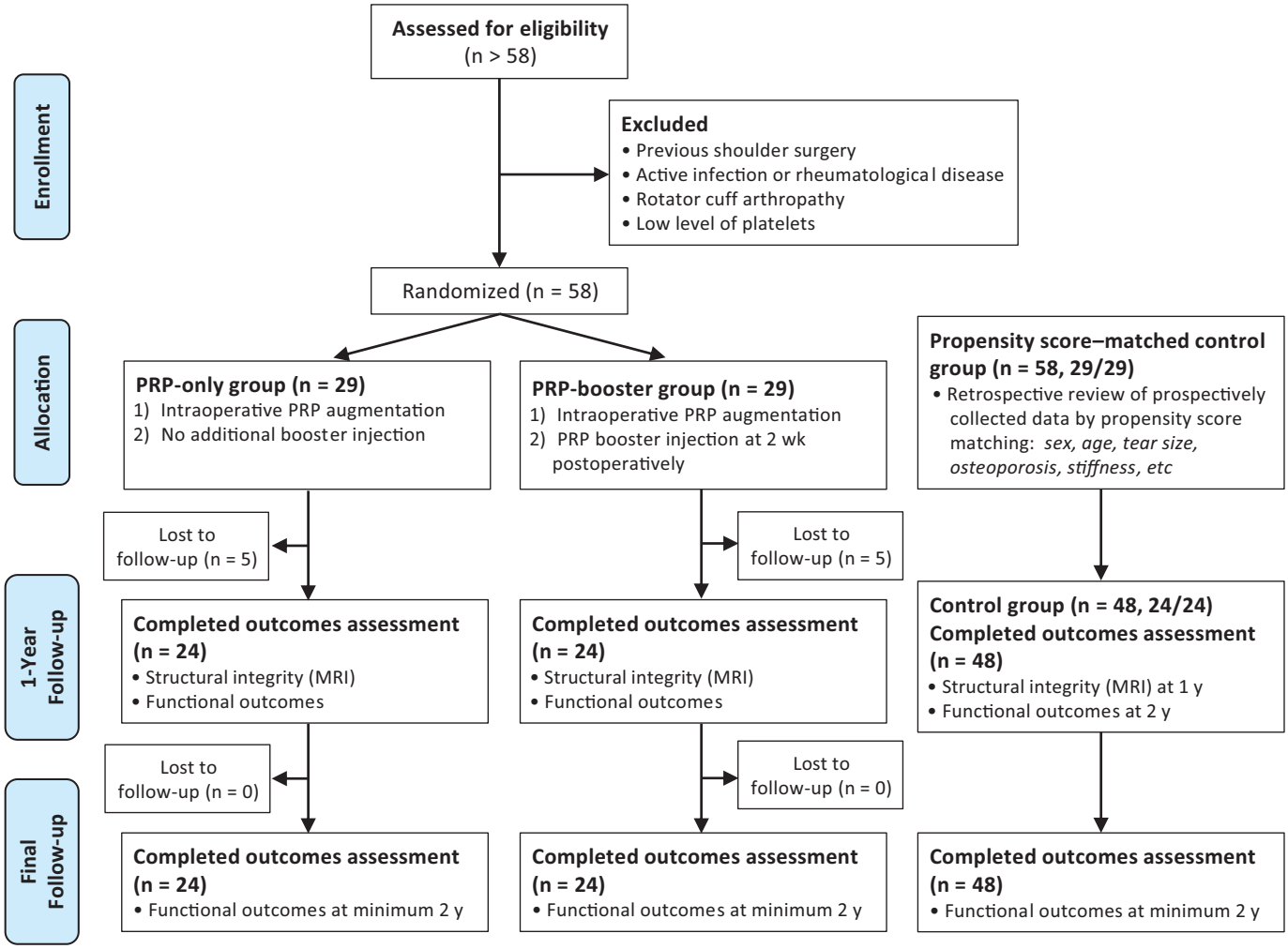


**Figure 1.** CONSORT (Consolidated Standards of Reporting Trials) flowchart. MRI, magnetic resonance imaging; PRP, platelet-rich plasma.

classification of Sugaya et al,[36] types I, II, and III are considered healed, and types IV and V are considered healing failure. In addition to the overall healing rate, the healing rate was compared according to tear size for rotator cuff healing as determined by a previous study[31]: $\leq$2 vs $>$2 cm. Clinical outcomes were evaluated using range of motion (ROM), visual analog scale (VAS) for pain and VAS for satisfaction, Constant score, American Shoulder and Elbow Surgeons (ASES) score, and Simple Shoulder Test score. Outcome evaluations were conducted preoperatively and at the annual follow-up by a clinical researcher who was blinded to the current study.

## Preparation of Autologous PRP

After induction of general anesthesia, at least 30 mL of whole venous blood was sampled from the peripheral limbs of all patients through use of 1 mL of anticoagulant citrate dextrose solution in a preloaded syringe. The anticoagulated blood was then transferred to a commercial kit (TriCell; RevMed), which was designed to produce leukocyte-rich PRP using double-spin centrifugation. The PRP was prepared using double-spin centrifugation. The first separating centrifugation (first spin) to separate the plasma layer was conducted at 1889*g* for 4 minutes. The separated top plasma layer then underwent a second condensation centrifugation (second spin) at 2009*g* for 3 minutes. Finally, 3 mL of PRP was collected, and the extracted PRP with 0.3 mL of 10% calcium gluconate loaded in a 5-mL syringe was used to produce a PRP gel (Figure 2).

## Surgical Procedures With the Application of PRP and Rehabilitation

All surgeries were performed by the senior author (J.H.O.) with patients in the lateral decubitus position under general anesthesia. After systemic glenohumeral joint and subacromial space exploration, the surgeon performed subacromial decompression to remove inflamed bursal tissue and acromioplasty confined to the anterolateral aspect of the acromion. The presence of superior labrum anterior to posterior (SLAP) lesions was recorded; however, no SLAP repairs

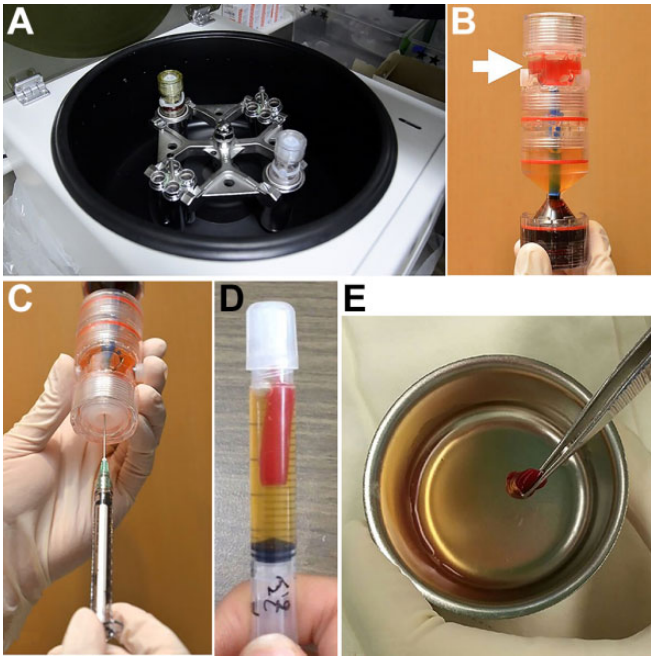


**Figure 2.** Preparation and activation of the platelet-rich plasma (PRP). (A) The first separating centrifugation was conducted at 1889*g* for 4 minutes, and the second was conducted at 2009*g* for 3 minutes. (B) After double-spin centrifugation, 3 mL of PRP (white arrow) was collected and used to produce PRP gel. (C) The extracted PRP with 0.3 mL of 10% calcium gluconate loaded in a 5-mL syringe was used to produce a PRP gel. (D) Gel-formed PRP within a 5-mL syringe. (E) The final form of the PRP gel.

were performed, as none of the patients had preoperative SLAP-related symptoms on physical examination. Distal clavicle resection was performed in patients who experienced symptomatic acromioclavicular arthritis, and biceps tenotomy or tenodesis was performed for symptomatic biceps tears involving >50% of the tendon according to the age and activity level of the patient. If the patient had a stiff shoulder, he or she underwent concomitant manipulation under anesthesia with an arthroscopic capsular release.

Rotator cuff repair was performed using the double-row suture bridge technique. 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. To enhance the healing of tendon to bone, the footprint was prepared using ring curette and rasp in all groups. After the medial row sutures were tied, the PRP gel was applied to the tendon-bone interface in a water arthroscopic setting through percutaneous injection without cannula. The PRP gel was delivered by the surgeon using a sterile surgical forceps and probe, which ensured that the PRP could be administered directly to the interface and would remain firmly between the bone and repaired rotator cuff. When the PRP gel was placed properly, the lateral row was secured using suture anchors. Finally, the PRP gel was interposed securely at the tendon-bone interface. We did not observe any dilution or washout effect using arthroscopic fluid lavage (Figure 3).

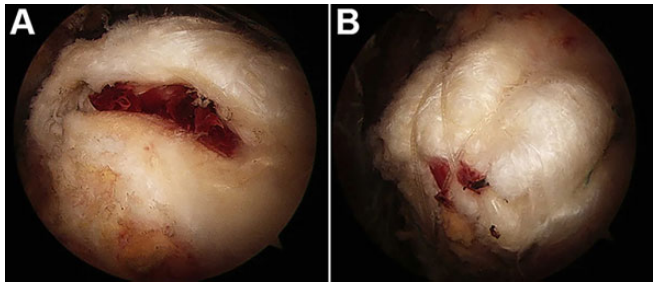


**Figure 3.** (A) Platelet-rich plasma (PRP) gel was applied to the tendon-bone interface after all medial-row sutures were tied. (B) When PRP gel was placed in the proper place, the lateral row of the double-row suture bridge was secured using suture anchors. The PRP gel was interposed securely at the tendon-bone interface.

For patients in the PRP-booster group, the additional PRP injection was performed under ultrasound guidance around the repair site at 2 weeks postoperatively. PRP preparation was carried out in the double-spin centrifugation, but calcium gluconate activation was not added, as it is not needed to make the gel. The same shoulder fellowship–trained orthopaedic surgeon applied 3 mL of PRP on and around the repair site under visualization using ultrasound. Needle placement was guided by identification of the echogenic suture material at the tendon repair site.

Immobilization after the surgical repair was maintained using an abduction brace for 5 to 6 weeks according to tear size.[28] Shrugging of both shoulders, active elbow flexion and extension, active forearm supination and pronation, and active hand and wrist motion were encouraged immediately after surgery. Active-assisted ROM exercises were allowed after patients were weaned from brace use. Muscle strengthening exercises were started at about 12 weeks, and sports activities were usually permitted at 6 months after surgery. All rehabilitation was supervised by the Department of Rehabilitation at Seoul National University Bundang Hospital.

### Statistical Analysis

The Kolmogorov-Smirnov normality test was conducted for continuous variables. Subsequently, an independent $t$ test or Mann-Whitney $U$ test was conducted according to the characteristics of the data distribution. The chi-square test or Fisher exact test was used for nominal variables. All statistical analyses except propensity score matching were conducted using the SPSS statistics software package (Version 19; IBM Corp); all tests were 2-sided, with a significance level of .05.

## RESULTS

### Patient Characteristics

The mean final follow-up period of the study participants was 51.9 ± 21.7 months (range, 24-100 months). No

TABLE 1
Preoperative Patient Characteristics and Intraoperative Findings Regarding Rotator Cuff Tears in the PRP and Control Groups[a]

| | | | | PRP Group | | |
|---|---|---|---|---|---|---|
| | Overall PRP Group (n = 48) | Control Group (n = 48) | *P* | PRP Only (n = 24) | PRP Booster (n = 24) | *P* |
| Age, y | 63.0 ± 9.9 | 63.3 ± 9.0 | .863 | 63.9 ± 8.0 | 62.1 ± 11.5 | .526 |
| Sex, male:female | 24:24 | 24:24 | >.999 | 10:14 | 14:10 | .513 |
| Osteoporosis | 10 (20.8) | 11 (22.9) | >.999 | 8 (33.3) | 4 (16.7) | .410 |
| Stiffness | 12 (25.0) | 13 (27.1) | >.999 | 8 (33.3) | 2 (8.3) | .108 |
| Tear size, mm | | | | | | |
| Anteroposterior | 23.3 ± 12.6 | 23.0 ± 14.8 | .573 | 21.8 ± 9.5 | 24.8 ± 15.2 | .418 |
| Mediolateral | 20.0 ± 9.1 | 20.6 ± 11.6 | .586 | 19.5 ± 8.5 | 20.3 ± 9.8 | .766 |
| Biceps lesion | 25 (52.1) | 25 (52.1) | >.999 | 11 (45.8) | 14 (58.3) | .386 |
| SLAP lesion | 16 (33.3) | 19 (39.6) | .525 | 5 (20.8) | 11 (45.8) | .066 |
| SLBC procedures | | | .859 | | | .741 |
| None | 21 (43.8) | 17 (35.4) | | 12 (50) | 9 (37.5) | |
| Debridement | 9 (18.8) | 11 (22.9) | | 3 (12.5) | 6 (25) | |
| Tenotomy | 10 (20.8) | 12 (25.0) | | 5 (20.8) | 5 (20.8) | |
| Tenodesis | 8 (16.7) | 8 (16.7) | | 4 (16.7) | 4 (16.7) | |
| Osteoarthritis | 5 (10.4) | 2 (4.2) | .435 | 1 (4.2) | 4 (16.7) | .156 |
| Follow-up time, mo | 53.5 ± 12.8 | 50.5 ± 28.0 | .508 | 50.1 ± 14.1 | 56.7 ± 10.5 | .071 |

[a]Data are expressed as mean ± SD or No. (%) unless otherwise noted. PRP, platelet-rich plasma; SLAP, superior labrum anterior to posterior lesion; SLBC, SLAP and long head of the biceps tendon pathologies.

TABLE 2
Healing Failure Rates in the PRP and Control Groups at 1 Year After Rotator Cuff Repair[a]

| | | | | PRP Group | | |
|---|---|---|---|---|---|---|
| | Overall PRP Group (n = 48) | Control Group (n = 48) | *P* | PRP Only (n = 24) | PRP Booster (n = 24) | *P* |
| All tears | 6:42 (12.5) | 14:34 (29.2) | **.038** | 2:22 (8.3) | 4:20 (16.7) | .383 |
| ≤2-cm tear | 2:15 (11.8) | 4:16 (20.0) | .498 | 1:8 (11.1) | 1:7 (12.5) | .929 |
| >2-cm tear | 4:27 (12.9) | 10:18 (35.7) | **.040** | 1:14 (6.7) | 3:13 (18.8) | .316 |

[a]Healing failure rates are expressed as ratios of failure and healing (percentages of failure). Shoulders classified as Sugaya types I, II, and III were considered healed, and types IV and V were considered healing failures.[36] Bolded *P* values indicate statistically significant difference between groups ($P < .05$). PRP, platelet-rich plasma.

differences were observed for preoperative characteristics and intraoperative findings, including tear size, biceps lesion, SLAP lesion, and glenohumeral osteoarthritis, which indicated that the randomization was well balanced (Table 1).

## Healing Failure Rate

All 96 study participants were available for MRI examination at 1 year postoperatively. The healing failure rate in the overall PRP group was significantly lower than that in the control group (12.5% vs 29.2%, respectively; $P = .038$). In patients whose tear size was >2 cm, the healing failure rate in the overall PRP group was also significantly lower than that in the control group (12.9% vs 35.7%; $P = .040$); however, this was not observed in patients whose tear size was ≤2 cm (11.8% vs 20.0%, respectively; $P = .498$). No significant difference was noted in the healing failure rates between the PRP-only and PRP-booster groups (8.3% vs 16.7%; $P = .383$) (Table 2).

## Functional Outcomes

No significant differences were noted in postoperative ROM or functional outcomes between the overall PRP group and the control group. The overall PRP group had lower VAS for pain scores compared with controls (0.5 ± 1.1 vs 1.3 ± 1.8; $P = .016$) and higher VAS for satisfaction scores (9.2 ± 1.2 vs 8.6 ± 1.7; $P = .023$) at the final follow-up; however, no statistical differences were found between the PRP-only and PRP-booster groups in functional outcomes (Table 3).

A subgroup analysis of functional outcomes according to healing failure was also conducted, and VAS for pain ($P = .004$), forward flexion ($P = .041$), Constant score ($P = .002$), ASES score ($P = .013$), and VAS for satisfaction ($P = .001$) were significantly better in the healed group than in the healing failure group (Table 4).

## DISCUSSION

The purpose of this study was to evaluate the efficacy of intraoperative PRP gel application between the tendon and

TABLE 3
Preoperative and Postoperative Functional Outcomes in the PRP and Control Groups[a]

| | | | | PRP Group | | |
|---|---|---|---|---|---|---|
| | Overall PRP Group (n = 48) | Control Group (n = 48) | *P* | PRP Only (n = 24) | PRP Booster (n = 24) | *P* |
| VAS for pain | | | | | | |
| Preoperative | 5.9 ± 2.3 | 6.6 ± 2.0 | .135 | 6.3 ± 2.1 | 5.6 ± 2.5 | .320 |
| Final follow-up | 0.5 ± 1.1 | 1.3 ± 1.8 | **.016** | 0.3 ± 0.8 | 0.8 ± 1.4 | .142 |
| *P* | **<.001** | **<.001** | | **<.001** | **<.001** | |
| VAS for satisfaction | | | | | | |
| Final follow-up | 9.2 ± 1.2 | 8.6 ± 1.7 | **.023** | 9.3 ± 1.3 | 9.1 ± 1.1 | .771 |
| Forward flexion, deg | | | | | | |
| Preoperative | 148.4 ± 21.7 | 141.3 ± 39.2 | .737 | 144.6 ± 23.1 | 152.3 ± 20.0 | .273 |
| Final follow-up | 160.0 ± 19.3 | 162.0 ± 13.5 | .854 | 160.8 ± 8.3 | 158.8 ± 26.3 | .178 |
| *P* | **.009** | **.001** | | **.006** | .320 | |
| External rotation, deg | | | | | | |
| Preoperative | 48.7 ± 15.8 | 52.0 ± 18.5 | .395 | 46.0 ± 15.5 | 51.3 ± 16.0 | .257 |
| Final follow-up | 69.2 ± 12.7 | 71.4 ± 18.6 | .261 | 67.1 ± 12.7 | 71.3 ± 12.6 | .260 |
| *P* | **<.001** | **<.001** | | **<.001** | **<.001** | |
| Internal rotation, vertebral level | | | | | | |
| Preoperative | T10.3 ± 2.8 | T9.8 ± 3.0 | .338 | T10.8 ± 3.0 | T9.7 ± 2.6 | .187 |
| Final follow-up | T8.5 ± 1.4 | T8.4 ± 1.8 | .860 | T8.5 ± 1.3 | T8.4 ± 1.5 | .678 |
| *P* | **<.001** | **.009** | | **.001** | **.019** | |
| Constant score | | | | | | |
| Preoperative | 51.8 ± 11.9 | 46.9 ± 20.4 | .359 | 48.4 ± 9.9 | 55.1 ± 12.9 | .052 |
| Final follow-up | 72.0 ± 6.1 | 69.9 ± 5.6 | .420 | 72.2 ± 3.3 | 71.3 ± 8.0 | .207 |
| *P* | **<.001** | **.017** | | **<.001** | **<.001** | |
| ASES score | | | | | | |
| Preoperative | 50.5 ± 19.9 | 44.8 ± 26.8 | .497 | 49.6 ± 19.9 | 51.5 ± 20.3 | .748 |
| Final follow-up | 95.2 ± 8.6 | 90.0 ± 8.5 | .060 | 97.6 ± 4.8 | 92.9 ± 10.9 | .148 |
| *P* | **<.001** | **.003** | | **<.001** | **<.001** | |
| SST score | | | | | | |
| Preoperative | 4.5 ± 3.3 | 3.6 ± 2.6 | .164 | 3.9 ± 3.2 | 5.1 ± 3.3 | .204 |
| Final follow-up | 10.9 ± 1.7 | 9.4 ± 2.4 | .185 | 11.2 ± 1.7 | 10.6 ± 1.8 | .128 |
| *P* | **<.001** | **.001** | | **<.001** | **<.001** | |

[a]Data are expressed as mean ± SD. Bolded *P* values indicate statistically significant difference between groups ($P < .05$). ASES, American Shoulder and Elbow Surgeons; PRP, platelet-rich plasma; SST, Simple Shoulder Test; T, thoracic vertebra; VAS, visual analog scale.

bone during ARCR and an ultrasound-guided PRP booster injection around the repair site at 2 weeks after surgery, using PRP that was prepared using the double-spin method activated via calcium without thrombin.[30,33] According to the current data, PRP was effective in rotator cuff healing compared with the control group, especially when the tear size was >2 cm. However, a booster injection of PRP did not improve rotator cuff healing. Furthermore, in terms of functional outcomes, we found that PRP injection could reduce pain and improve the patients' subjective satisfaction until at least 2 years after surgery. However, we found no significant improvement in functional outcomes between the PRP-only and PRP-booster groups.

PRP is a platelet concentrate that contains a 3- to 5-fold increase in growth factor concentrations and is expected to improve rotator cuff healing by releasing these growth factors at higher concentrations than physiologic levels.[9,39] Several animal studies have reported that PRP may aid in the regeneration of tendon tissue through collagen synthesis, vascularization, and tendon cell proliferation when PRP is incorporated at the site of the tendon-bone interface in the setting of operative repair.[1,22,23,34] However, despite the theoretical advantages, clinical results of PRP in human rotator cuff healing have varied, and previous meta-analyses have not concluded that PRP is effective in all rotator cuff repairs.[2,10,34] One of the reasons for such a difference might be the heterogeneity of the PRP that was used in each study.[15,19,21] No properly standardized PRP preparations or activation methods have been established,[15] but several experimental studies have been conducted on animals with regard to PRP preparation methods. For example, one animal study reported that an increase in platelet counts was observed after use of the double-centrifugation method compared with the single-centrifugation procedure while leukocytes were not concentrated.[35] Another study concluded that the double-centrifugation protocol resulted in higher platelet concentrations but was more likely to result in platelet morphologic changes.[25] Moreover, a study[30] involving 14 healthy participants found that PRP prepared using the double-spin method generally led to a higher concentration of platelets relative to the single-spin method.

Regarding the activation of PRP, the kinetics of growth factor release are varied according to each commercial

TABLE 4
Postoperative Clinical Outcomes According to Healing Failure[a]

| | Healed | Healing Failure | P |
|---|---|---|---|
| VAS for pain | 1.0 ± 1.9 | 2.4 ± 2.6 | **.004** |
| VAS for satisfaction | 8.7 ± 1.5 | 6.1 ± 3.5 | **.001** |
| Forward flexion, deg | 162.4 ± 12.4 | 150.9 ± 26.7 | **.041** |
| External rotation, deg | 68.1 ± 16.9 | 61.9 ± 19.2 | .176 |
| Internal rotation, vertebral level | T8.0 ± 2.5 | T8.5 ± 3.9 | .384 |
| Constant score | 68.9 ± 7.8 | 62.5 ± 8.2 | **.002** |
| ASES score | 89.4 ± 19.8 | 68.7 ± 33.7 | **.013** |
| SST score | 10.3 ± 2.9 | 7.9 ± 4.8 | .097 |

[a]Data are expressed as mean ± SD. Bolded *P* values indicate statistically significant difference between groups ($P < .05$). ASES, American Shoulder and Elbow Surgeons; SST, Simple Shoulder Test; T, thoracic vertebra; VAS, visual analog scale.

separation system.[3,19] As we know, platelet activation is essential for the release of growth factors, and most of these factors have short half-lives after release (from minutes to a few hours).[35] Thus, it is important to use the activated platelets at the proper time or find a way to sustain the concentration of growth factors to guarantee the clinical therapeutic efficacy of PRP. Calcium is most widely used for PRP activation due to its low cost, higher availability, and rare side effects, but doubts about its activation potential remain.[38] Previous studies have revealed that calcium-only activation without thrombin[15,33] has a significant effect on increasing overall cytokine release as well as sustaining the concentration of growth factors (over 7 days) using the double-spin PRP preparation method. Therefore, in this study, we focused on PRP preparation and activation using the double-spin centrifugation technique and calcium-only activation without thrombin to evaluate the clinical efficacy of these preparation and activation methods.

Another issue pertains to the delivery of PRP during ARCR. Although several previous systematic reviews and meta-analyses have questioned the effects of PRP in rotator cuff repair,[4,10,34] Salzman et al[34] mentioned the potential of PRP in specific situations: a solid PRP matrix,[5] which could avoid a washout effect occurring with arthroscopic fluid lavage, application of PRP at the tendon-bone interface, double-row repair,[14] and small- and/or medium-sized rotator cuff tears. Therefore, we applied the PRP gel to the tendon-bone interface during ARCR using the double-row suture bridge technique.

The timing of PRP application warrants discussion because healing of the rotator cuff continues 3 to 6 months after surgical repair.[40] Hence, it is crucial to determine the optimal timing for postoperative delivery of the PRP booster injection. Although most PRP applications for rotator cuff healing are performed during arthroscopic rotator cuff surgery, postoperative PRP application also has been used.[8,40] However, fewer studies have evaluated the efficacy of postoperative PRP application versus intraoperative application. Until now, PRP application protocols during rotator cuff surgery, including intraoperative administration as well as the postoperative booster injection, have varied, and there is insufficient literature on the delivery timing of postoperative PRP booster injections. In most previous PRP studies, PRP has been delivered at the time zero point of rotator cuff repair. However, it has been proposed that biologic augmentation of tendon repairs too early in the tendon healing process may be ineffective.[12] Moreover, intraoperative PRP injection may result in dilution.[32] To overcome this problem, a study was conducted to evaluate the effect of 2 consecutive PRP injections spaced over a week. Wang et al[40] reported the results of repeated application of PRP to the tendon repair site after double-row ARCR on postoperative days 7 and 14. However, postoperative PRP injections did not improve the healing failure rate at later follow-up points. Because some growth factors, such as transforming growth factor β1, have maximum expression effects at day 14 after augmentation, we decided that a booster injection at 2 weeks after surgery, together with a routine visit to the clinic, would be beneficial. However, we found that a postoperative PRP injection after rotator cuff repair was not effective in tendon healing regardless of tear size.

We found that PRP was effective in enhancing rotator cuff healing in the PRP group compared with the control group. The healing failure rate of the overall PRP group was significantly lower than that of the control group; however, subgroup analysis showed that this difference was not statistically significant for tear sizes ≤2 cm. Several previous meta-analyses and systematic reviews have reported healing rates according to tear size after the application of PRP in rotator cuff repair.[2,34,39,41] Some of those studies[2,34,39] suggested that PRP improved the healing rate in small- and/or medium-sized rotator cuff tears. The contradictory findings in the present study may be due to the correlation of healing with initial tear size,[28,29] which means that a lower possibility of healing failure is attributable to the small-sized tear itself. In other words, a small tear originally showed good healing, around 90%,[28,30] without PRP augmentation. However, a significantly higher failure rate (near 35%) was revealed in patients with a tear >2 cm,[6,30] which indicates that PRP augmentation plays a role in enhancing tendon healing, just as the current study showed that the healing failure rate was 12.9% in the PRP group and 35.7% in the control group.

The secondary aim of this study was to evaluate the functional outcomes of PRP augmentation at the final follow-up visit >24 months after surgery. Several studies have revealed that PRP application could reduce pain,[13,20] and another study showed the PRP application in terms of pain relief and functional outcome improvement.[13] In the present study, the VAS for pain scores decreased significantly, and VAS for satisfaction scores increased significantly in the PRP group; however, the functional outcomes did not present significant differences. These results were similar to those of previous studies.[2,10,34,41,42]

This study had several strengths. It was a prospective, randomized controlled study that directly compared the efficacy of intraoperative PRP gel application between the

tendon and bone during ARCR and a postoperative PRP booster injection. Furthermore, we compared the efficacy of intraoperative PRP augmentation with a control group that was selected using propensity score matching.

Nevertheless, there were several limitations. The sample size was relatively small for the subgroup analysis. Because the purpose of this study was to evaluate and compare the efficacy of PRP augmentation via a postoperative booster injection, we considered that a sufficient number of participants were enrolled to achieve this study objective. Moreover, the randomization to the PRP-only and PRP-booster groups was well-balanced, and propensity score matching to evaluate the efficacy of PRP augmentation itself was performed using the essential variables. Therefore, we believe that the bias based on the small sample size was relatively well controlled by the statistical methods.

Another limitation was that our design called for control group participants to be retrospectively enrolled in the same study period. However, during the PRP study period, propensity score matching resulted in a small number of control participants. To achieve a statistical power of 80% at a significance level of 5%, at least 48 participants were required to detect an MCID. Therefore, to include a sufficient number of control participants, we enrolled the control group in a different period of time. However, control group participants underwent exactly the same surgical technique performed by the same surgeon as did the PRP study group. Furthermore, preoperative characteristics and intraoperative findings of PRP and control group participants showed no statistical difference, which means they were well balanced.

Concomitant shoulder lesions were not excluded in our study, which may be another limitation, because they could have affected functional outcomes. As well, there was no blinding of patients in the PRP group. Thus, subjective outcomes (eg, VAS for pain or satisfaction scores) might have been more at risk of bias from lack of blinding. However, the VAS for pain and satisfaction scores were obtained by an independent researcher who was not related to this research. In addition, future investigators should consider matching factors that could affect PRP efficacy in rotator cuff healing, such as smoking and diabetes. If we had excluded patients with concomitant shoulder disease (eg, acromioclavicular arthropathy, subacromial impingement), it would have been difficult to enroll enough participants. In addition, we could not control for all other concomitant lesions in this prospective study; for example, subacromial impingement is a common symptom of rotator cuff tear. However, we routinely examine patients for biceps tendinopathy, SLAP lesion, and glenohumeral osteoarthritis during diagnostic arthroscopy because we believe these factors could influence postoperative functional outcomes. Our data analysis found no significant difference between the study group and control group, which means these factors are unlikely to have caused statistical bias in our study.

Although the intraoperative PRP augmentation and postoperative PRP booster injections shared the same preparation, the lack of calcium activation in PRP booster delivery may preclude a comparison of their efficacy regarding rotator cuff healing. However, doubts remain about the activation potential of calcium; we were also concerned that patients would experience shoulder stiffness caused by a calcium-activated gel-type PRP booster injection because it was delivered at the tendon repair site under the subacromial space at 2 weeks after surgery, when patients were still using the abduction brace. Therefore, we did not use calcium gluconate activation for the PRP booster injection. In addition, intraoperative PRP gel was applied to the tendon-bone interface and interposed securely using a double-row suture bridge technique, whereas the postoperative PRP booster injection was applied on and around the repair site in the subacromial space. This method was used because it is almost impossible to deliver an ultrasound-guided PRP booster injection at the tendon-bone interface in the clinic after repair has been performed.

Last, it is known that PRP gels under different preparations and activation protocols may show significant differences in healing effect. In addition, we did not characterize PRP samples separately in this research. However, according to a previous study of PRP preparations and activation protocols, PRP prepared using the double-spin method generally leads to a higher concentration of platelets relative to the single-spin method.[30] Another study demonstrated that only calcium used for activation without thrombin had a significant effect on increasing the overall cytokine release and sustaining the concentration of growth factors (over 7 days) using the double-spin PRP preparation method.[33] Therefore, in this study, we focused on PRP preparation and activation using the double-spin centrifugation technique and calcium-only activation without thrombin in order to evaluate the clinical efficacy of these preparation and activation methods. Therefore, the protocol used in this study requires further testing, including PRP characterization and comparison of various PRP preparations.

## CONCLUSION

Intraoperative PRP augmentation during ARCR demonstrated superior results in anatomic healing in rotator cuff tears >2 cm as well as a reduction in pain and an increase in subjective satisfaction. However, a PRP booster injection 2 weeks after surgical repair provided no additional benefit to the tendon integrity or functional recovery. These findings provide evidence of clinical effectiveness to support the use of PRP augmentation during ARCR of tears >2 cm without a booster injection to enhance tendon healing under ARCR.

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