Efficacy of platelet-rich plasma in arthroscopic repair of full-thickness rotator cuff tears: a meta-analysis

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Background: The use of platelet-rich plasma (PRP) is an innovative clinical therapy, especially in arthroscopic rotator cuff repair. The purpose of this study was to compare the clinical improvement and tendon-to-bone healing with and without PRP therapy in arthroscopic rotator cuff repair.

Methods: A systematic search was done in the major medical databases to evaluate the studies using PRP therapy (PRP+) or with no PRP (PRP-/) for the treatment of patients with rotator cuff tears. We reviewed clinical scores such as the Constant score, the American Shoulder and Elbow Surgeons score, the University of California at Los Angeles (UCLA) Shoulder Rating Scale, the Simple Shoulder Test, and the failure-to-heal rate by magnetic resonance imaging between PRP+ and PRP- groups.

Results: Five studies included in this review were used for a meta-analysis based on data availability. There were no statistically significant differences between PRP+ and PRP- groups for overall outcome scores (P > .05). However, the PRP+ group exhibited better healing rates postoperatively than the PRP- group (P = .03) in small/moderate full-thickness tears.

Conclusion: The use of PRP therapy in full-thickness rotator cuff repairs showed no statistically significant difference compared with no PRP therapy in clinical outcome scores, but the failure-to-heal rate was significantly decreased when PRP was used for treatment of small-to-moderately sized tears. PRP therapy may improve tendon-to-bone healing in patients with small or moderate rotator cuff tears.

Level of evidence: Level I, Meta-analysis.

Keywords: Rotator cuff repair; platelet-rich plasma; tendon-to-bone healing; meta-analysis; biological therapy
postoperatively may have better overhead function. Although transosseous suture-bridge techniques have been developed to improve the mechanical properties of the rotator cuff, the healing rate was still less than satisfactory, possibly as a result of the abnormal regeneration of tissue at the tendon-to-bone interface that was replaced with fibrous scar tissue. Some researchers have attempted to promote tendon-to-bone healing with the use of biological strategies, such as growth factors, stem cells, and biomaterials.

Platelet-rich plasma (PRP) has been defined as “a sample of autologous blood with concentrations of platelets above baseline values” and was first used in plastic surgery in the 1990s. Compared with mesenchymal stem cells (MSCs), it is simpler to isolate PRP from a wide variety of tissue sources. PRP is rich in several growth factors and cytokines, such as platelet-derived growth factors, transformation growth factor-β, and insulin-like growth factor, which play key roles in hemostasis, construction of new connective tissue, and revascularization, and might improve tendon-to-bone healing. This is a retrospective meta-analysis of the use of PRP in arthroscopic rotator cuff repairs.

Materials and methods

A literature search was conducted from January 1990 to January 2015 in the electronic databases of PubMed, Web of Science (SCI-EXPANDED/SSCI/ADI/SCI), and EMBASE with the following parameters: “platelet-rich plasma” or “platelet gel” or “platelet plasma” or “PRP” combined with the keywords “rotator cuff tear” or “shoulder” or “tendon.”

The retrieved articles were initially screened for relevance by the title and abstract. Inclusion criteria were (1) Level I evidence studies of PRP use in repairs compared with repairs without PRP; (2) adequate statistical power to detect differences with 95% confidence intervals (CIs) and follow-up; (3) adequate statistical power to detect differences with 95% confidence intervals (CIs) and follow-up; (4) full-thickness rotator cuff tears; and (4) arthroscopic rotator cuff repairs. Exclusion criteria were case control studies, case reports, and studies without abstracts, and patients with partial-thickness rotator cuff tears, a history of previous injury or surgery to the same shoulder, postoperative infection, arthrofibrosis, rheumatoid arthritis, inadequate follow-up, and thrombocytopenia.

The full text of the remaining articles was obtained and further reviewed for quality by 2 separate observers, based on the Cochrane Handbook for Systematic Reviews of Interventions. To determine the possibility of bias, we examined selection bias, performance bias, incomplete attrition bias, detection bias, and publication bias. An additional quantification of the degree of possible bias was performed by the modified Coleman Methodology Score. Level of evidence (LOE) was determined for all included studies (as given at http://handbook.cochrane.org/). After this evaluation, articles were selected on the basis of the risk of bias, modified Coleman score, and LOE to answer our clinical research question.

Data were collected from the remaining high-quality articles that were all Level I studies with a high modified Coleman score (>80), including authors, number of patients, mean age, method of preparation (focused on type of preparation, blood volume, final PRP concentration, activating agent, and site of application), and outcomes including the Constant score, the American Shoulder and Elbow Surgeons (ASES) score, the UCLA Shoulder Rating Scale, the Simple Shoulder Test (SST), and magnetic resonance imaging (MRI). The Constant, ASES, UCLA, SST, and MRI were compared approximately 12 months postoperatively. Rotator cuff integrity was classified as intact or return.

Statistical analysis was performed using Review Manager 5.3 (Cochrane Collaboration, Nordic Cochrane Centre, Copenhagen, Denmark). Continuous variables were analyzed using the weighted mean difference, and categoric variables were assessed using relative risks. P < .05 was considered to be statistically significant, and 95% CIs were reported. Homogeneity was tested by the Q statistic (significance level at P < .1) and the I² statistic (significance level at I² > 50%). A random-effects model was used if the Q or I² value was statistically significant; otherwise, a fixed-effects model was used.

Results

The literature search identified 207 relevant articles. The titles of these articles were carefully screened, and 167 were excluded for not investigating the topic. After application of inclusion and exclusion criteria, 35 articles were excluded (13 laboratory or animal studies, 8 reviews and meta-analyses, 2 case reports, and 12 with Level II, III, or IV evidence), leaving 5 selected articles for analysis. The flow diagram is shown in Fig. 1. All studies involved patients with arthroscopic rotator cuff repairs, clinical outcome scores, and healing rates reported with at least 12 months of follow-up. The quality of included studies was determined on the risk of bias, including selection, performance, attrition, detection, and reporting bias, and Coleman score (Table I). The funnel plots demonstrated no visual evidence of publication bias (Fig. 2). All included studies were randomized controlled trials with a high level of methodologic quality in which 303 patients were enrolled (150 for PRP and 153 for control). The characteristics of the included studies are summarized in Table II.

There was no evidence indicating a difference in pooled clinical outcomes between the PRP group (PRP+) and the control group (PRP−) for the Constant score (0.70 [95% CI, −1.62 to 3.03], P = .55, I² = 0%; Fig. 3), the UCLA score (0.36 [95% CI, −1.48 to 2.19], P = .70, I² = 60%; Fig. 4), SST (0.49 [95% CI, −0.11 to 1.09], P = .11, I² = 0%; Fig. 5), and the ASES score (0.91 [95% CI, −3.72 to 5.54], P = .70, I² = 0%; Fig. 6) with no significant heterogeneity. However, the pooled outcome of overall rotator cuff failure-to-heal rate in PRP+ was significant lower, with no heterogeneity (0.05 [95% CI, 0.31-0.83], P = .007, I² = 0; Fig. 7), compared with PRP−. Furthermore, based on the initial tear size, subgroups of mild-to-moderate and severe-to-massive tear size were analyzed.
The failure-to-heal rate was significantly lower in the PRP+ group (0.35 [95% CI, 0.14-0.90], \( P = .03, I^2 = 0\% \); Fig. 8) in mild-to-moderate tears, but there was no difference in severe-to-massive tears (0.64 [95% CI, 0.15-2.79], \( P = .55, I^2 = 88\% \); Fig. 9).

**Discussion**

This meta-analysis of Level I studies looked at the efficacy of PRP therapy in arthroscopic rotator cuff repairs. A lower failure-to-heal rate was found in patients using PRP with small and moderately sized tears compared with no PRP treatment at 1 year postoperatively, although there was no difference in clinical outcomes.
PRP has been currently investigated for its biologic effects on the human rotator cuff. Sadoghi et al. applied PRP to human rotator cuff fibroblasts and noted a significant effect on fibroblast proliferation and rotator cuff activity. Jo et al. demonstrated the efficiency of PRP on rotator cuff cell proliferation from a genetic standpoint. Furthermore, some animal studies have shown beneficial effects on the initial stage of rotator cuff tendon-to-bone healing with the application of PRP. However, compared with no PRP treatment, this meta-analysis found no superiority in clinical outcomes with PRP application. Several clinical factors affect rotator cuff healing in the PRP group. First, clinical scores were good in patients whose arthroscopically repaired rotator cuff tears failed to

### Table II

<table>
<thead>
<tr>
<th>First author</th>
<th>Design</th>
<th>Patients (No.)</th>
<th>Mean age (y)</th>
<th>Procedure</th>
<th>Applied site</th>
<th>Follow-up (y)</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randelli</td>
<td>Double-blind RCT</td>
<td>PRP: 26 Control: 27</td>
<td>61.6</td>
<td>Arthroscopic, single-row technique</td>
<td>Bone–tendon interface</td>
<td>2</td>
<td>Constant score, UCLA, SST, tendon integrity</td>
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<tr>
<td>Weber</td>
<td>Double-blind RCT</td>
<td>PRP: 30 Control: 30</td>
<td>59.7</td>
<td>Arthroscopic, single-row technique</td>
<td>Bone–tendon interface</td>
<td>1</td>
<td>UCLA, ASES, tendon integrity</td>
</tr>
<tr>
<td>Castricini</td>
<td>RCT</td>
<td>PRP: 43 Control: 45</td>
<td>55.2</td>
<td>Arthroscopic, double-row technique</td>
<td>Bone–tendon interface</td>
<td>2</td>
<td>Constant score, tendon integrity</td>
</tr>
<tr>
<td>Jo</td>
<td>Single-blind RCT</td>
<td>PRP: 24 Control: 24</td>
<td>64.2</td>
<td>Arthroscopic, double-row technique</td>
<td>Bone–tendon interface</td>
<td>1</td>
<td>Constant scale, UCLA, SST, ASES, tendon integrity</td>
</tr>
<tr>
<td>Malavolta</td>
<td>Double-blind RCT</td>
<td>PRP: 27 Control: 27</td>
<td>55.3</td>
<td>Arthroscopic, double-row technique</td>
<td>Bone–tendon interface</td>
<td>2</td>
<td>Constant scale, UCLA, tendon integrity</td>
</tr>
</tbody>
</table>

ASES, American Shoulder and Elbow Surgeons; PRP, platelet-rich plasma; RCT, randomized controlled trial; SST, Simple Shoulder Test; UCLA, University of California Los Angeles.

By Z.Cai et al., YZ Cai et al.
Figure 5  Difference in SST scale. CI, confidence interval; IV, inverse variance; PRP, platelet-rich plasma; SD, standard deviation. The solid squares indicate the mean difference and are proportional to the weights used in the meta-analysis. The solid vertical line indicates no effect. The horizontal lines represent the 95% CI. The diamond indicates the weighted mean difference, and the lateral tips of the diamond indicate the associated 95% CI.

Figure 6  Difference in ASES scale. CI, confidence interval; IV, inverse variance; PRP, platelet-rich plasma; SD, standard deviation. The solid squares indicate the mean difference and are proportional to the weights used in the meta-analysis. The solid vertical line indicates no effect. The horizontal lines represent the 95% CI. The diamond indicates the weighted mean difference, and the lateral tips of the diamond indicate the associated 95% CI.

Figure 7  Difference in the rotator cuff failure-to-heal rate. CI, confidence interval; M-H, Mantel-Haenszel; PRP, platelet-rich plasma. The solid squares indicate the mean difference and are proportional to the weights used in the meta-analysis. The solid vertical line indicates no effect. The horizontal lines represent the 95% CI. The diamond indicates the weighted mean difference, and the lateral tips of the diamond indicate the associated 95% CI.

Figure 8  Difference in the rotator cuff failure-to-heal rate of minor-to-moderately sized rotator cuff tear. CI, confidence interval; M-H, Mantel-Haenszel; PRP, platelet-rich plasma. The solid squares indicate the mean difference and are proportional to the weights used in the meta-analysis. The solid vertical line indicates no effect. The horizontal lines represent the 95% CI. The diamond indicates the weighted mean difference, and the lateral tips of the diamond indicate the associated 95% CI.
Thus, although the healing rate in small/moderate full-thickness tears in the PRP+ group was higher, clinical outcomes showed no statistically significant differences. One of the most difficult problems with PRP therapy is that there are no standard preparation protocols, and different concentration of growth factors exist in various PRP products. This meta-analysis reported on nonhomogeneous methods for PRP preparation and applied site (Table III). Although approximately 1000–10^3 platelets/μL is clinically efficacious, and calcium chloride could be used as a convenient activating agent for PRP, this may not be the best case for arthroscopic rotator cuff repair. Irrigation during surgery and swelling after surgery may also reduce the effectiveness of PRP. Although this analysis looked only at the use of 1-step PRP applications, Wang et al reported no differences in clinical outcomes in patients who received multiple weekly injections of PRP after arthroscopic rotator cuff repair compared with those who received only 1 PRP injection.

This meta-analysis demonstrated that PRP was effective in the healing of mild-to-moderate rotator cuff tears but had no efficacy to promote healing of large-to-massive tears. Perhaps PRP therapy alone, without stem cells, could not affect tendon-to-bone healing in large-to-massive rotator cuff tears.

Based on the fact that microfracture could release bone marrow-derived cells, Mazzocca et al reported that MSCs arising from the holes after microfracture may promote better histologic healing of repaired tendons. Furthermore, Osti et al and Hernigou et al showed a significant improvement in healing rate in MSC-treated patients. In addition, some basic and clinical studies investigated that PRP could stimulate local osteogenic cells and promote MSCs proliferation, which was effective in the treatment of delayed union or nonunion.

As further investigational studies are done with PRP, so too will the demand for its clinical use increase. PRP is a whole-blood fraction that can be simply isolated with a simple device, which suggests that the preparation is less expensive than other biological factors such as MSCs. Gosens et al compared the costs between PRP and corticosteroid in the treatment of lateral epicondylitis and reported that PRP treatment cost approximately twice as much as corticosteroid treatment but just half that of débridement; however, PRP was

### Table III Platelet-rich plasma preparation protocols

<table>
<thead>
<tr>
<th>First author</th>
<th>PRP system</th>
<th>Whole blood volume (mL)</th>
<th>Centrifugal time (min)</th>
<th>Final PRP volume (mL)</th>
<th>Obtained product</th>
<th>Platelet concentration (x 10^3/μL)</th>
<th>Leukocytes</th>
<th>Activating Agent</th>
<th>Application volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randelli28</td>
<td>GPS II</td>
<td>54</td>
<td>15</td>
<td>6</td>
<td>PRP</td>
<td>780</td>
<td>No</td>
<td>10% calcium chloride</td>
<td>6-mL injection volume</td>
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<tr>
<td>Weber37</td>
<td>Cascade</td>
<td>10</td>
<td>5</td>
<td>3.5</td>
<td>PRFM clot</td>
<td>301</td>
<td>No</td>
<td>Calcium</td>
<td>1 x 1 mL</td>
</tr>
<tr>
<td>Castricini6</td>
<td>Cascade</td>
<td>52</td>
<td>17</td>
<td>6</td>
<td>PRP matrix</td>
<td>780</td>
<td>No</td>
<td>Calcium chloride</td>
<td>1 x 1 mL</td>
</tr>
<tr>
<td>Jo20</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>PRP gel</td>
<td>1000</td>
<td>No</td>
<td>10% calcium gluconate</td>
<td>3 x 3 mL</td>
</tr>
<tr>
<td>Malavolta22</td>
<td>–</td>
<td>400</td>
<td>15</td>
<td>40</td>
<td>PRP</td>
<td>–</td>
<td>No</td>
<td>10% calcium chloride</td>
<td>10-mL injection volume</td>
</tr>
</tbody>
</table>

Cascade, MTF Sports Medicine, Edison, NJ, USA; GPS II, Biomet Biologics, LLC, Warsaw, IN, USA; PRFM, platelet-rich fibrin matrix; PRP, platelet-rich plasma.

* COBE Spectra LRS Turbo, Cardian BCT, Lakewood, CO, USA.

Figure 9 Difference in the rotator cuff failure-to-heal rate of severe-to-massively sized rotator cuff tear. CI, confidence interval; M–H, Mantel-Haenszel; PRP, platelet-rich plasma. The solid squares indicate the mean difference and are proportional to the weights used in the meta-analysis. The solid vertical line indicates no effect. The horizontal lines represent the 95% CI. The diamond indicates the weighted mean difference, and the lateral tips of the diamond indicate the associated 95% CI.
more cost-effective and reliable than corticosteroid treatment at a 2-year follow-up. Another study\textsuperscript{11} concluded that PRP gel was less expensive than other treatments in managing non-healing diabetic foot ulcers.

The limitations of the present study are: first, we did not investigate the clinical scores and healing rate at short-term follow-up, although PRP is considered to accelerate revascularization and the healing process in the early phase of tendon healing; second, we included Level I studies to enhance the power of our analysis, which may have induced reporting bias to the results; and third, the clinical heterogeneity of the included studies was high. Different studies used different surgical techniques (single-row and double-row repair), and tear size varied from small to large. In addition, different PRP products and arbitrary volume of PRP were used among studies.

**Conclusion**

PRP therapy in full-thickness rotator cuff repair showed no statistically significant difference compared with no PRP therapy in clinical outcomes; however, tendon-to-bone healing rates were better in patients with small and moderately sized tears. Further, randomized controlled studies with PRP, with larger numbers of patients, may eventually show enhanced clinical outcomes based on better healing rates.

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