Does Autologous Leukocyte-Platelet–Rich Plasma Improve Tendon Healing in Arthroscopic Repair of Large or Massive Rotator Cuff Tears?

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Purpose: To evaluate the clinical and magnetic resonance imaging (MRI) outcome of arthroscopic rotator cuff repair with the use of leukocyte-platelet–rich plasma (L-PRP) in patients with large or massive rotator cuff tears. Methods: A comparative cohort of patients with large or massive rotator cuff tears undergoing arthroscopic repair was studied. Two consecutive groups of patients were included: rotator cuff repairs with L-PRP injection (group 1, n = 35) and rotator cuff repairs without L-PRP injection (group 2, n = 35). A double-row cross-suture cuff repair was performed by a single surgeon with the same rehabilitation protocol. Patients were clinically evaluated with the Constant score; Simple Shoulder Test score; University of California, Los Angeles (UCLA) score; and strength measurements by use of a handheld dynamometer. Rotator cuff healing was evaluated by postoperative MRI using the Sugaya classification (type 1 to type 5).

Results: We prospectively evaluated the 2 groups at a minimum 2-year follow-up. The results did not show differences in cuff healing between the 2 groups (P = .16). The size of recurrent tears (type 4 v type 5), however, was significantly smaller in group 1 (P = .008). There was no statistically significant difference in the recurrent tear rate (types 4 and 5) between the 2 groups (P = .65). There was no significant difference between group 1 and group 2 in terms of University of California, Los Angeles score (29.1 and 30.3, respectively; P = .90); Simple Shoulder Test score (9.9 and 10.2, respectively; P = .94); Constant score (77.3 and 78.1, respectively; P = .82); and strength (7.5 and 7.0, respectively; P = .51).

Conclusions: In our study the use of autologous L-PRP did not improve the quality of tendon healing in patients undergoing arthroscopic repair of large or massive rotator cuff tears based on postoperative MRI evaluation. The only significant advantage was that the L-PRP patients had smaller iterative tears. However, the functional outcome was similar in the 2 groups of patients. Level of Evidence: Level III, case-control study.

Arthroscopic repair of massive rotator cuff tears is associated with less favorable clinical results and a higher retear rate than repair of smaller tears, with structural failure in up to 90% at 1 and 2 years postoperatively.1–4 One biological therapeutic approach to enhance healing of repaired cuff tears is the use of autologous growth factors. The degranulation of the alpha granules in the platelets releases many different growth factors.

Therefore platelet-rich plasma (PRP) has gained popularity in many fields, such as wound healing5 and sports medicine6,7 especially to increase tendon healing.8 The platelets release different growth factors: platelet-derived growth factor (PDGF), transforming growth factor β, vascular endothelial growth factor (VEGF), epithelial growth factor, hepatocyte growth factor, and insulin-like growth factor. These growth factors are believed to stimulate tendon healing through cell regeneration, collagen regeneration, and well-ordered angiogenesis.8,9

Autologous growth factors are delivered locally in the form of PRP, and the ability of these growth factors to augment cuff tear healing is currently under investigation. Barber et al.10 and Randelli et al.11 found improved healing of cuff tears augmented with PRP, whereas Chaahal et al.12 stated in a systematic review that PRP does not have an effect on the overall retear rate after arthroscopic rotator cuff repair.
The purpose of this study was to evaluate the clinical and magnetic resonance imaging (MRI) results of arthroscopic rotator cuff repair with the use of leukocyte-platelet–rich plasma (L-PRP) in patients with large or massive posterosuperior rotator cuff tears. Our hypothesis was that the injection of L-PRP during large or massive cuff tear repair would result in improved tendon healing and better clinical outcomes.

Methods

The inclusion criteria were as follows: the presence of a reparable large or massive full-thickness posterosuperior rotator cuff tear according to the Codman classification, with no previous surgery on the shoulder in question, no degenerative arthritis of the glenohumeral joint, no autoimmune or rheumatologic disease, and no sign of adhesive capsulitis or shoulder instability.

We excluded patients with a partial-thickness tear, a small to medium full-thickness tear, an irreparable tear, or a full-thickness tear with extension anteriorly to include more than the subscapularis tendon. Patients with thrombocytopenia or blood dyscrasia were also excluded.

Seventy patients who presented to our hospital from June 2008 through June 2010 to undergo arthroscopic repair of large or massive rotator cuff tears met our inclusion criteria and were prospectively enrolled in our study. All were diagnosed with full-thickness rotator cuff tears based on both physical examination and preoperative MRI. MRI scans were performed at a median of 19 days (range, 9 to 40 days) before the patients’ inclusion. Fatty degeneration of the rotator cuff muscles was documented on MRI and classified as described by Goutallier et al. and Fuchs et al. (grade 0, no fatty infiltration; grade 1, some fatty streaks; grade 2, more muscle than fat; grade 3, as much muscle as fat; or grade 4, less muscle than fat).

The patients were divided into 2 consecutive groups: 35 patients in whom repairs were augmented with autologous L-PRP injection (group 1) and 35 patients without L-PRP injection (group 2). The patients were not blinded. The PRP group was treated first, and we explained to these patients that they would be included in a study to evaluate the effect of PRP augmentation on cuff tear repair. We explained to the patients in the second group that they would receive the conventional treatment for cuff tears.

Each patient’s suitability for inclusion was confirmed once the dimension of the rotator cuff tear had been verified at the time of arthroscopy. The institutional review board of our center approved the study, and each patient signed a detailed informed-consent form.

Surgical Procedure

The surgical procedure was performed with the patient under general anesthesia with an interscalene block.

Fig 1. Final arthroscopic view of repaired cuff tear.

PRP Preparation

Autologous L-PRP Preparation. L-PRP was obtained by use of the GPS III Platelet Concentration System (Biomet Biologics, Warsaw, IN) per the instructions for use. With the patient under anesthesia, 54 mL of blood was obtained from a venous puncture and mixed with 6 mL of anticoagulant citrate dextrose formula A. The 60 mL of anticoagulated blood was put into a specially designed disposable and centrifuged for 15 minutes at 3,220 rpm in a dedicated centrifuge (model 755VES 230V; The Drucker Company, Philipsburg, PA). After centrifugation, the concentrated platelets, in between the 2 buoys, were resuspended to form 6 mL of L-PRP, which was stored in a dedicated sterile syringe until use.

Autologous Thrombin Preparation. Autologous thrombin was prepared by use of the Clotalyst Autologous Clotting Factor System (Biomet Biologics). Eleven milliliters of the patient’s blood was obtained by venipuncture at the same time as the blood for the L-PRP and was mixed with 1 mL of anticoagulant citrate dextrose formula A. Four milliliters of the Clotalyst reagent (Thromogenesis, Rancho Cordova, CA) was put into the Clotalyst disposable, followed by 12 mL of the anticoagulated blood. The Clotalyst disposable was incubated in the Clotalyst heater (Biomet Biologics) at 25°C for 20 to 25 minutes. The Clotalyst disposable was then centrifuged for 5 minutes at 3,200 rpm in a dedicated centrifuge (model 755VES 230V). After centrifugation, the autologous thrombin was aspirated and stored in a dedicated sterile syringe until use (Fig 1).

Surgical Technique

Cuff repair was conducted with the patient in the beach-chair position with the usual arthroscopic materials (knot pusher, cuff-penetrating graspers) and with BioZip bioabsorbable anchors double loaded with Force Fiber ultrahigh–molecular weight polyethylene–containing sutures (Stryker, Kalamazoo, MI).
The surgeon measured the tear size in the anteroposterior dimension using a calibrated probe introduced through the posterior portal while viewing from the lateral portal. An arthroscopic double-row cross-suture rotator cuff repair was performed in all cases by the same surgeon according to a previously described technique. In brief, this technique consists of a “cross” and “bridge” fixation using standard suture anchors. For the lateral row, we used two 6.5-mm anchors placed 2 cm below the edge of the greater tuberosity, with a 2-cm distance between the anchors. For the medial-row anchors, we used two 5-mm anchors placed just lateral to the bone-cartilage junction in alignment with the 6.5-mm lateral anchors. Four anchors were used in all cases.

Arthroscopic acromioplasty was carried out in every patient, and the distal clavicle was resected if the patient had a symptomatic, degenerative acromioclavicular joint preoperatively. Biceps tears and instability were treated with either tenodesis or tenotomy.

The repair was completed in all cases. Regarding the cuff tear size, a tear measuring greater than 5 cm was found in 8 patients in group 1 and 6 patients in group 2, without a significant difference between the groups (P = .73).

**Surgical Application of PRP**

At the end of the arthroscopic procedure, the inflow cannula was closed and the arthroscopic fluid carefully aspirated through the outflow cannula, producing a dry subacromial space. A final L-PRP volume of 6 mL was obtained by the adopted protocol. By use of the lateral portal, the spray applicator kit loaded with syringes of L-PRP and autologous thrombin was positioned through the repaired rotator cuff (Figs 2 and 3). The blood products were then slowly injected and uniformly applied. A dry arthroscopic check was performed to evaluate clot formation (Fig 4).

In the non-PRP patients, dry arthroscopy was performed in the same manner, without any injection.

**Postoperative Rehabilitation Protocol**

All patients followed the same postoperative protocol. They were supported in a sling, and pendulum exercises and relaxation of the muscles around the shoulder girdle were initiated on the day after surgery with the assistance of a physical therapist. Passive shoulder motion was initiated 5 days after surgery. The sling was removed 3 weeks postoperatively, and active-assisted motion was started at that time. Full active shoulder motion was allowed at 6 to 8 weeks postoperatively, and strengthening exercises were initiated at 3 months. Full return to sports and heavy labor was allowed at 6 months according to the individual’s functional recovery.
The clinical postoperative follow-up was performed at 3 weeks and 3, 6, 12, and 24 months. The integrity of the repair was evaluated with MRI.

**MRI Evaluation of Cuff Integrity**

The primary outcome was tendon healing evaluated by MRI (1.5 T) in all patients. MRI scans were acquired 6 months after repair. All MRI studies were evaluated by 1 independent musculoskeletal radiologist with extensive experience in interpretation of shoulder MRI studies. He was blinded to the patient’s treatment assignment and not involved in the clinical evaluation. The images were used for structural and qualitative assessment of the rotator cuff, and repair integrity was determined according to the classification of Sugaya et al.17 This classification distinguishes 5 repair categories with the use of oblique coronal, oblique sagittal, and transverse T2-weighted images. Type 1 indicates a repaired rotator cuff that has sufficient thickness with homogeneously low intensity on each image; type 2, sufficient thickness with a partial high-intensity area; type 3, insufficient thickness without discontinuity; type 4, presence of a minor discontinuity in more than 1 slice of each image, suggestive of a small tear; and type 5, presence of a major discontinuity on each image, suggestive of a large tear.

**Clinical Outcome**

Secondary outcomes included the Constant score; Simple Shoulder Test score; University of California, Los Angeles score; and strength measurements by use of a handheld dynamometer. We measured strength of elevation in the scapular plane. Clinical evaluations were performed by a blinded study nurse.

**A Priori Power Analysis**

An a priori power analysis was performed for the primary outcome measure (proportion of retears of repaired cuffs). On the basis of our experience, as well as previous studies, the retear rate for the repaired cuff is approximately 50%.18 Given the timeframe allowed for our study, we expected to treat 35 patients in each group. We chose the traditional values $\alpha = .05$ and $\beta = .20$, implying a power of 0.80. With these values, the probability to see a significant decrease in the retear rate in a comparison test of 2 proportions will be at least 80% if the retear rate decrease is at least 26%—that is, if the retear rate in the L-PRP group is lower than 14% and the retear rate of the control group is at least 40%.19

**Statistical Analysis**

Two-sided unpaired Mann-Whitney tests were used to compare the 2 groups. Exact $P$ values could not be computed because there were ties in the data. $P$ values were therefore estimated by normal approximations. Significance was set at $P = .05$. Statistical analyses were performed with the use of the software R, version 2.14.1-1.

**Results**

At 2 years’ follow-up, there were no intraoperative or postoperative complications. Both groups were homogeneous, with no significant differences regarding demographic characteristics, fatty degeneration, preoperative functional scores, and follow-up (mean, 28.6 months; range, 24 to 34 months) (Table 1).

**Cuff Integrity**

Group 1 (L-PRP group) included 31 patients (4 patients were lost to follow-up at 6 months), and group 2 (control group) included 30 patients (5 patients were lost to follow-up at 6 months). Table 2 shows the number and proportion of patients in each Sugaya category for the 2 groups. The general tendency

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**Table 1. Baseline Characteristics for Matched Study Groups**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (L-PRP) (n = 35)</th>
<th>Group 2 (Control) (n = 35)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Dominance</td>
<td>26</td>
<td>23</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Duration &gt;12 mo</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Upper limb worker</td>
<td>13</td>
<td>16</td>
<td>.6098</td>
</tr>
<tr>
<td>Fatty infiltration</td>
<td>1.5</td>
<td>1.6</td>
<td>.9053</td>
</tr>
<tr>
<td>SST score</td>
<td>3.1</td>
<td>2.9</td>
<td>.98</td>
</tr>
<tr>
<td>Pain rating</td>
<td>3.7</td>
<td>4.8</td>
<td>.9894</td>
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<tr>
<td>Constant score</td>
<td>47.9</td>
<td>48.3</td>
<td>.7474</td>
</tr>
<tr>
<td>UCLA score</td>
<td>11.1</td>
<td>12.2</td>
<td>.7794</td>
</tr>
<tr>
<td>Initial strength</td>
<td>2.8 kg</td>
<td>2.8 kg</td>
<td>.7843</td>
</tr>
<tr>
<td>Tear size &gt;5 cm</td>
<td>8</td>
<td>6</td>
<td>.7371</td>
</tr>
</tbody>
</table>

NOTE. For ordinal data, results are expressed as mean, range, and standard deviation; for categorical data, results are expressed as number of occurrences.

SST, Simple Shoulder Test; UCLA, University of California, Los Angeles.
showed more patients in the Sugaya type 1 category in the L-PRP group than in the control group. This tendency was not significant when Sugaya type 1 and type 2 were taken together ($P = .16$). The retear rates were 35.5% for the L-PRP group and 40% for the control group; this difference was not significant ($P = .65$). However, the size of retears was significantly smaller in the L-PRP group ($P = .008$) (Table 2, Figs 5-7).

### Clinical Outcomes

Clinical outcome measures for both groups were compared at 2 years' follow-up. There was no significant difference between group 1 and group 2 in terms of University of California, Los Angeles score (29.1 and 30.1, respectively; $P = .90$); Simple Shoulder Test score (9.9 and 10.2, respectively; $P = .94$); Constant score (77.3 and 78.1 respectively; $P = .82$); or strength (7.5 and 7.0 respectively; $P = .51$) (Table 3).

### Discussion

The ultimate goals of tendon reinsertion are (1) to improve the biological environment around the repair to promote the regeneration of the native insertion site and (2) to prevent scar tissue formation. A reliable reinsertion technique, faster mobilization of fibroblasts and collagen, and increased local vascularization are essential to optimize healing. For this reason, we assessed whether combining a double-row suture anchor technique with an L-PRP injection would improve outcomes. The double-row suture anchor technique for rotator cuff reinsertion, which has been developed to restore the footprint better, resulted in most studies in a significant improvement in terms of biomechanics. Thus, in a cohort study including 78 patients, Park et al.20 found that double-row repair resulted in significantly better outcomes than single-row repair for patients with large to massive tears (>3 cm), leading them to recommend double-row repair for larger tears. This is why, in this study, we focused on the treatment of large and massive tears with a double-row repair technique that led to very satisfactory biomechanical results.16

The biological study of tendon healing showed that growth factors are 1 of the most important molecular

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**Table 2. Comparison of Structural Integrity of Cuff Repair Assessed by MRI**

<table>
<thead>
<tr>
<th>Repair Integrity (Sugaya Category)</th>
<th>Group 1 (L-PRP)</th>
<th>Group 2 (Control)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>11 (35.5%)</td>
<td>5 (16.7%)</td>
<td>.16</td>
</tr>
<tr>
<td>Type 2</td>
<td>5 (16.1%)</td>
<td>10 (33.3%)</td>
<td>.5</td>
</tr>
<tr>
<td>Type 3</td>
<td>4 (12.9%)</td>
<td>3 (10.0%)</td>
<td>.65</td>
</tr>
<tr>
<td>Type 4</td>
<td>9 (29.0%)</td>
<td>3 (10.0%)</td>
<td>.008</td>
</tr>
<tr>
<td>Type 5</td>
<td>2 (6.5%)</td>
<td>9 (30.0%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>31 (100%)</td>
<td>30 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

*The hypothesis was that the 2 repartitions were identical (types 1 and 2).

†The hypothesis was that the rates of the iterative tears (types 4 and 5) were the same for the 2 groups.

‡The hypothesis was that the sizes of the iterative small and large tears (types 4 and 5) were equal for the 2 groups.

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**Fig 5.** Postoperative MRI scan showing anatomic healing (Sugaya type 1) in L-PRP–treated patient.

**Fig 6.** Postoperative MRI scan showing small retear (Sugaya type 4) in L-PRP–treated patient.
families for tissue healing. The use of PRP in the treatment of tendon lesions over several years led to a significant improvement in healing thanks to the numerous growth factors that it releases. Indeed, activated platelets release alpha granules that contain growth factors and act as messengers by traveling to cell receptors and promoting cell proliferation (these factors act as signaling agents to promote and accelerate tissue healing).

We used L-PRP, which contains a large number of platelets (4 to 8 times the circulating levels) and leukocytes, in this study. It also contains significant concentrations of the growth factors (PDGF, basic fibroblast growth factor, transforming growth factor β, VEGF, and insulin-like growth factor 1) that are essential for healing. We noted that the proportion of L-PRP patients in the type 2 and type 4 categories of the Sugaya classification decreased in comparison with the repartition of the control group, but the tendency was not significant ($P = .16$). The iterative tears (type 4 and type 5) were smaller in the L-PRP group than in the control group ($P = .008$). However, the overall number of iterative tears (type 4 plus type 5) was 35.5% in the L-PRP group and 40% in the control group ($P = .65$), which may explain the fact that patients in the L-PRP group did not show better functional improvement than control patients.

A variety of blood sample kits with different types of centrifugation, in terms of speed and time, are currently available. The resulting growth factor concentration obtained is variable, as shown by Castillo et al. We can especially differentiate PRP (in liquid or gel form after activation) and platelet-rich fibrin matrix (PRFM), which becomes solid after 2 centrifugations through the formation of a fibrin matrix. Leukocytes may or may not be present, depending on the kit used. Castillo et al. found significantly higher levels of VEGF and PDGF in L-PRP (Biomet system; Biomet, Warsaw, IN) than PRFM without leukocytes (Cascade system; MTF Sports Medicine, Edison, NJ). In a prospective randomized study, Randelli et al. found that patients treated with L-PRP had accelerated functional recovery and particularly pain reduction, although no difference in tendon healing could be observed. Barber et al. found a significant improvement in tendon healing for tears of various sizes, but the functional results were identical in all patients. However, Jo et al., Rodeo et al., Bergeson et al., and Castrici et al. could not observe any improvement in terms of function or healing. In fact, Rodeo et al. even showed that PRFM could have a negative effect on healing by modifying the biological interface between the tendon and the bone. Gumina et al., who used another form of PRFM that included leukocytes (L-PRFM), compared 2 groups with large tears and noted a significant improvement in healing in patients treated with L-PRP but no difference in functional recovery. These findings are in accordance with a recent meta-analysis that suggests that the PRP products have no benefits on the overall clinical outcomes and retear rates for the arthroscopic repair of full-thickness rotator cuff tears. However, a decrease occurred in the rate of retears among patients treated with PRP for small- and medium-sized rotator cuff tears but not for large- and massive-sized tears.

### Limitations

The main limitation of our study was that the starting hypothesis could not be confirmed because we were not able to decrease the rate of iterative tears (types 4 and 5) with L-PRP treatment. The a priori analysis showed that with our statistical choices, a decrease in the rate of iterative tears of at least 26% was mandatory to reach a probability of 80% to see a significant difference between the 2 groups. We only observed a decrease of 4.5% (40% for the control group and 35.5% for the L-PRP group). If 0.400 and 0.355 were the proportions of the full populations and not of 2 samples, the same power analysis would show that 1,434 patients would be required in each group to have a probability of 80% to see a significant difference.

### Table 3. SST Score, Pain Rating, Constant Score, UCLA Score, and Strength at Latest Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (L-PRP)</th>
<th>Group 2 (Control)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SST score</td>
<td>Mean 9.9</td>
<td>Range 4-12</td>
<td>SD 2.9</td>
</tr>
<tr>
<td>Pain rating</td>
<td>Mean 1.3</td>
<td>Range 0-4</td>
<td>SD 1.6</td>
</tr>
<tr>
<td>Constant score</td>
<td>Mean 77.3</td>
<td>Range 39-89</td>
<td>SD 9.9</td>
</tr>
<tr>
<td>UCLA score</td>
<td>Mean 29.1</td>
<td>Range 27.9-35</td>
<td>SD 2.3</td>
</tr>
<tr>
<td>Strength</td>
<td>Mean 7.5 kg</td>
<td>Range 0-14 kg</td>
<td>SD 3 kg</td>
</tr>
</tbody>
</table>

SST, Simple Shoulder Test; UCLA, University of California, Los Angeles.
between the 2 groups. This suggests that our study was underpowered to detect differences in structural integrity. It is generally strongly advised to avoid carrying out a posteriori power analyses because they can be very misleading;

hence the previous statement should be taken as a rough hint, not as a precise figure.

Another shortcoming of our study is that the protocol used, which included only 1 intraoperative injection for large or massive tears, may not be very effective. Thus 1 or 2 additional injections could be planned within 3 weeks of repair, when healing is undergoing its most substantial remodeling. In fact, multiple injections proved efficiency for the treatment of Achilles tendinitis and other chronic tendinopathies.

A final limitation of our study is that the number of platelets and levels of growth factors injected were not calculated. McCarrel and Fortier, comparing L-PRP with PRP, showed that the levels of inflammation factors were increased when injecting leukocytes. We do know the levels in vitro obtained with different techniques (PRP/PRFM), but the levels in vivo at the time of the injection and a few hours or days later are still missing. Further investigations are needed to better determine the amount and the kinetics of the growth factors released within the cuff tear repair. This would certainly help to develop a postoperative protocol comprising multiple PRP injections, which may improve tendon healing rates in massive rotator cuff tears.

Conclusions

In our study the use of autologous L-PRP did not improve the quality of tendon healing in patients undergoing arthroscopic repair of large or massive rotator cuff tears based on postoperative MRI evaluation. The only significant advantage was that the L-PRP patients had smaller iterative tears. However, the functional outcome was similar in the 2 groups of patients.

References


