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Platelet-Rich Plasma Augmentation for Arthroscopic Rotator Cuff Repair

A Randomized Controlled Trial

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Background: After reinsertion on the humerus, the rotator cuff has limited ability to heal. Growth factor augmentation has been proposed to enhance healing in such procedure.

Purpose: This study was conducted to assess the efficacy and safety of growth factor augmentation during rotator cuff repair.

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

Methods: Eighty-eight patients with a rotator cuff tear were randomly assigned by a computer-generated sequence to receive arthroscopic rotator cuff repair without (n = 45) or with (n = 43) augmentation with autologous platelet-rich fibrin matrix (PRFM). The primary end point was the postoperative difference in the Constant score between the 2 groups. The secondary end point was the integrity of the repaired rotator cuff, as evaluated by magnetic resonance imaging. Analysis was on an intention-to-treat basis.

Results: All the patients completed follow-up at 16 months. There was no statistically significant difference in total Constant score when comparing the results of arthroscopic repair of the 2 groups (95% confidence interval, –3.43 to 3.9) (P = .44). There was no statistically significant difference in magnetic resonance imaging tendon score when comparing arthroscopic repair with or without PRFM (P = .07).

Conclusion: Our study does not support the use of autologous PRFM for augmentation of a double-row repair of a small or medium rotator cuff tear to improve the healing of the rotator cuff. Our results are applicable to small and medium rotator cuff tears; it is possible that PRFM may be beneficial for large and massive rotator cuff tears. Also, given the heterogeneity of PRFM preparation products available on the market, it is possible that other preparations may be more effective.

Keywords: rotator cuff; tendon; growth factors; platelet-rich plasma; sports; arthroscopy

Rotator cuff (RC) tendon tears account for more than 4.5 million physician visits per year, and over 250 000 RC repair surgeries performed annually in the United States.[39] The pathogenesis of RC tears is debated.[18,21,22,28] The RC has limited ability to heal back to its insertion on the humerus after repair,[15] possibly because of the poor vascularization of tendon tissue and also because the histopathologic changes that accompany a rupture are localized not only at the site of rupture but also in the macroscopic intact tendon portion, suggesting more generalized involvement of the tendon.[19,20,25] Given this limited ability for healing,[24] several strategies—including growth factors and cytokines, gene therapy, tendon augmentation graft, and tissue engineering with mesenchymal stem cells—have been proposed to enhance tendon healing.[15,23] Several growth factors are upregulated during RC healing, and they may be used to augment RC repairs.[15,26]

Platelet-rich plasma (PRP) and platelet-rich fibrin matrix (PRFM), or autologous platelet-derived growth factors, are bioactive components of whole blood that are now being widely tested in different fields of medicine to aid

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healing in tissue with poor healing potential.[¶] Cascade Autologous Platelet System (MTF [Musculoskeletal Transplant Foundation], Edison, New Jersey) is a completely autologous platelet biologic matrix[27] with a high concentration of viable platelets, extracted from a small amount of the patient's own blood, spun through a centrifugation process and resulting in a dense suturable PRFM that can be delivered directly to the tear site and sutured in place to potentially stimulate a reparative healing response for soft tissue and bone repair.

To date, there are no data from randomized trials assessing the efficacy and safety of PRFM for augmentation of RC repair. We therefore performed a randomized controlled trial to compare the efficacy and safety of augmentation with PRFM for arthroscopic RC repair compared with nonaugmented repair of the RC, to test the hypothesis that augmentation with PRFM would result in increased improvement in shoulder function and better MRI in patients undergoing surgical repair of small and moderate RC tears.

METHODS

Our institutional review board approved the study (ISRCTN.org number ISRCTN49643328). Recruitment started in January 2007 and was completed in April 2008. Eligibility criteria are reported in Table 1. Eighty-eight patients were eligible and were randomized: 45 patients to arthroscopic RC repair without augmentation with PRFM (group 1), and 43 patients to arthroscopic RC repair and augmentation with PRFM (group 2). All patients received the allocated treatment. Of participants randomized, at least 16-month clinical results were available for all patients, and radiologic results for 78 (Figure 1).

End Points

The primary end point was the difference in change from baseline to 16 months in the Constant score between the 2 groups. The secondary end point was the integrity of the repaired RC, as evaluated by MRI. All adverse events and serious adverse events were reported; investigators assessed whether they were related to procedure. Investigators informed the local ethical committees/institutional review board of any serious adverse events or serious adverse effects.

Evaluation

We performed preoperative evaluations the day before surgery, and reported the results of postoperative evaluation at a final follow-up at an average of 20.2 months (range, 16-30 months) from the operation. Each patient was evaluated for preoperative and postoperative Constant-Murley scoring.[3] Nonarthrographic MRI studies were performed on all patients preoperatively and postoperatively at the final follow-up appointment.[40] Oblique coronal, oblique sagittal, and axial T2-weighted spin-echo MRI scans (repetition time, 3200 milliseconds; echo time, 85 milliseconds) were obtained in all patients. We employed T2-weighted, gradient-echo (GE) spectral presaturation inversion recovery (SPIR) sequences in true axial scans and T1-weighted, GE SPIR sequences in oblique coronal planes that are parallel to the course of the supraspinatus muscle, and oblique sagittal planes that are parallel to the glenoid fossa. Imaging time was approximately 18 minutes per patient.

All scans were evaluated independently by 2 orthopaedic surgeons who received specific training in shoulder MRI and were blinded to patients' clinical information and surgical history. Disagreements were discussed in a consensus meeting, where the scans were reevaluated and a final decision was made.[2] Postoperative scans were evaluated for the presence of a full-thickness tear, defined as absence of visible tendon fiber extending across the entire tendon from inferior to superior[2] (see below for details). Tendon signal intensity was divided into 3 grades[37] (see below for details). On this scale, a tendon repair with a completely normalized appearance had a score of 9, while 3 is the worst possible score.

The Constant-Murley scoring system shoulder rating scale was used to evaluate preoperative and postoperative shoulder pain (15 points), activities of daily living (20 points), range of movement (40 points), and power (25 points). The total possible score is 100 points, indicating an asymptomatic and healthy person, while the worst score is 0 points.[3]

TABLE 1
Eligibility Criteria

Inclusion criteria	Rotator cuff tear diagnosed on clinical grounds
	Isolated supraspinatus tear
	Failure of 6 months of nonoperative treatment
	No episodes of shoulder instability
	No radiographic signs of fracture of the glenoid or the greater or lesser tuberosity
	MRI evidence of cuff tear
	A repairable full-thickness tear of the rotator cuff found at the time of surgery
	Associated injury of the long head of the biceps
Exclusion criteria	Inflammatory joint disease
	Irreparable full-thickness tear or partial-thickness tear of the rotator cuff found at the time of surgery
	Symptomatic arthritis of the acromioclavicular joint
	Rotator cuff arthropathy
	Pathologic abnomalities of the subscapularis tendon
	Workers' compensation claims
	Prior surgery on the affected shoulder

[¶]References 7, 8, 16, 17, 29, 30, 33-35.

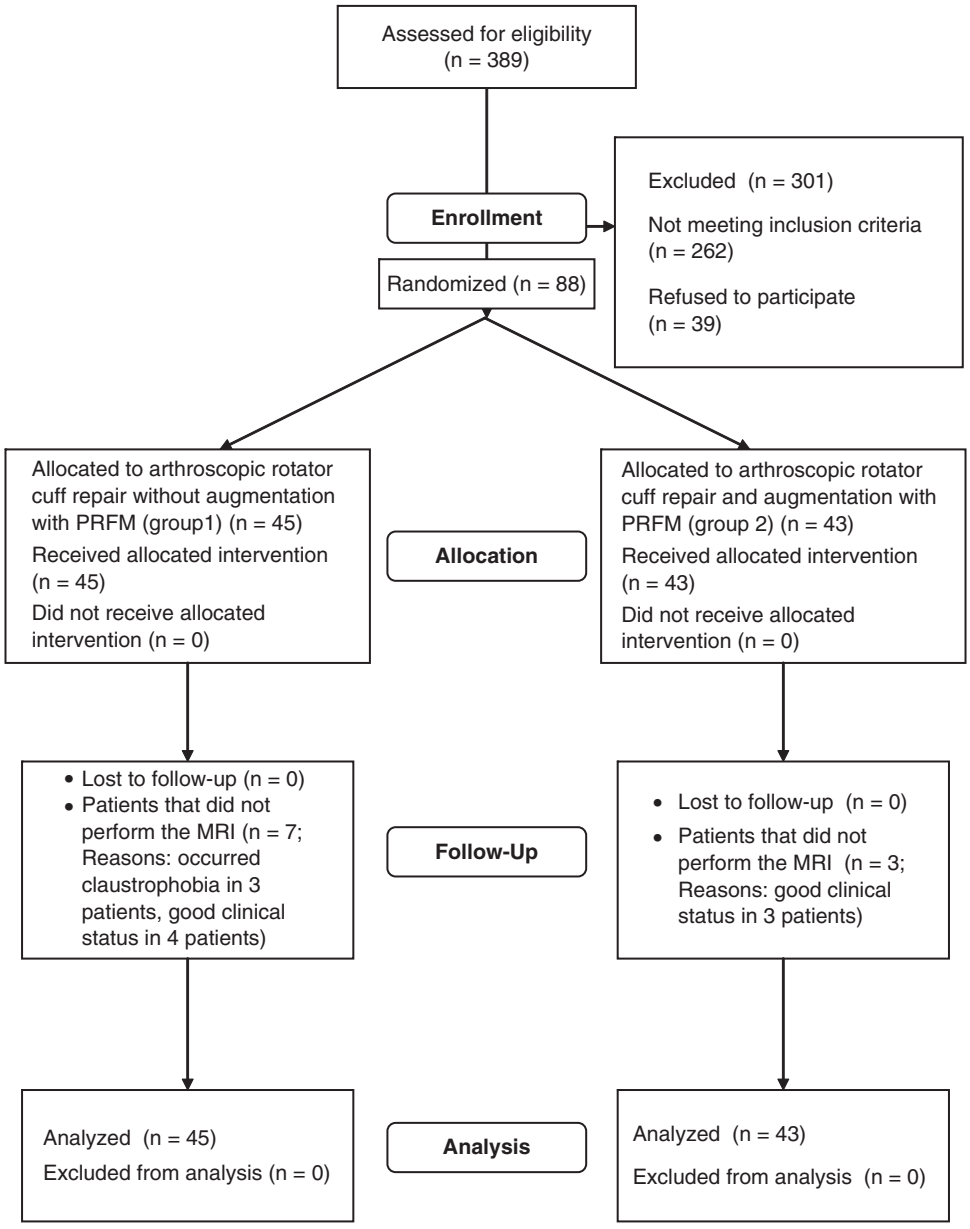

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flowchart.

For muscle strength evaluation, we used a digital dynamometer (Myometer 500 N, Atlantech Medical Devices, Nottingham, United Kingdom). The mean value of 3 repeated measurement at 90° of elevation in the scapular plane was recorded and used for scoring strength in the Constant-Murley score.[38] A standard universal goniometer was used for measurement with scales marked in 1° increments. Three measurements were taken for each shoulder, and the mathematical average used for statistical purposes.[11]

Rotator cuffs without a recurrent tear were evaluated for tendon thickness, coverage of the greater tuberosity, and the intensity of the signal.[2] Each of these parameters was also graded numerically on a scale from I to III. Tendon thickness was compared with normal tendon using a division in 3 grades: grade III, normal thickness; grade II, >50% normal thickness; and grade I, <50% normal thickness. The size of the supraspinatus tendon footprint was compared with the size of the footprint of a normal supraspinatus tendon, which covers the entire greater tuberosity from medial to lateral. In cases where the tendon attachment was medialized, the width of the medialized footprint was compared with width of the greater tuberosity. Grade III coverage was 3/3, grade II coverage was 2/3, and grade I coverage was 1/3 of the greater tuberosity.

Tendon signal intensity was divided into 3 grades[33]: grade III, if the tendon evidenced a light and diffused increase of the signal (different from that of the synovial

fluid); grade II, if the tendon appeared undamaged but there was a focal increase of the signal (the same as that of the synovial fluid) on the bursal or articular side; and grade I, if the increase of the signal's intensity (the same as that of the signal of the synovial fluid) involved the entire thickness of the tendon, with or without tendinous retraction. A tendon repair with a completely normalized appearance had a score of 9, with 3 being the worst possible score.

Randomization Procedure

After a diagnostic arthroscopy assessing the status of the shoulder joint and the presence and the size of the RC tear, we ascertained whether the tear was mobile, evaluating the medial-to-lateral and anterior-to-posterior mobility of the tear margins using a soft tissue grasper. If this was the case, at that stage patients were randomized into 1 of 2 groups. We used a random numbers table to allocate study participants. Starting with an arbitrary point in the table, we selected 88 sequential random numbers. The first 45 numbers were assigned to group 1, and the next 43 were assigned to group 2. These assignments were then arranged in an ascending order. This procedure produced a random sequence of consecutive treatment allocations. Sealed, opaque numbered envelopes containing the treatment assignments were prepared, with care being taken to make sure that the order of the envelopes exactly matched the allocation schedule.

Production of PRFM

Nine milliliters of venous blood were drawn with an aseptic technique from the antecubital vein by standard venipuncture using a sterile vacuum tube containing trisodium citrate and a thixotropic polyester separator gel. The red blood cells and PRP were separated by spinning the tube for 6 minutes in a standard centrifuge at 1100 rounds/min. The supernatant PRP was transferred from the first tube into a 35-mm Wheaton bottle, containing calcium chloride (1.0 M), using a 20-mL syringe and a 19-gauge needle. The Wheaton bottle was placed back into the centrifuge equipped with a flat carrier-container and spun at a higher *g* force (4500 relative centrifugal force [RCF]) for 25 minutes. A flat, circular membrane of PRFM formed at the bottom of the container as it was spun using radial centrifugation. The final product was a membrane of autologous suturable fibrin that had to be used within 30 minutes.[27]

Surgical Technique

All arthroscopies were performed by the same fully trained surgeon. The greater tuberosity was decorticated with a motorized shaver. The RC was repaired with a double-row technique. The medial row consisted of 1 metal suture anchor (Fastin RC Anchor [DePuy Mitek, Raynham, Massachusetts] with No. 2 Ethibond Excel [Ethicon, Somerville, New Jersey]) (Figure 2) placed at the articular margin of the humeral head in a mattress fashion. Subsequently, a lateral row of anchors was inserted in the lateral aspect of the greater tuberosity. One of the suture limbs was used to position the PRFM under the supraspinatus tendon, above the bleeding surface of the greater tuberosity. The limb of the suture coming out through the cannula in the lateral portal was passed through the PRFM using a free needle (Figure 3) and reinserted via the cannula after removing the rubber diaphragm. One or 2 passages were generally sufficient. The PRFM was brought inside the joint by traction on the other end of the suture (Figure 4). With a suture passer, the portion of the suture containing the implant was passed through the supraspinatus. The lateral sutures were tied using a sliding knot with 3 alternating half-hitches. The medial sutures, which passed through the implant, were tied with a nonsliding knot to prevent damage to the implant itself, in a mattress configuration (Figure 5).

All biceps tenodeses were performed using an established technique.[9] One of the suture limbs from 1 of the medial anchors was passed through the biceps tendon and then through the rotator cuff. The remaining intra-articular tendon stump of the biceps was resected in all the patients.

The operated shoulder was immobilized for 3 weeks using a sling with an abduction pillow. Pendulum exercises were allowed starting from the first postoperative day. After the immobilization period, passive and assisted active exercises were initiated for forward flexion and external rotation. After 6 weeks, patients began strengthening exercises of the RC and scapular stabilizers. Rehabilitation was performed with the assistance of physical therapists. Three months after the operation, patients were allowed to practice light sports activity. Heavy manual work and overhead activities were allowed after 6 months.

Statistical Analysis

Statistical analyses were blinded, and performed according to the "intention-to-treat" principle. The analyses were performed by using SPSS version 16.0.1 (SPSS Inc, Chicago, Illinois). The primary end point was the postoperative difference in the Constant score between the 2 groups. The distribution of the Constant score for the 2 groups was normal. Therefore, we used the unpaired *t* test to compare the postoperative results between the 2 groups; 95% confidence intervals were calculated.

The results of each variable of the adopted MRI score were compared with the χ^2 test. A significance level of .05 was used.

Power Analysis

We performed a pilot study on 20 patients randomized to arthroscopic repair of an RC with or without growth factor augmentation to determine the sample size of participants required to achieve statistical significance in the Constant score at a .05 level with 95% power. In the control group, the Constant rating system showed an average of 89 (standard deviation [SD] 7.87). In the study group,

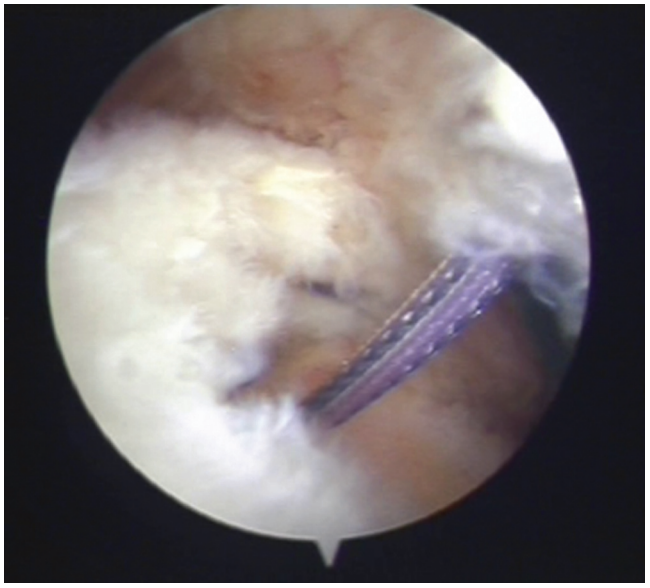

Figure 2. Arthroscopic view of a rotator cuff tear. A metal suture anchor (Fastin RC Anchor with No. 2 Ethibond Excel) was placed at the articular margin of the humeral head.

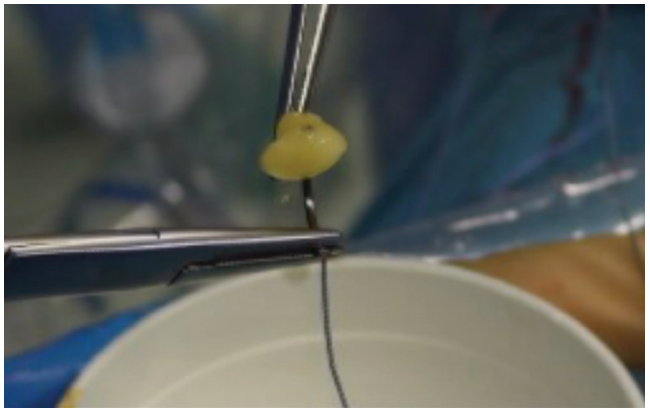

Figure 3. The limb of the suture coming out through the cannula in the lateral portal was passed through the platelet-rich fibrin matrix using a free needle.

the Constant rating system showed an average of 93.5 (SD 3.53). Based on these results, a total sample size of 82 participants (41 participants per group) was required to achieve statistical significance at a .05 level with 95% power. To compensate for possible loss, we decided to enroll 88 patients in the study. The variable used to calculate sample size was the postoperative Constant score, at 16 months after surgery. No power analysis was made on the secondary variables.

RESULTS

No patient experienced infection, neurologic, or vascular complications.

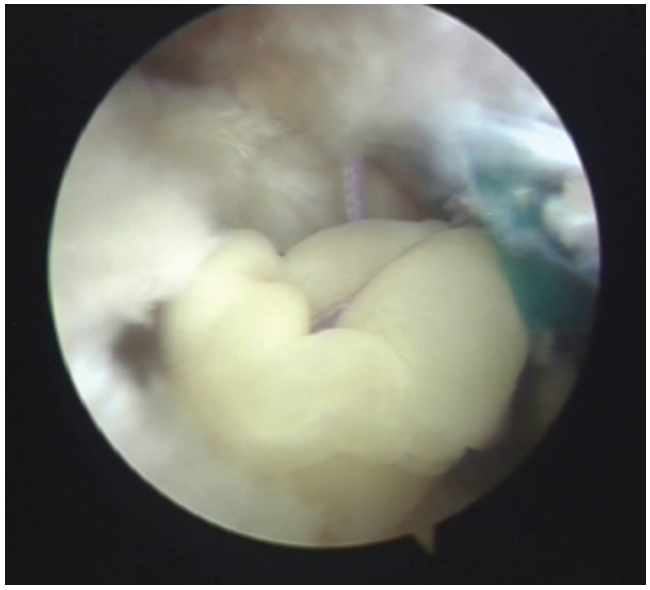

Figure 4. The platelet-rich fibrin matrix was introduced into the shoulder joint.

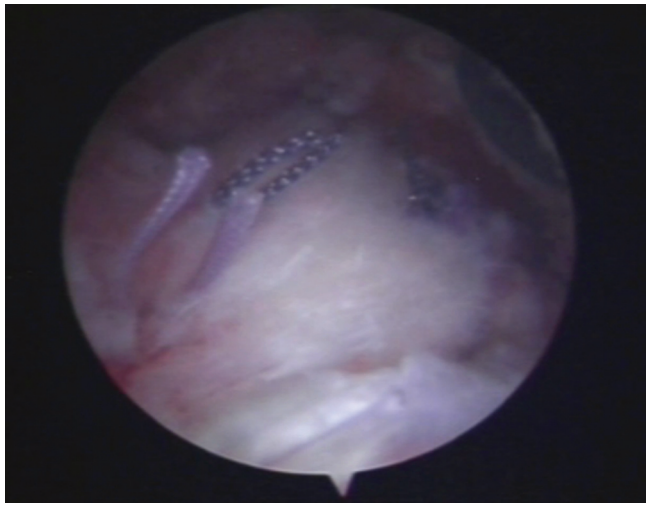

Figure 5. Subacromial view of the final stage of the repair.

Details of the operated patients are reported in Table 2. Two patients in group 1 and 1 patient in group 2 experienced a stiff shoulder. They were managed nonoperatively, with physiotherapy (manual passive motion of the shoulder) for 9 months, when the symptoms resolved.

Constant Score

Group 1. The Constant rating system showed a statistically significant improvement from a preoperative average rating of 42.7 (SD 7.92) (95% confidence interval [CI], 40.37-45.13) to an average of 88.6 (SD 7.78) postoperatively (95% CI, 86.32-91) ($P < .001$).

We repeated the statistical analysis including only the 38 patients for whom postoperative MRI was available.

TABLE 2
Descriptions of the Two Groups

	No. of Patients	Men/ Women	Mean Age (Range), y	Rotator Cuff Tear Size[5]	Tenodesis/ Tenotomy[10,12]	No. of Anchors	Acromioplasty	Infection, Neurologic, or Vascular Complications
Group 1	45	23/22	55.2 (37-69)	Small (<1 cm) in 20 patients Medium (1-3 cm) in 25 patients	22/5	2 anchors for each patient	25	0
Group 2	43	17/26	55.5 (41-72)	Small (<1 cm) in 18 patients Medium (1-3 cm) in 25 patients	21/3	2 anchors for 41 patients and 3 anchors for 2 patients	12	0

TABLE 3
Details of Constant Score for Each Group[a]

	Group 1 (Without Augmentation With Platelet-Rich Fibrin Matrix [PRFM])		Group 2 (With PRFM Augmentation)	
Constant Score	Preoperative	Postoperative	Preoperative	Postoperative
Shoulder pain	3.1 (0-5)	14.3 (10-15)	3.6 (0-5)	14.3 (10-15)
Activities of daily living	10.1 (8-12)	18.8 (14-20)	9.8 (6-12)	19.3 (16-20)
Range of movement	26.5 (12-39)	38.8 (26-40)	26 (16-32)	39.1 (36-40)
Strength	3.2 (1-9)	16.5 (4-25)	2.6 (0-6)	15.7 (4-24)
Total score	42.9 (22-55)	88.4 (54-100)	42 (30-53)	88.4 (72-99)

[a]Average values are given, with the numbers in parentheses indicating the range of values.

TABLE 4
Magnetic Resonance Imaging Score

Variable	Group 1 (Without Augmentation With Platelet-Rich Fibrin Matrix [PRFM])			Group 2 (With PRFM Augmentation)		
Grade	I	II	III	I	II	III
Tendon thickness	5	12	17	2	10	27
Size of the tendon footprint	1	10	23	0	4	35
Alterations of signal intensity	10	21	3	2	13	24

The Constant rating system showed a statistically significant improvement from a preoperative average rating of 43.42 (SD 7.7) (95% CI, 40.89-45.95) to an average of 89.2 (SD 8) postoperatively (95% CI, 86.6-91.87) ($P <$ .001). Details of the Constant score are reported in Table 3.

Group 2. The Constant rating system showed a statistically significant improvement from a preoperative average rating of 42.1 (SD 6.65) (95% CI, 40.06-44.16) to an average of 88.58 (SD 7.62) postoperatively (95% CI, 86.23-90.92) ($P <$ .001). Details of the Constant score are reported in Table 3. We repeated the statistical analysis including only the 40 patients for whom postoperative MRI was available. The Constant rating system showed a statistically significant improvement from a preoperative average rating of 42.45 (SD 6.70) (95% CI, 40.30-44.59) to an average of 89 (SD 7.61) postoperatively (95% CI, 86.56-91.43) ($P <$ .001).

Magnetic Resonance Imaging

Of 88 participants, MRI results were available for 78 (38 for group 1 patients, and 40 for the group 2 patients). In 5 patients, there was MRI evidence of a rerupture: 4 patients in group 1 (10.5%) and 1 (2.5%) in group 2 (P = .07). These patients did not receive any treatment, as they were satisfied with their clinical conditions. The MRI score was evaluated in the remaining 34 patients in group 1 and 39 patients in group 2 (Table 4).

Comparison Between the 2 Groups

There was no statistically significant difference in total Constant score when comparing the results of arthroscopic repair of the 2 groups (95% CI, –3.43 to 3.9) ($P = .44$).

There was no difference in tendon thickness between the 2 groups as evaluated with the χ^2 test ($P = .181$).

There was no difference in size of the tendon footprint tendon thickness between the 2 groups as evaluated with the χ^2 test ($P = .057$).

There was difference in alterations of signal intensity between the 2 groups as evaluated with the χ^2 test ($P < .01$).

DISCUSSION

This randomized controlled trial showed that, in patients with small and medium RC tears, augmentation of the repair with PRFM did not result in significant improved shoulder function (as evaluated with the Constant score) or structural outcome (as evaluated by MRI) when compared with arthroscopic repair without augmentation of the repair at a minimum 16 months of follow-up. There were no serious adverse events related to use of PRFM. At a minimum 16 months of follow-up, surgical repair of an RC tear resulted in significant clinical and structural improvement in both groups, independently of the use of augmentation with PRFM.

To our knowledge, this is the first randomized controlled trial to compare the outcome of arthroscopic double-row anchor suture repair RC surgery with or without augmentation with PRFM using both clinical and imaging criteria.

We used MRI to evaluate the anatomical appearance after operative RC repair because it allows good definition of the RC and tendon defects, and differentiation of RC degeneration from partial or complete RC tears. Other strengths of this study include the use of a single surgeon, its prospective randomized nature, and the use of independent assessors of the outcome. Also, postoperative management was standardized. A weakness of our study is the absence of information about the number of platelets actually delivered in patients who received the PRFM. Further study is clearly required to evaluate the role of PRFM in RC repair. Other limitations include the fact that the strength of the shoulder may differ by gender and deteriorate with age, and we did not include this in our statistical analysis because of the relatively small number of patients.

It is difficult to compare the findings of the present study with those of previous reports, as we know of no other prospective studies comparing the clinical and anatomical outcome of small and medium RC tears repaired with or without augmentation with PRFM. In a pilot nonrandomized single group study of 14 patients, autologous PRP for arthroscopic RC repair provided good clinical results.[32] A recent randomized controlled trial in patients with chronic Achilles tendinopathy showed no advantages of a PRP injection compared with a saline injection.[4] On the other hand, data from another recent randomized controlled trial showed that treatment of patients with chronic lateral epicondylitis with PRP reduces pain and significantly increases function, exceeding the effect of corticosteroid injection.[31] In a randomized controlled trial, exogenous application of platelet-leukocyte gel during open subacromial decompression contributed to improved patient outcome: recovery was faster and patients returned earlier to daily activities and also took less pain medication than controls.[6]

Rotator cuff surgery aims to provide tendon fixation secure enough to hold the repaired tendon in place until biological healing occurs. Several factors may be implicated in failure of RC repairs, including suture or knot failure, inadequate tendon-to-bone fixation, and lack of tendon-to-bone healing.[1] As we re-insert tendinous tissue into bone, theoretically only the reconstitution of enthesial fibrocartilage would guarantee an optimal outcome.[14] The concept of autologous platelet-derived growth factors for augmentation of RC repair is appealing, as it should help the reconstitution of enthesial fibrocartilage. However, in the present study, we did not find any beneficial effect of addition of PRFM. Also, the use of autologous platelet-derived growth factors results in longer surgical time, is more expensive, and may well be technically more demanding.

The only difference we were able to find between the 2 groups was in tendon signal. It is difficult to give a clinical significance to this finding. Of concern is that, despite high patient satisfaction rates, healing rates after arthroscopic rotator cuff repair as low as 6% have been reported.[13] A recent systematic review[36] sought to clarify the correlation between structural integrity of the RC and clinical outcomes. On the basis of the published cohort studies, there were several key differences between healed and nonhealed repairs in terms of subjective and objective outcomes. Patients with healed RC repairs after arthroscopic repair can probably expect better strength and possibly better functional outcomes. No definitive conclusion, however, could be drawn because of the variability in the studies (ie, different outcome scales, strength measurements, and RC tear characteristics). Furthermore, because the studies were not Level I studies, no meta-analysis could be performed to determine whether a true difference exists between healed and nonintact RC repairs.

In conclusion, our study does not support the use of autologous platelet-derived growth factors in the form of PRFM for augmentation of a double-row repair of a small or medium RC tear to improve the healing of the RC. We did not demonstrate superior clinical or structural performance when compared with the more traditionally, technically less demanding, and economically more advantageous technique of nonaugmented suture anchor repair. Our results are applicable to small and medium RC tears; it is possible that the use of autologous growth factors contained in PRP may be beneficial for large and massive RC tears. Also, given the heterogeneity of PRP preparation products available on the market, it is possible that other preparations may be more effective.

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