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Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up

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Hypothesis: Local application of autologous platelet rich plasma (PRP) improves tendon healing in patients undergoing arthroscopic rotator cuff repair. Study design: Prospective, randomized, controlled, double blind study; considering an alpha level of 5%, a power of 80%, 22 patients for group are needed.
Materials and methods: Fifty-three patients who underwent shoulder arthroscopy for the repair of a complete rotator cuff tear were randomly divided into 2 groups, using a block randomization procedure. A treatment group ($N = 26$) consisted of those who received an intraoperative application of PRP in combination with an autologous thrombin component. A control group ($N = 27$) consisted of those who did not receive that treatment. Patients were evaluated with validated outcome scores. A magnetic resonance image (MRI) was performed in all cases at more than 1 year post-op. All patients had the same accelerated rehabilitation protocol.
Results: The 2 groups were homogeneous. The pain score in the treatment group was lower than the control group at 3, 7, 14, and 30 days after surgery ($P < .05$). On the Simple Shoulder Test (SST), University of California (UCLA), and Constant scores, strength in external rotation, as measured by a dynamometer, were significantly higher in the treatment group than the control group at 3 months after surgery (strength in external rotation [SER]: 3 ± 1.6 vs 2.1 ± 1.3 kg; SST: 8.9 ± 2.2 vs 7.1 ± 2.7; UCLA: 26.9 ± 3 vs 24.2 ± 4.9; Constant: 65 ± 9 vs 57.8 ± 11; $P < .05$). There was no difference between the 2 groups after 6, 12, and 24 months. The follow-up MRI showed no significant difference in the healing rate of the rotator cuff tear. In the subgroup of grade 1 and 2 tears, with less retraction, SER in the PRP group was significant higher at 3, 6, 12, and 24 months postoperative ($P < .05$).
Conclusion: The results of our study showed autologous PRP reduced pain in the first postoperative months. The long-term results of subgroups of grade 1 and 2 tears suggest that PRP positively affected cuff rotator healing.
Level of evidence: Level I, Randomized Controlled Trial, Treatment Study.

Keywords: Rotator cuff repair; arthroscopy; shoulder; growth factors; platelet rich plasma

IRB: This study has been approved with no. 1979, issued 8th March 2007, National Ethical Committee Authorization, ASL (Local Health Unit) Az sanitaria locale della prov. di Milano 2, Milan, Italy.

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A full-thick ness rotator cuff tear is one of the most common pathologies affecting the shoulder joint. Even in an asymptomatic population, the incidence is known to increase with age.[38] A cadaveric study showed the incidence of full-thickness rotator cuff in subjects older than 60 years was 30% as compared to 6% in those younger than 60 years.[8]

Despite multiple surgical techniques to improve bone-to-tendon healing, recurrent tearing of the rotator cuff is still a significant postoperative issue. Considering the relatively high percentage of repair failure, reported at 11-94%,[8] it is important to explore techniques of biological augmentation to reduce the post-surgical recurrence rate and improve long-term shoulder function after rotator cuff repair.

Rotator cuff tears have demonstrated improved healing when biologic factors are added during surgery.[19,23,35] Platelet rich plasma (PRP) is a whole blood fraction containing high platelet concentrations that, once activated, provides a release of various growth factors that participate in tissue repair processes.[13] PRP includes many of the growth factors identified as crucial in normal bone-to-tendon healing: transforming growth factor beta (TGF-β), fibroblast growth factor (FGF), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), connective tissue growth factors, and epidermal growth factor (EGF).[14]

A previous study[34] investigating local application of autologous PRP after rotator cuff repair demonstrated that it was safe for use, but did not compare augmented rotator cuff repairs with a control. A clinical study using PRP as an augment to rotator cuff repair versus a conventional repair was performed at our institution to address the question of whether PRP improves clinical outcomes.

Material and methods

Study design

This was a prospective, randomized, controlled, double blind study, designed to ascertain if local application of autologous platelet rich plasma (PRP) to augment an arthroscopic rotator cuff repair improves postoperative outcomes compared to a control group. The state institutional ethics committee approved the study, and all patients gave written informed consent to participate in this clinical study.

Sample size

A power analysis was performed based on the effects of PRP treatment on shoulder function. The primary outcome measure was the mean score of the validated Constant questionnaire.[10] The alternative hypothesis was that the Constant score would be 7 points higher in the treatment group (patients undergoing an arthroscopic rotator cuff repair with local delivery of activated PRP) in comparison to a control group (patients undergoing an arthroscopic rotator cuff repair with no PRP supplementation). The standard deviation of the Constant score was estimated at 8 points. With these parameters, 44 participants were needed (22 in each group) to detect a difference of 7 points in the Constant score between the PRP and control group. These numbers were based on a power (1-β) of 0.80 and a significance level of 5% (2-sided). With an expected dropout rate of 15%, this number was increased to 53 participants.

Patient enrollment

Patients were recruited among those electing to undergo an arthroscopic cuff repair. Inclusion criteria were: 1) a complete rotator cuff tear confirmed intraoperatively; 2) agreed to wear a dedicated brace for 4 weeks postoperative; 3) gave written informed consent; 4) had a preoperative platelet count greater than 150,000; 5) had a minimum preoperative hemoglobin of 11.0g/dL or more; 6) had no infectious diseases or diseases that may have limited follow-up (eg, immunocompromised, hepatitis, active tuberculosis, neoplastic disease, septic arthritis etc.); and 7) had a body mass index of 33 or less.

Exclusion criteria were: 1) had undergone a previous rotator cuff repair; 2) had an active infection, osteomyelitis or sepsis, or distant infections, which may spread to the site of operation; 3) had osteomalacia or other metabolic bone disorders, which may impair bone or soft tissue function; 4) were uncooperative or had disorders that made them incapable of following directions, or who were unwilling to return for follow-up examinations; 5) had vascular insufficiency, muscular atrophy, or neuromuscular diseases of the affected arm; 6) smoke cigarettes; or 7) had received steroid injection(s) in the affected shoulder.

Recruitment started in April 2007 and was completed in January 2008. Of 110 screened for eligibility, 53 patients were eligible and randomized: 26 patients to PRP application and 27 patients to control group. Of the 53 randomized participants, 45 completed clinical and radiological follow-up. Eight patients (4 for the treatment group and 4 for the control group) did not return at the final follow-up (Fig. 1). One patient in the PRP group died at about 1 year after the surgical intervention from cardiac arrest.

Randomization

A block randomized procedure was used to generate a randomization list. The block randomization list was generated by dedicated software (StatsDirect Ltd, Cheshire, UK). An independent operator not involved in the surgical treatment prepared sealed, opaque numbered envelopes containing the treatment assignment. After a diagnostic arthroscopy to confirm the presence of a rotator cuff tear, the patients were randomized into the 2 treatment groups.

Patient follow-up

Each patient was evaluated at a preoperative clinical evaluation, as well as at 3, 6, 12, and 24 months postoperative. Final assessment was by using a Visual Analog score for pain (VAS), Constant score, strength in external rotation (SER), Simple Shoulder Test (SST), and University of California (UCLA). Additionally, pain was assessed using a VAS at 3,7,14, and 30 days postoperative.

The Constant score was calculated following a detailed physical examination in a standardized fashion. The strength for the

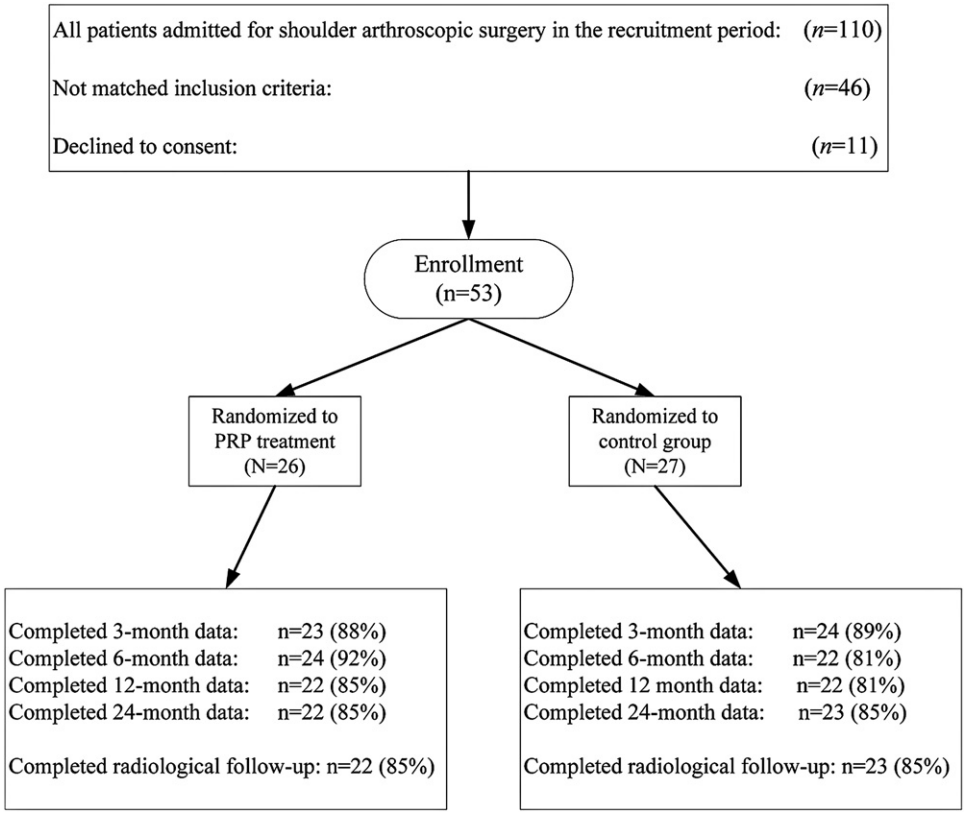


Figure 1 Flow chart of study participants.

UCLA score was assessed in external rotation, according to the modified UCLA parameters.[6] Active strength in forward flexion for the Constant score was tested as an average of 3 pulls in 90° of abduction in the scapular plane. The wrist was fixed in pronation, with the hand facing the floor and elbow fully extended. The subjects were instructed to pull upward with maximum effort until requested to stop. Patients with active abduction of <90° were given 0 points for strength. The SER was measured in a sitting position with the arm at side (neutral position).

A Kern digital dynamometer was used to record results (Kern & Sohn GmbH, Balingen, Germany). The reading of the dynamometer was taken after 5 seconds of maximum pull. An adjustable inextensible strap was placed around the wrist and attached to the dynamometer. In addition to these measures, all local or general complications during the operative or follow-up phases were recorded. All clinical follow-up was performed by a single independent examiner who was blinded to the treatment group of each patient.

Radiological assessment

Tendon integrity was evaluated by a magnetic resonance imaging (MRI) examination at a minimum of 12 months after surgery. This timing was thought to be appropriate to assess a secure healing of the tendon.[3,17,18,29] Twelve patients agreed to the application of contrast medium into the joint and underwent a MRI arthrography. Thirty patients declined the contrast medium and were evaluated using standard MRI. Three patients refused to undergo an MRI and were evaluated by ultrasound.

All MRIs were performed using a 1.5 Tesla unit (Sonata Maestro Class; Siemens, Erlangen, Germany) equipped with a 40 mT/m gradient power and a dedicated channel phased-array coil. MRI imaging was performed using multiple sequences: coronal and sagittal oblique planes with short-tau inversion recovery (STIR) and turbo spin echo (TSE) T1-weighted, axial TSE Proton Density restoring (DPr) weighted, and sagittal STIR. The magnetic resonance arthrography protocol was performed with: an axial plane TSE T1-weighted fat saturation; coronal and sagittal oblique planes with TSE T1-weighted fat saturation; coronal oblique TSE T2-weighted fat-saturation; and oblique coronal 3-dimensional double echo steady state (DESS) sequence (Table I).

Criteria for re-tear were lack of continuity of the tendon in 1 slice of the coronal plane. Very thin bands of tissue were defined as failure of healing, assuming that this would not be a normal, but rather a thin tendon or even just fibrous tissue. We only differentiated between re-tear and intact tendon. Evaluation of muscle atrophy and fatty infiltration in the rotator cuff muscles was not performed in this study. All images were interpreted by a single radiologist with extensive experience in interpretation of shoulder MRI. The radiologist was blinded to the treatment group and not involved in the clinical evaluation.

Operative technique

A single surgeon (PR) not involved in clinical follow-up performed all the procedures. All the operations were performed in a lateral decubitus position under interscalene block with associated sedation. The arm was maintained at approximately 30° of

Table I Technical parameters of magnetic resonance examination

	Cor and Sag STIR	Cor TSE T2	Cor TSE T1	Axial PD	TSE T1 fat sat	DESS
Repetition time	4170 ms	4170 ms	544 ms	3000 ms	763 ms	20 ms
Echo time	21 ms	21 ms	9.3 ms	13 ms	15 ms	6 ms
Inversion time	130	130	-	-	-	-
Thickness	3.5 mm	3.5 mm	3.5 mm	3 mm	4 mm	1.5 mm
Gap	21%	21%	21%	20%	10%	-
Flip angle	180°	180°	150°	150°	150°	40°
Matrix	256 × 179 mm	256 × 179 mm	256 × 179 mm	256 × 256 mm	256 × 100 mm	256 × 256
Field of view	280 × 280 mm	280 × 280 mm	280 × 280 mm	280 × 280 mm	280 × 280 mm	300 × 300

TSE, turbo spin-echo; *PD*, proton density; *STIR*, short-tau inversion recovery; *DESS*, double echo in the steady state; *Cor*, coronal; *Sag*, sagittal.

abduction and 30° of forward flexion with 4 kilograms of traction. Diagnostic glenohumeral arthroscopy was completed using a 30° arthroscope through a standard posterior portal and an arthroscopic pump maintaining a pressure between 60 and 90 mm Hg. If bleeding compromised visibility, the pump pressure was increased. Standard anterior and lateral portals were introduced via an outside-in technique.

The cuff tear was marked initially via a PDS shuttle inserted percutaneously and retrieved from the anterior portal. The optic camera was then switched to the subacromial space and the suture marker used to localize the lesion. The shape of the lesion was classified as U, L, or crescent.[6] The extent of the tear was intraoperatively classified in the coronal plane. If the tear edge was lying over the greater tuberosity, the tear retraction was classified as a grade 1 tear. If the tear exposed the humeral head but did not retract to the glenoid articular surface, retraction was considered to be a grade 2 tear. Tears that extended to the glenoid were considered to have severe retraction and were classified as grade 3I tears. Tears that were retracted medial to the glenoid were classified as grade 4 tears.[3]

Mobilization of the cuff was done as necessary, performing it subacromially as well as intraarticularly. The most lateral edges of the lesion were débrided, and a combination of margin convergence techniques and direct lateral repair were used, depending on the tear shapes and mobility.[5]

Absorbable anchors (Bio-Corkscrew; Arthrex, Naples, FL, USA) of 5 and 6.5 mm in diameter were used to repair the rotator cuff tears. A single row technique was adopted. A standard acromioplasty was performed in all cases. Biceps tear and instability were assessed and treated with either tenodesis or tenotomy.

Autologous platelet rich plasma (PRP) preparation

Fifty-four millileters of whole blood was drawn from patients randomized to the PRP group using a sterile technique. The blood sample was mixed with 6 mL of anticoagulant Citrate Dextrose Solution (Solution A Citra Anticoagulant, Inc., Braintree, MA, USA). The anticoagulated blood was then transferred to a specially designed disposable tube (GPS® II - Plasmax - Platelet Concentration System; Biomet Biologics, Warsaw, IN, USA), which was placed in a centrifuge (Centra CL2; IEC International Equipment Company, Needham Heights, MA, USA) for 15 minutes at 3,200 RPM. Following centrifugation, the platelet poor plasma at the top of the tube was centrifuged again for 2 minutes at 2,000 RPM to obtain concentrated plasma with a 3-fold increase in fibrinogen concentration. The concentrated platelets, on top of the floating buoy, were re-suspended to form the PRP, mixed to the concentrated plasma, and stored in a dedicated sterile syringe.

During the initial bloodletting procedure, an additional 20 mL of whole blood was taken from the patient without addition of anticoagulant. Two 9 mL vacuum tubes were filled and shaken to enhance the blood coagulation process. The tubes were then centrifuged (Centra CL2; IEC International Equipment Company) for 2.5 minutes at 3,200 RPM. The vacuum tubes were then pulled out and the floating serum, containing autologous thrombin, was aspirated. A ratio of 1:5 of 10% calcium chloride solution was added to the serum to counteract the citrate-based anticoagulant when the autologous serum was mixed with the PRP.

Surgical application of PRP

At the end of the arthroscopic procedure patients assigned to treatment group had a local delivery of activated PRP. A final PRP volume of 6 mL was obtained by the adopted protocol. The traction was released and the resistance to pullout of the repaired construct was tested by gently mobilizing the arm. Using the lateral portal, the spray applicator kit loaded with syringes of PRP and autologous thrombin was positioned in between the bone and the repaired rotator cuff without a cannula. The inflow was then closed and the arthroscopic fluid carefully aspirated via the outflow cannula. All other cannulae were removed, producing a dry subacromial space. The blood products were then slowly injected. During this phase, the assistant put their fingers on the portals to reduce out-flow of the injected solutions. Approximately 5 minutes after complete injection of the autologous blood products, about 100 cc of air was introduced through a sterile syringe connected to the camera inflow. A dry arthroscopic check was performed to evaluate the clot formation of the applied solution.

Postoperative rehabilitation

Patients in both groups followed the same accelerated rehabilitation protocol. They were discharged the day after the operation wearing a sling (Ultrasling II; Don Joy, Carlsbad, CA, USA). Patients were instructed to wear the sling continuously for 10 days postoperative. At postoperative day 10, passive assisted exercises were begun. Once passive, ROM was completely restored; and at a minimum of 30 days from the operation patients were allowed to start assisted active range-of-motion exercises. Selective strengthening exercises were started a minimum of 2 months postoperative.

Statistical analysis

Values are given as means ± SD. We tested differences between the treatment and control group for continuous variables with an unpaired Student *t* or Mann−Whitney test, according to the characteristics of the data distribution. The 95% confidences intervals were calculated for significant differences of continuous variables.

We tested differences for categorical variables with a chi-square test or Fisher's exact test, using the chi-square test to assess a linear trend for the increasing degree of tear retraction. Since clinical outcome variables were repeatedly measured over time, a multivariate analysis of variance (MANOVA) for repeated measures was carried out. MANOVA allowed investigation of an overall time effect, the general group effect, and the time by group interaction effect.

A paired samples Student *t* test or nonparametric sign test was used to test pre- and postoperative values of continuous variables. Statistical analysis was carried out using SPSS software (SPSS, Chicago, IL). For all analyses, a value of $P < .05$ was considered significant.

Results

Demographics data

The 2 groups of patients matched for age, gender, dominance arm, and body mass index ($P > .05$). No difference was observed for intraoperative findings, suggesting that the randomized procedure produced well-balanced and comparable groups. Table II summarizes the demographic and intraoperative data of the 2 groups.

In 11 patients in the PRP group and in 13 patients in the control group, lesions affected only the supraspinatus. All 3 tendons were involved in 6 patients in the PRP group and for 4 patients in the control group.

Early pain results (VAS)

All patients completed early pain follow-ups. A significant difference was found in pain scores between the PRP and control groups at baseline. The VAS score was found to be significantly lower in the PRP group at 3, 7, 14, and 30 days postoperative (Table III).

The mean VAS score was significantly lower than the preoperative value as soon as 3 days after surgery in the PRP group ($P = .04$). On the other hand, no reduction of the pain score was observed at 3 days compared to the preoperative value in the control group. At postoperative day 7, pain decreased significantly for the control group compared to the preoperative value ($P = .003$).

No difference was found for pain at 3, 6, and 12 months; however, a significant difference was found between the 2 groups at 24 follow-up months ($P = .09 \pm .4$ for the PRP group and 1.5 ± 2.1 for the control group; $P = .002$).

Table II Demographic and intraoperative data for the PRP and control group. The body-mass index is the weight in kilograms divided by the square of the height in meters. Values are expressed as mean ± standard deviation or number (%)

	PRP group	Control group
Epidemiological factors		
Age	61.6 ± 8.3	59.5 ± 10.7
Body−mass index	25.4 ± 3.7	25.6 ± 2.7
Male−no. (%)	8 (29.6)	13 (50)
Dominance−no. (%)	19 (70.4)	22 (84.6)
Intraoperative features		
Tear shape−no.		
Crescent	12	17
U	9	5
L/ inverted L	5	5
Retraction of tears-no.		
Minor (stage 1)	9	12
Moderate (stage 2)	7	7
Severe (stage 3)	3	4
Massive (stage 4)	7	4
Biceps-no.		
Spontaneous rupture	4	2
Tenodesis	4	1
Tenotomy	15	18
Anchors	2 ± 0.9	1.6 ± 0.7
Sutures	4.2 ± 1.9	3.7 ± 1.7

PRP, platelet rich plasma; *no.*, number.

Clinical outcomes

Functional scores were not different at baseline. There was a statistically significant difference between the PRP and control groups for all the clinical outcomes (Constant, SER modified UCLA, SST) at the 3-month follow-up. The 95% confidence interval (95% CI: 1-13.3) included the predefined value used for power analysis (7 points of Constant score) at 3 months postoperatively. There were no significant differences between the PRP and control groups at 6, 12, and 24 months (Table II).

In the PRP group, all clinical scores significantly improved in comparison to the preoperative values at 3 months after surgery. A significant increase was seen for both subjective (including pain and daily activities) 17.7 (±5.1) to 28.2 (±11.6) and objective (including range of motion and strength in forward flexion) 29.2 (±3.4) to 36.1 (±7.3) ($P < .001$; $P = .003$) Constant scores at 3 months postoperative. SER improved from 1.9 kg (±1.7 kg) to 3 kg (±1.6 kg) ($P = .003$) at first follow-up. The objective Constant score improved significantly until 24 months after surgery ($P = .01$) (Fig. 2). The SER increased until 6 months after surgery ($P < .001$); thereafter, SER score progression was not significant (Fig. 3).

In the control group, UCLA, SST, and subjective Constant score significantly improved at 3 months. No significant differences were seen for SER and objective Constant score at 3 months compared to preoperative values. SER and objective Constant score significantly

Table III Clinical outcomes in the PRP and control group before surgery and at 3, 6, 12, and 24 months follow-up post-op. Plus–minus values are means ± SD. A value of $P < .05$ was considered significant

	Pre-op.	3 days	7 days	14 days	30 days
VAS					
PRP group	4.8 ± 2	4 ± 3.2	3 ± 3	1.6 ± 2.5	1.1 ± 2.2
Control group	6.4 ± 2	6.3 ± 2.8	4.9 ± 2.4	3.1 ± 2.4	2.4 ± 2.6
P value	.003	.007	.002	.004	.01
	Pre-op.	3 months	6 months	12 months	24 months
Constant					
PRP group	44 ± 16.5	65 ± 9	73.1 ± 8.7	78.3 ± 6.4	82.4 ± 6.3
Control group	42.2 ± 15.2	57.8 ± 11	72.3 ± 12.6	75.7 ± 9.5	78.7 ± 10
P value	.6	.02	.7	.3	.1
SER (Kg)					
PRP group	1.9 ± 1.7	3 ± 1.6	3.9 ± 2.1	4.2 ± 2.8	4.3 ± 2.3
Control group	2.3 ± 2	2.1 ± 1.3	3.3 ± 1.3	3.7 ± 1.5	4 ± 1.9
P value	0.4	.04	.2	.5	.5
UCLA					
PRP group	15.3 ± 5.9	26.9 ± 3	30.6 ± 4.1	31.2 ± 5.2	33.3 ± 2.2
Control group	14.5 ± 5.6	24.2 ± 4.9	29.2 ± 4.9	31 ± 4.1	31.3 ± 4.1
P value	.6	.03	.3	.7	.06
SST					
PRP group	4.8 ± 3.1	8.9 ± 2.2	10.6 ± 1.4	11.1 ± 0.9	11.3 ± 0.9
Control group	4.7 ± 2.8	7.1 ± 2.7	10.5 ± 2.3	10.6 ± 1.5	10.9 ± 1.4
P value	.9	.02	.9	.3	.3

VAS, Visual Analog Score for Pain; *PRP*, platelet rich plasma; *SER*, strength in external rotation; *UCLA*, University of California; *SST*, Simple Shoulder Test.

increased starting from 6 months after surgery (Figs. 2 and 3); thereafter, SER progressed significantly, only at the last follow-up ($P = .01$). Objective Constant score improved significantly until 24 months post-operatively.

Multivariate analysis

Outputs of multivariate analysis for objective Constant score demonstrated the following significant effects: 1) a time effect and 2) a time by group interaction effect. The first result meant there was a significant change over time in the objective Constant score. The second result demonstrated the there was a significant difference between the 2 groups which developed over time.

Cuff integrity

A total of 45 patients were available for radiological examination. The overall mean time between surgical operation and postoperative radiological follow-up was 23 ± 5 months (25 ± 5 months for the control group and 21 ± 5 months for the PRP group). The mean radiological follow-up time was slightly longer in the control group ($P = .003$). The number of identified re- tears was 9 (40%) in the PRP group and 12 (52%) in the control group. This difference was not statistically significant ($P = .40$).

The repair integrity of the overall sample was significantly associated with age, shape and tear retraction (Table IV). The mean age of patients with a torn cuff was higher than those with an intact cuff. Crescent shape tears were more likely to have an intact cuff after repair compared to those with an L, inverted L, or U shape tear. Massive tears (stage 4) had the highest chance of re-tears after repair.

The effect of prognostic factors was more evident in the PRP group (Table IV). Although there was a trend, the association with prognostic factors failed to be significant in the control group (Table IV). Furthermore, postsurgical tear recurrence in the PRP group showed a significant linear trend for the increasing grade of tear retraction ($P < .001$ by the chi-square test for trend).

Clinical outcomes were affected by cuff integrity. In particular, the repeated measures analysis, performed for active strength in forward flexion, indicated that the average over time for intact repairs was significantly different from the average for failed repairs for both treatment groups (Figs. 4 and 5). The best way to describe the development over time was a linear function in the PRP group. A different progression over time was found between intact and failed repairs in the control group.

Stratified analysis

A stratified analysis of study populations was performed to focus on subjects with less extensive tears. We were interested to study smaller tears, as they may be more responsive

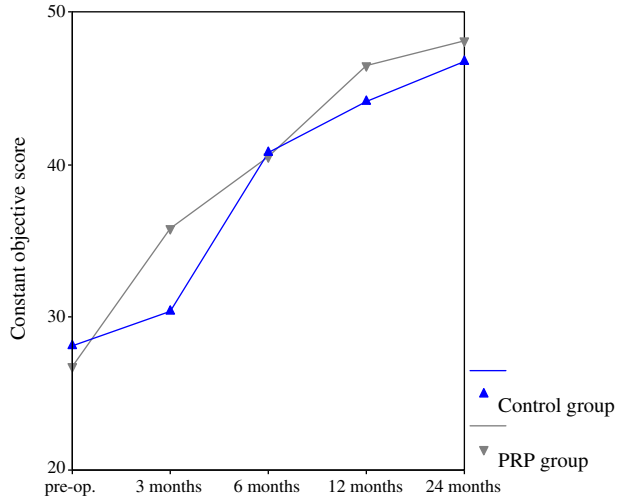


Figure 2 Constant objective score for the platelet rich plasma and control group at the 3-, 6-, 12-, and 24-month postoperative follow-ups.

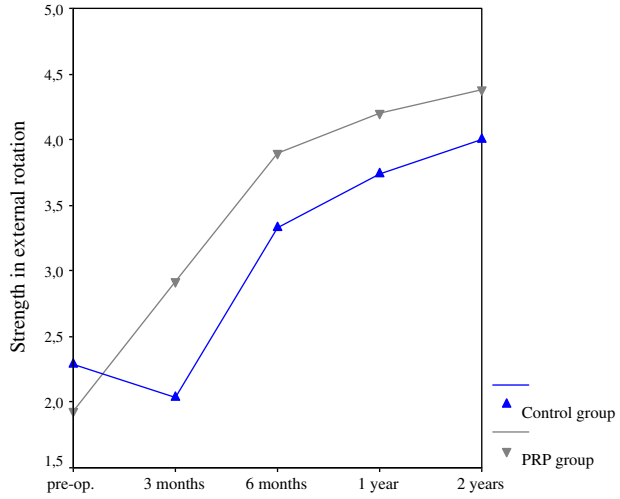


Figure 3 Strength in external rotation for the platelet rich plasma and control group at the 3-, 6-, 12-, and 24-month postoperative follow-ups.

to biological augmentation. Stratification allowed us to compare study populations with a tear size having a similar healing ability.

We compared clinical outcomes of patients that had grade 1 or 2 sized tears. There were 35 patients (66%): 16 patients in the PRP group (treatment subgroup) and 19 patients in the control group (control subgroup). Demographic characteristics were similar for the 2 subgroups ($P > .05$) (Table V).

In those with a grade 1 or 2 tear, there was no significant difference in functional score between the 2 subgroups at baseline ($P > .05$). There was a statistically significant difference, favoring the PRP treatment group, in all the clinical outcomes at 3 months postoperative (Constant: 68 ± 7 vs 56 ± 13 $P = .006$; SER: 3.5 ± 1.3 vs 2 ± 1.3 $P = .004$; modified UCLA: 27 ± 3 vs 24 ± 5.4 $P = .03$; SST: 9.3 ± 2 vs 7 ± 3 $P = .01$). Objective measures of the Constant score in the PRP group were significantly higher than the control group at 3 and 12 months (37.9 ± 5.2 vs 29.3 ± 9.4 $P = .005$; 48.5 ± 4.5 vs 44 ± 6.8 $P = .02$). At 24 months, the PRP scores were higher, but not at a significant level (50.6 ± 3.5 vs 47 ± 6.9 $P = .07$). SER was significantly higher in the PRP group compared to the control group at 3, 6, 12, and 24 months postoperative (Fig. 6).

The number of identified re-tears in grade 1 or 2 tears was 2 (14%) in the PRP group and 6 (37%) in the control group ($P = .2$ by Fisher's exact test). A difference in the re-tear rate for patients with minor tear retraction (grade 1) was observed at a significance level of 8% (Fisher's exact test; 0% in the PRP versus 40% in the control group). No significant differences were seen between the 2 groups for the patients with stage 3 and 4 tears.

Complications

A patient in the control subgroup underwent an arthroscopic revision of a failed rotator cuff repair 26 months after the primary surgery. The radiological diagnosis of partial re-tear of supraspinatus tendon was confirmed by a diagnostic glenohumeral arthroscopy. The weak tendon was re-tensioned by 2 suture anchors.

Discussion

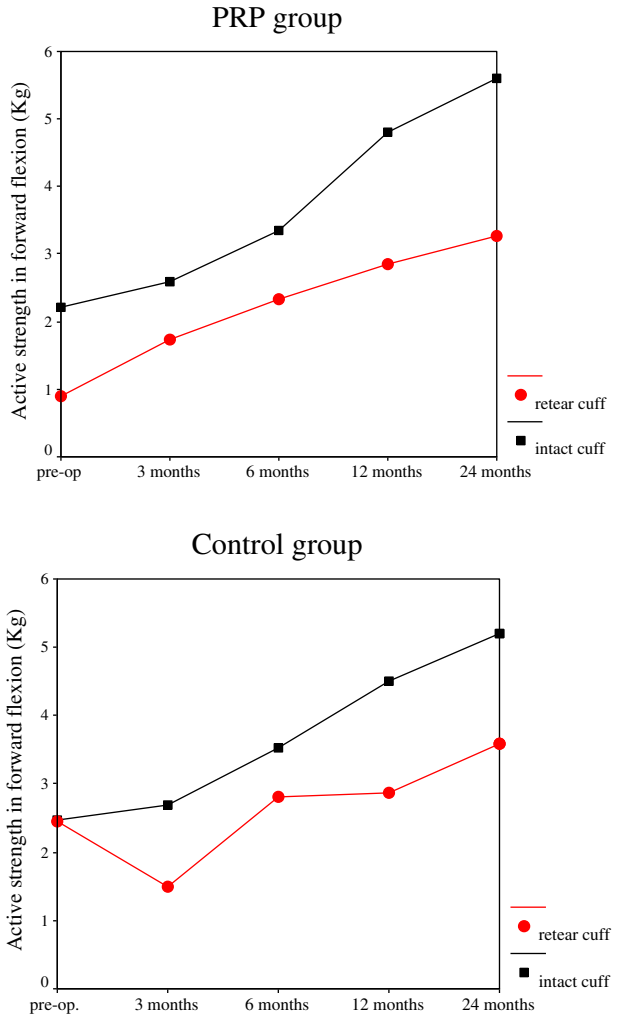
The prevalence of degenerative rotator cuff tears is increasing as the population ages.[38] Failed healing and re-tearing of the rotator cuff are frequent complications following rotator cuff repair.[8] Autologous PRP is an attractive biologic strategy to augment tissue healing.[15,26] Natural tendon healing occurs in 3 phases: inflammation, proliferation, and remodeling. These overlapping phases are regulated by a variety of growth factors. Many of these growth factors are stored in platelet α- granules; therefore, PRP will contain supraphysiologic doses of them. These native cytokines may help initiate or accelerate tendon healing. Vascular endothelial growth factor, platelet derived growth factor, and transforming growth factor β have the potential to play a role in regeneration of tendon tissue through increased tendon cell proliferation, collagen synthesis, and vascularization. In vitro and animal studies of PRP application have reported a positive effect on tendon collagen deposition and tendon vascularization.[4,11,28]

Evidence on surgical or nonsurgical use of PRP in treatment of tendon pathologies are available in the literature.[20] An early recovery after local application of platelet rich fibrin has been demonstrated during open Achilles tendon repair in athletes. These subjects were able to return to their previous sport activity at an average of 14 weeks,

Table IV Prognostic factor: the association between age, tear and retraction tears, and re-tear rate was studied in both the 2 groups and in the overall population. Nonsignificant *P* value (>.05; ns) are not reported in the table

	PRP group			Control group			Overall		
	Intact ($n = 13$)	Retear ($n = 9$)	*P*	Intact ($n = 11$)	Retear ($n = 12$)	*P*	Intact ($n = 24$)	Retear ($n = 21$)	*P*
Prognostic factors									
Age	55,6	64,9	0,04	59,5	62,6	n.s	57,4	63,6	0,02
Tear shape- %									
Crescent	82%	18%		61%	36%		72%	28%	0,01
U	25%	75%	n.s.	22%	80%	n.s.	22%	78%	
L/ inverted L	43%	57%		17%	75%		36%	64%	
Retraction of tears - %									
Minor (stage 1)	100%	0%		60%	40%		79%	21%	0,001
Moderate (stage 2)	60%	40%	0,003	67%	33%	n.s.	64%	36%	
Severe (stage 3)	33%	67%		25%	75%		29%	71%	
Massive (stage 4)	0%	100%		0%	100%		0%	100%	

PRP, platelet rich plasma; *ns*, nonsignificant.



Figures 4 and 5 Strength in forward flexion: intact vs failed repair in the platelet rich plasma and control group at 3-, 6-, 12-, and 24-month postoperative follow-ups.

compared with an average of 22 weeks in the untreated group.[36]

Mishra and Pavelko[30] showed that a local injection of PRP positively affected symptoms in chronic elbow tendinopathy compared with a control group. A significant improvement in both VAS and Mayo Elbow Performance scores were seen at 8 weeks follow-up. A recent double-blind, randomized, controlled study investigating PRP versus cortisone injection for chronic lateral epicondylitis showed more reduction in pain and higher Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire scores at 52 weeks.[33]

Kon et al[22] recently published a prospective evaluation of 20 male athletes with chronic patellar tendinosis who each received 3 PRP injections into the tendon at 15-day intervals. No severe adverse events were observed, and statistically significant improvements in all scores were noted at 6 months follow-up. The method was considered efficacious for the treatment of jumper's knee.

We are aware of a single randomized controlled study that reported no differences in pain and activities scores in a group of patients with chronic mid-portion Achilles tendinopathy treated with an eccentric exercise program and a single PRP injection compared to a control group.[12] Due to the pressure within tendon, a limited fraction of PRP could be left in the tendon after the single PRP injection; but, tendon healing was not better compared to a eccentric exercises program.

To our knowledge, only a single human study has studied long-term results of PRP augmentation in rotator cuff repair.[34] This pilot study concluded their technique for PRP application in arthroscopic was safe with no reported complications. In the current, randomized, double blinded, controlled study, we found that application of PRP positively affects the healing of a rotator cuff repair when compared to a control group.

Table V Demographic characteristics of PRP and control subgroup. The body-mass index is the weight in kilograms divided by the square of the height in meters. Values are expressed as mean ± standard deviation or number (%)

	PRP subgroup ($N = 16$)	Control subgroup ($N = 19$)
Age	57 ± 12	60 ± 8.6
Body—mass index	24.6 ± 2.6	25.2 ± 4.2
Male—no. (%)	7 (43.8)	4 (21.1)
Dominance—no. (%)	14 (87.5)	13 (68.4)

PRP, platelet rich plasma; *no.*, number.

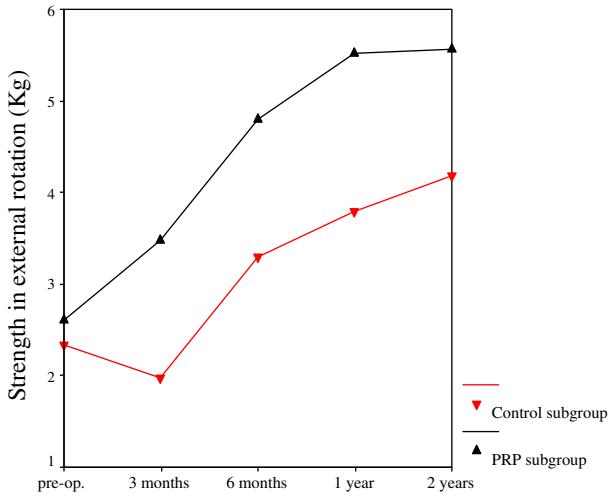


Figure 6 Strength in external rotation for platelet rich plasma and control subgroup at 3-, 6-, 12-, and 24-month postoperative follow-ups.

During the design of the study, a difference of 7 points on the Constant score between the 2 groups was determined to be clinically relevant. This was based on literature reports of a reduction of approximately 30% in strength compared to the nonoperative shoulder (which correlates to 7 points on the Constant score) that has been observed several months after cuff repair.[25,27] We decided to assess this difference at 3 and 6 months to investigate the early phases of tendon healing, 12 months to investigate the middle portion of tendon healing, and 24 months to study the long-term outcome.

Using a multivariate model to analyze the objective Constant score, we observed a different progression over time between the 2 study groups. The objective Constant scores for the PRP group were significantly improved compared to preoperative values at 3 months. A significant improvement was not seen in the control group until 6 months postoperative. The fact that the objective Constant score significantly increased after 6 months in the control group is consistent with a recent study[7] analyzing the time for functional recovery after arthroscopic cuff repair, which concluded pain and activity score significantly improved at 3 months postoperative, with functional recovery coming longer postoperative.

A lower pain score was observed in the PRP group in the first month after surgery. Even if these differences could be affected by preoperative values, an effect of PRP application also occurred as we observed an early significant reduction at 3 days postoperative only in the PRP group. A possible explanation for this result was related to platelet analgesic properties. Recently, platelets have been identified to have analgesic properties by releasing protease-activated receptor 4 peptides.[1]

Although the Constant score remained higher in the PRP group until the last follow-up time, the difference was not significant between the 2 groups at 6, 12, and 24 months. The PRP group did better compared to the control group with respect to cuff integrity (60% vs 48%); however, the difference was nonsignificant at a mean follow-up of 23 months after surgery.

Tendons have low metabolic rates at baseline and are predisposed to slow healing after injury.[37] PRP application accelerates tendon healing after rotator cuff repair, possibly promoting a faster return to pre-injury activity level. We found higher subjective scores (including daily living activities) at 3 months postoperative in the PRP group compared to the control group.

The findings of this study demonstrate an accelerated repair of rotator cuff utilizing PRP application. It is reasonable to consider this accelerated healing could correlate with an earlier return to work or sport. Investigation into the potential for PRP application improving return to work time following rotator cuff repair should be performed in future studies of PRP application during rotator cuff repair.

Furthermore, these findings of short-term improvement support PRP use in sport medicine patients. This active patient population demands a rapid return to their pre-injury level of function after rotator cuff repair. Given the findings of the current work, it is reasonable to hypothesize PRP application could accelerate the return to pre-injury level. This should also be investigated in future work. Recently, the WADA (World Anti-Doping Agency) Executive Committee has addressed the topic of PRP use and decided that tendon injuries in athletes can be treated with platelet-derived preparation.

We found an overall healing rate of 54%. This result was in agreement with data reported in the literature; a rate of 53% has been previously described after arthroscopic rotator cuff repair by MRI postoperative follow-up.[2] Similar to the others reports, we found the re-tear rate was influenced by age and tear severity.[9,21,32] This finding was true when the PRP and control group were pooled; however, when the patients were divided into PRP and control groups, we found this association to only be significant in the PRP group. Interestingly, we found a significant linear relationship between the risk for re-tears and the grade of retraction in the

PRP group. This means that the chance for an intact cuff was inversely proportional to the grade of tear retraction. Although there was a similar trend for this association in the control group, it was not significant as failed repairs were more equally distributed between stages of tear retraction.

In analyzing clinical outcomes of patient subgroups with less extensive tears, we found higher clinical scores at medium- and long-term follow-up in the PRP side. The objective Constant score was significantly higher at 3 months, as well as at 12, in the PRP sub-group compared to the control sub-group. The difference in objective Constant score between the 2 groups was borderline significant at the 24-month follow-up ($P = .07$). SER was different from average value of control sub-group at all follow-up intervals. Despite the limited number of patients with minor tear retraction (stage 1), we found a borderline significant difference in re-tear rate between the 2 groups ($P = .08$).

Literature studies have reported substantial rates of clinical failure in the surgical treatment of smaller tears.[2,3,16,21,24,39] The findings of the present investigation support the assumption that PRP application can positively affect long-term results of patients with less extent tears. Future investigations are needed to confirm and strengthen these results.

A limitation of our study is that the amount of platelets and the quantity of growth factors that were present in the activated PRP was unknown. Nonetheless, good platelet collection efficiency was reported with the use of the platelet separation system used in our study, and a positive correlation between the number of platelets and the harvest of growth factors has been shown.[13,31] A further weakness of the current study is the difference in radiologic follow-up time between the 2 groups. The likelihood of this difference affecting the conclusions is mitigated by the fact that we did not find an association between radiological follow-up time and cuff integrity.

Conclusion

The results of this study support the use of PRP during arthroscopic rotator cuff repair. We found PRP positively affected the early healing after rotator cuff repair compared to a control group. In particular, PRP was seen to accelerate the functional recovery of the repaired rotator cuff. In addition, significant differences in some outcome measures were seen at longer-term follow-ups when patients with stage 1 or 2 cuff tears were compared. Secondarily, PRP was seen to decrease the postoperative pain at early follow-ups.

Disclaimer

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