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ORIGINAL STUDY

Platelet-rich fibrin in arthroscopic repair of massive rotator cuff tears : A prospective randomized pilot clinical trial

Samuel Antuña, Raúl Barco, José M. Martínez Díez, José Miguel Sánchez Márquez

From Hospital Universitario La Paz, Madrid, Spain

The objective of this study was to prospectively evaluate the feasibility of a large- scale project on the influence of local application of Platelet Rich Fibrin (PRF) on the functional outcome and integrity of the arthroscopically repaired tendons in patients with massive tears of the rotator cuff.

A prospective, randomized pilot clinical trial was performed on 28 patients (22 females, 6 males) with an average age of 65 years (range : 53 to 77) undergoing complete arthroscopic repair of a massive rotator cuff tear. After the repair was completed, 6 ml PRF (Vivostat®) was locally applied to the repair site in 14 patients ; no similar action was done in the other 14 patients. All patients underwent a clinical examination and an arthro-MRI to evaluate the integrity of the repair, one year after the operation. They were followed clinically for a minimum of 2 years. Functional outcome was evaluated with the Constant and DASH scores.

There were no reported complications in either group. None of the patients was lost to follow-up. Globally, the Constant score improved from 45 preoperatively (range : 25 to 65) to 64 at one year (range : 20 to 79) ($p < 0.001$), with no significant change at two years (mean 63, range : 20 to 77). The VAS for pain improved from 5.6/10 preoperatively to 1.7/10 at the most recent examination ($p < 0.001$). All but two patients were satisfied. With the numbers of patients available, we could not detect a significant difference in the preoperative (46 vs. 43 ; $p = 0.37$) or postoperative Constant score (61 vs. 68 ; $p = 0.125$) between the control group and the PRF group. On arthro-MRI, 19 of the 28 patients (68%) were found to have a large re-tear : 10/14 in the PRF group and 9/14 in the control group.

Local application of autologous PRF to the repair site of massive rotator cuffs fully reconstructed arthroscopically failed to improve the clinical outcome and the healing rate, compared with a standard repair. However, a large-scale study would be necessary to confirm these results.

Keywords : shoulder ; rotator cuff ; platelet rich plasma.

INTRODUCTION

Rotator cuff tears are very prevalent, especially among individuals older than 60 years. Functional outcomes after surgical reconstruction of symptomatic

■ Samuel Antuña, MD, PhD, Orthopaedic Surgeon.
■ Raúl Barco, MD, PhD, Orthopaedic Surgeon.
■ José M. Martínez Díez, MD, Orthopaedic Resident.
■ José Miguel Sánchez Márquez, MD, Orthopaedic Surgeon.
Shoulder & Elbow Unit, Department of Orthopaedic Surgery, Hospital Universitario, La Paz, Madrid, Spain.
Correspondence : Dr. Samuel Antuña, Shoulder & Elbow Unit, Department of Orthopaedic Surgery, Hospital Universitario La Paz, Paseo de la Castellana 261, 28046 Madrid, Spain.
E-mail : santuna@asturias.com

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small and medium sized tears are very satisfactory despite a significant amount of structural failures on the repair site (*3*). Healing of massive tears has been shown to be very low, with a re-tear rate up to 96% of cases (*10,11*). Even though patients with structural failure commonly achieve a significant pain relief, they often complain of weakness and a variable degree of functional impairment (*15*).

In addition to improving the strength of the repair construct, novel adjuvants have been investigated to aid rotator cuff healing and reduce failure rates. Several studies have investigated the use of platelet-rich plasma (PRP) or plasma rich fibrin (PRF) during rotator cuff repair. Although the reported results are contradictory, the majority of series have not found any benefit with its use (*1,2,4,17*). However, all the available series include small and medium size tears, the group where the risk of tendon healing failure is lower. We are not aware of any prospective randomized trials that have been carried out to specifically examine if augmentation with PRF is superior to standard repair in massive rotator cuff tears (MRCT).

We therefore performed a randomized controlled pilot trial to assess the feasibility of a larger project and compare the efficacy and safety of PRF for arthroscopic MRCT repair compared with non-augmented repair. The primary null hypothesis of this clinical trial was that there is no difference between standard arthroscopic repair of MRCT and repair with PRF augmentation in improvement of the functional outcome, assessed with the Constant Score, twenty-four months after surgery. Secondary study questions addressed differences in disability and structural tendon healing assessed with arthro-MRI.

PATIENTS AND METHODS

The present study received institutional review board, and informed consent was obtained from all patients. Patients were enrolled in a consecutive prospective manner on a voluntary basis. The trial design and reporting follow the CONSORT (Consolidated Standards of Reporting Trials) principles. The study was registered in the public trial registry (ClinicalTrials.gov Identifier : NCT01612845).

From May 2007 to June 2009, 28 patients (22 women and 6 men), with an average age of 65 years (range, 53 to 77) were prospectively recruited for the study (Fig. 1).

The criteria for inclusion were patients with a diagnosis of a MRCT of the postero-superior rotator cuff (two tendons, larger than 5 cms) made by clinical examination and magnetic resonance imaging (MRI). All patients had undergone a failed trial of conservative treatment for at least six months before they were scheduled for surgery. Only patients with tears affecting the supraspinatus and infraspinatus tendons were included.

Exclusion criteria were evidence of anterosuperior tears affecting the subscapularis, previous surgical procedures on the affected shoulder, evidence of major joint trauma to the shoulder, radiographic evidence of substantial osteoarthritis, a major medical condition that would affect quality of life, and patients with Workers' Compensation claim or an unwillingness to be followed for the duration of the study. A haematological study was performed in all cases, and those patients with evidence of chronic infectious disease, anaemia, coagulation disorders, low platelet count or history of difficulty in venous puncture were also excluded from the study.

Final eligibility of the participants for the study occurred following intraoperative visual inspection of the rotator cuff tear and following determination of repairability. The MRCT was considered repairable if the tendon could be restored to a point where the insertion footprint was covered when traction was applied without undue tension. Patients were excluded from the study if the tear was not considered repairable or if there were significant doubts about tendon repairability during the initial intraoperative assessment. All surgical procedures were performed by one of two fellowship-trained shoulder surgeons (S.A. or R.B.). Patients were allocated to undergo either an arthroscopic repair alone or an arthroscopic repair augmented with PRF, using a series of opaque envelopes containing the group assignment based on a computer-generated randomization list. The randomization envelope was opened following intraoperative inspection of the shoulder. The surgeon was not blinded to the treatment allocation, but the research assistant performing follow-up evaluations and the radiologist were blinded.

In all cases antibiotic prophylaxis was administered before surgery. The 28 patients underwent arthroscopic repair of the cuff in the lateral decubitus position under general anaesthesia and interscalene nerve block. Bioabsorbable suture anchors were used in every case (Biocorkscrew, Arthrex, Naples, Fl, USA) and in all cases the repair was considered complete. Identical

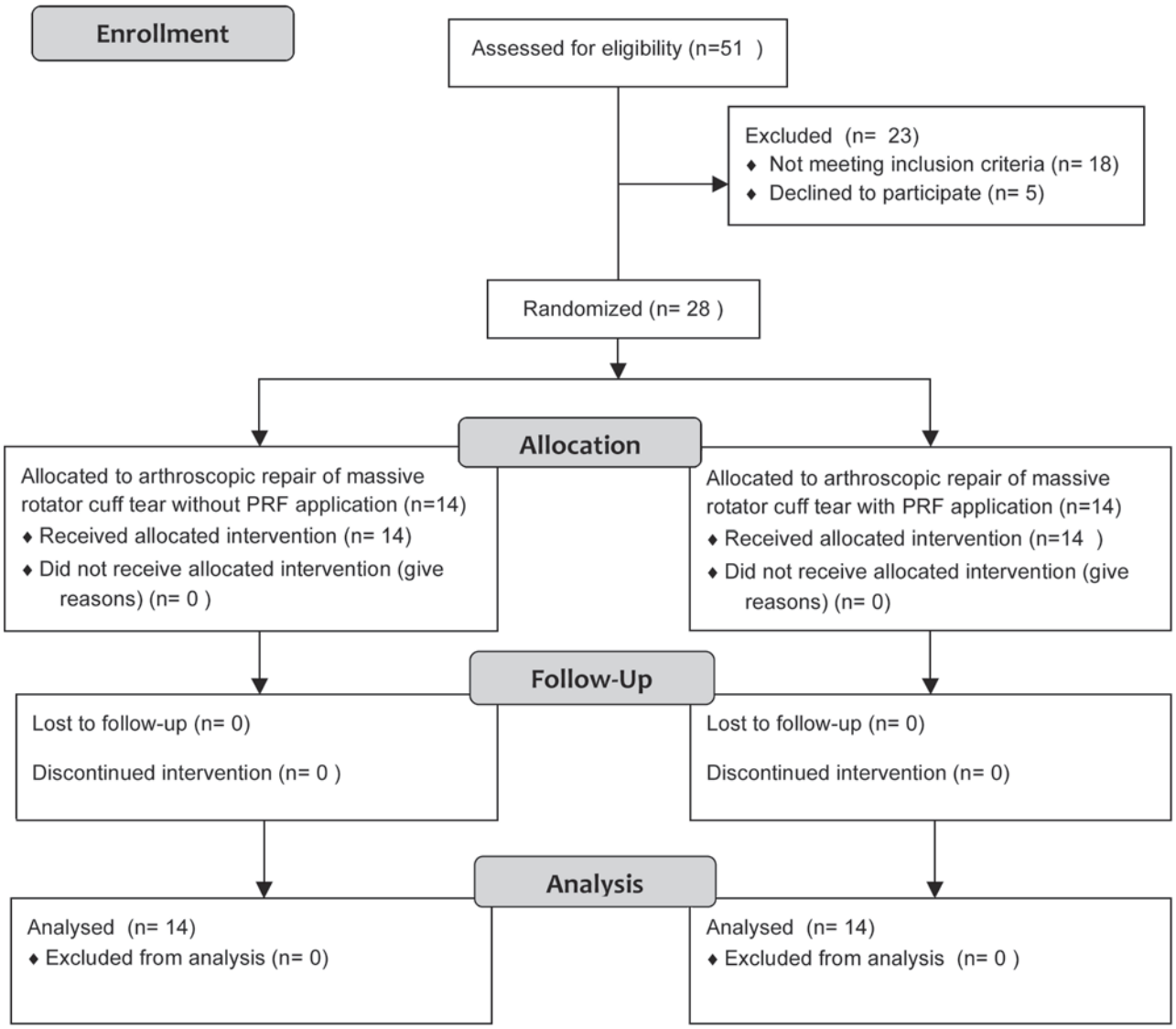

Fig. 1. — Flow diagram of subject progress through the phases of the study

standard surgical techniques for tendon release, advancement and fixation were used for both groups. Resection of an anterior spur was performed in three patients but no acromioplasty was done routinely.

In the experimental group, 120 ml blood was extracted and the sample was processed according to the manufacturer's indications. Once the repair was completed, 6 ml PRF (Vivostat PRF®, Alleroed, Denmark) were directly applied over the repair site under direct visualization with an endoscopic device. In the control group, the repair was completed and no additional treatment was applied.

Postoperatively, all patients were immobilized with an abduction sling for six weeks. During this period they were only allowed to perform pendulum exercises. Thereafter, a standard rehabilitation program with gradual progression from passive motion to active-assisted, stretching and strengthening exercises was implemented.

The primary outcome measure was the validated Constant Score for the assessment of shoulder function (6).

Functional outcomes were assessed preoperatively, and at 12 and 24 months postoperatively. A physical examination was performed to evaluate range of motion and strength in forward flexion. Range of motion was measured with a goniometer. Active strength in forward flexion was tested as an average of 3 pulls in 90º of abduction in the scapular plane. The wrist was fixed in pronation, with the hand facing the floor and the 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. An analogic dynamometer was used to record results. The reading of the dynamometer was taken after 5 seconds of maximum pull. In addition to these measures, all local or general complications during the operative or follow-up phases were recorded.

Secondary clinical outcome measures included a self-report scale to evaluate the upper-extremity disability (Disabilities of the Arm, Shoulder and Hand Questionnaire, DASH). This questionnaire evaluates the ability to carry out activities of daily living, pain on loading and at rest, tenderness, and loss of strength and range of motion. The score is scaled between 0 and 100, with higher scores indicating worse upper-extremity function. Other secondary measures were pain and degree of satisfaction, assessed by a Visual Analog Score (VAS). An independent orthopaedic surgeon not previously involved in the treatment performed the 12-month and 24-month clinical follow-ups.

As a secondary outcome measure, all patients underwent a gadolinium arthro-MRI 12 months after the operation in order to evaluate the integrity of the repair. With the aid of a dedicated radiologist blinded to the treatment group, the status of the tendon was categorized. According to Galatz *et al* (*10*), the transverse dimension or the width of the tear as it was detached from the bone of the greater tuberosity was evaluated. The recurrent defects were categorized as the "same size" if the defect was within 2 mm of the size on the preoperative MRI, or as "smaller" if the defect was > 2 mm smaller than the preoperative transverse dimension.

Statistical Analysis

Statistical analysis consisted of means and standard deviations for continuous data and frequency counts for discrete data. Inferential analysis was conducted with use of a Wilcoxon paired rank test to account for potentially non-normal data distributions for continuous variables and a chi-square test for discrete variables. A two-tailed p value of ≤ 0.05 was considered significant.

RESULTS

Patient flow through the stages of the study is shown in Figure 1. All patients completed the primary (24-month) follow-up. There were no complications related to the surgical procedure or to the blood sample extraction for PRF preparation. All patients were satisfied or very satisfied with the procedure at final follow-up, except for two patients, one in each group.

For the 28 patients, the average Constant score improved from 45.1 (range : 25 to 65) preoperatively to 64.4 (range : 20 to 79) at the one year follow-up ($p < 0.005$). The mean Constant score did not change significantly two years after the operation (63.2, range : 20 to 77). When analyzed individually, all the variables explored to complete the Constant Score showed a significant improvement. The VAS score for pain improved from 5.6 points (range : 0.5 to 9), before the operation to 1.5 points (range : 0 to 8) at one-year follow up, and 1.7 (range : 0 to 8) at two years ($p < 0.001$). The DASH score improved from 54.8 (range : 13 to 90.2) to 26.4 (range : 0 to 76.7) at one year and 29 at two years (range : 0 to 76.7) ($p < 0.0005$).

When we compared the clinical results between the PRF group and the control group at one year, with the numbers available for the study, we could not detect any significant difference in the postoperative Constant (60.8 versus 68 ; $p = 0.466$) or DASH (25.8 versus 27 ; $p = 0.379$) scores. No significant clinical global changes over time were detected in either group (mean Constant score, 58.5 versus 67.7 ; mean DASH score 30.1 versus 27.7). However, four patients, all of them in the PRF group, had worsened their clinical status between the one-year and two-year examination : three of them had more pain in the shoulder but not enough to pursue further treatment, and one patient underwent reverse shoulder arthroplasty 22 months after the index procedure owing to significant pain and functional impairment.

On the postoperative arthro-MRI, 19 of the 28 patients (68%) had an obvious large full-thickness tear of the same size or bigger than the initial tear : ten in the PRF group and 9 in the control group. Four additional patients (three in the PRF

group, one in the control group) showed a tear, which was considered smaller than the original one. With the numbers available for the study, we could not detect any significant difference between both groups on the re-tear rate.

DISCUSSION

This randomized controlled pilot trial showed that it would be safe and feasible to develop a large-scale, maybe multicentre trial on the use of PRF in patients with MRCT. Although it must be acknowledged that the present study may be underpowered due to the limited number of patients included, we should probably accept that considering the low prevalence of massive tears undergoing complete repair, the results of the present should be taken into consideration.

Our data shows that in patients with massive rotator cuff tears, local application of PRF to the repair site of fully reconstructed tendons did not result in significantly improved shoulder function (as evaluated with the Constant score) or structural outcome (as evaluated by arthro-MRI) when compared with standard arthroscopic repair. There were no adverse events related to use of PRF. At a minimum 24 months clinical follow-up, arthroscopic surgical repair of a MRCT resulted in significant improvement independently of the use of PRF. To our knowledge, this is the first randomized controlled trial to specifically compare the outcome of arthroscopic repair of MRCT with or without augmentation with PRF using both clinical and imaging criteria.

The mechanism of action of PRP is based on an increase in the number of platelets above baseline values. Platelets play an instrumental role in the normal healing response via the local secretion of growth factors. Numerous growth factors have been identified as crucial in the healing process of tendon injuries (*14*). Several studies have provided some evidence that PRP can stimulate healing signaling associated with tendon healing by increasing the collagen gene expression and increased production of growth factors. Although there is little clinical information available, some authors have described the intraoperative use of PRP in tendon repair (*7,16-17*).

Recently, a few studies have evaluated the influence of PRP on the healing rate of rotator cuff repairs (*1-2,4,17-18*). These series almost universally show that, when applied to small and medium tears, there is no significant benefit with its use, neither clinically or in the healing rate. Patients with smaller tears usually achieve good clinical outcomes with acceptable rates of recurrent tears regardless of the surgical technique used. Among the very few published series addressing this problem, only Randelli *et al* (*17*) found some benefit on the postoperative pain relief and final strength in external rotation, but no significant differences in overall functional scores or re-tear rates. Even though the scientific evidence seems to conclude that PRP application on the repair site of small and medium tears does not offer any benefit over standard techniques, we must acknowledge that the heterogeneity of the PRP products used and the variability in patient selection may influence these results (*9*). From our study, we can only conclude that the endoscopic application of a fibrin clot rich in platelet derived growth factors directly at the repair interface of fully reconstructed massive tears offered no clear clinical benefit.

Even though rotator cuff repair is a gratifying procedure, with high rates of patient satisfaction and functional improvement, larger and massive tears represent a challenge (*10,13*). Despite an adequate surgical reconstruction, the tendons very often do not heal. The rate of healing in our group was 18%, similar to what has been reported by other authors. Although the majority of patients with non-healed cuffs are elderly and report a high degree of satisfaction due to pain relief, some of them may complain of shoulder weakness, which limits some activities (*3,10,15*). Therefore, any biologic treatment directed to enhance the healing rate of massive tears would represent a considerable improvement in rotator cuff surgery (*9-10,11*).

The strengths of our study are that it represents the first prospective controlled trial of PRP administration in massive tears, the system we elected for PRF administration (Vivostat®) allows arthroscopic application and contains a very high concentration of growth factors, and the same surgical team with

identical technique performed all the surgical procedures.

The main limitation of our study is that the number of patients included is low, and therefore it should be only considered an initial exploratory clinical trial. However, the information derived from this study should be considered valuable because the prevalence of reparable massive tears is low, and in order to achieve a high statistical power we would have had to operate many patients with a scientifically unproved technique over a long period of time.

Our results confirm that arthroscopic repair of massive rotator cuff tears yields a high patient satisfaction. Regardless of the surgical technique used, the re-rupture rate is high. Growth factors may not play a direct role in enhancing tendon integration into the bone. The status of the affected muscle, and the decreased potential for healing of the degenerated tendon may be more relevant than the surgical technique used, and should probably be the focus of future research (*5,8,12*).

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