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Original article

In vivo clinical and radiological effects of platelet-rich plasma on interstitial supraspinatus lesion: Case series

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ABSTRACT

Background: Rotator cuff tear (RCT) is a frequent condition of clinical relevance that can be managed with a symptomatic conservative treatment, but surgery is often needed. Biological components like leukocytes and platelet rich plasma (L-PRP) could represent an alternative curative method for interstitial RCT.
Hypotheses: It has been hypothesized that an ultrasound guided L-PRP injection in supraspinatus interstitial RCT could induce radiological healing.
Material and methods: A prospective case series including 25 patients was performed in order to assess the effect of L-PRP infiltration into supraspinatus interstitial RCTs. Primary outcome was tear size change determined by magnetic resonance imaging arthrogram (MRA) before and 6 months after L-PRP infiltration. Secondary outcomes were Constant score, SANE score, and pain visual analog scale (VAS) after L-PRP infiltration.
Results: Tear volume diminution was statistically significant ($P = .007$), and a >50% tear volume diminution was observed in 15 patients. A statistically significant improvement of Constant score ($P < .001$), SANE score ($P = .001$), and VAS ($P < .001$) was observed. In 21 patients, Constant score improvement reached the minimal clinical important difference of 10.4 points.
Discussion: We observed a statistically significant and clinically relevant effect on RCT size and clinical parameters after L-PRP infiltration. Such an important improvement of supraspinatus interstitial RCT with conservative management is uncommon, therefore intratendinous L-PRP infiltrations could have been beneficial. This encouraging result could pave the way for future randomized studies in order to formally determinate whether L-PRP infiltrations are a possible alternative to surgical treatment of interstitial RCT.
Level of evidence: Prospective observational study; Level of evidence II.

1. Introduction

The shoulder is a common source of disability resulting from traumatic and degenerate tears of the rotator cuff, with an estimated prevalence of 4–26% [1–6]. About 1% of adults 45 years old and over consult their general practitioner with a new presentation of shoulder pain every year [7]. Superior RCT most often appears at the bone-tendon junction, the so called enthesis, and can present different patterns of tendinopathies or tears. RCT could be classified into partial bursal-side supraspinatus tendon tear, partial articular-side supraspinatus tendon tear, interstitial or full-thickness tears. Non-operative management of interstitial RCT has

Abbreviations: RCT, rotator cuff tear; L-PRP, leukocytes and platelet rich plasma; MRA, magnetic resonance imaging arthrogram; VAS, pain visual analog scale; NSAIDs, non-steroidal anti-inflammatory drugs; PRC, platelet rich concentrates; MCID, minimal clinically important difference.

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focused on treatment of the predisposing factors, physiotherapy, the use of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) usually in association with local anesthetic and steroid injections. Frequently, a combination of conservative treatment options are used and it is difficult to predict the success of each individual therapy [8]. In case of conservative treatment failure, open or arthroscopic surgeries may consequently become a treatment option. However, repairs of degenerate and torn tissue are prone to failure due to many intrinsic and extrinsic factors. Therefore, new treatment strategies in interstitial RCT are necessary.

Biological therapies might become another conservative treatment that may improve clinical, mechanical, and radiologic outcomes. Because of the high concentration of growth factors in platelet rich concentrates [9], injections of L-PRP may have led to reduced pain and improved recovery in other degenerate pathology areas, together with the restoration of function [10–12]. There remains ongoing controversy regarding its clinical efficacy, as in vivo studies failed to demonstrate an improvement after PRC therapy associated to rotator cuff repair [13–15]. Nevertheless, during these previous studies, Platelet rich concentrates (PRC) were deposited at the tendon-bone interface during surgery; an important concentration of PRC was inevitably lost in the glenohumeral joint and the subacromial space, or was diluted by arthroscopic lavage or hematoma, as the substance was not injected in a confined space. The authors of the present study thus believe that ultrasound guided intratendinous injection of PRC remain a good indication in case of interstitials lesions. In the latter condition, the concentrates that contain many of the fundamental growth factors at high dosages, potential carrier for stem cell, would release the growth factors over time, and would not be washed out of the bone-tendon interface, as has probably been the case in previous studies.

The aim of the present study was to assess effectiveness of L-PRP infiltrations into supraspinatus interstitial RCT on tendon healing and clinical outcome. We therefore hypothesized that ultrasound guided L-PRP injection in supraspinatus interstitial RCT would induce radiological tendon healing and improve clinical symptoms.

2. Methods

2.1. Patient selection

Between October 2012 and April 2014, all patients above the age of 18 having a supraspinatus interstitial RCT were considered potentially eligible for inclusion in this prospective case series study. Twenty-eight patients were assessed for eligibility, and were all included into the study. Inclusion criteria were (1) an isolated supraspinatus interstitial RCT and (2) a previous conservative treatment that resisted to 6 months of physiotherapy including treatment of kinematic alterations consistent with scapular dyskinesis [16–18]. Exclusion criteria included supraspinatus tendon calcification, rotator cuff surgery during the first 6 months after L-PRP infiltration, corticoid infiltration on the 3 months following the L-PRP infiltration, immune system compromise, pregnancy, significant upper extremity comorbidity, anticoagulation therapy, and history of shoulder surgery. All patients underwent L-PRP infiltration after a magnetic resonance imaging arthrogram (MRA) supraspinatus evaluation with gadolinium. An MRA was performed using a 1.5 Tesla scanner (GE general system, Sigma, HDX 1.5). Axial (T1 fat-saturated, 3D merge), coronal (T1 fat-saturated, T2 fat-saturated), and sagittal (T1, T2 fat-saturated) views were obtained. All sequences were performed with a 16-cm field of view, 256×512 matrix and 3-mm slice thickness. On initial MRA, a supraspinatus tear was considered as interstitial when (1) the lesion was totally surrounded by supraspinatus tendon or greater tuberosity in all slices; (2) the contrast product was not in contact with the lesion; (3) the subacromial bursa was not in contact with the lesion. Six months after L-PRP infiltration, MRA was repeated. Exercise or work soliciting shoulders were avoided during the 72 h following L-PRP infiltration. No physiotherapy or steroid *injections* were performed during the study interval. The latter are reported to have a negative effect on rotator cuff tendon-to-bone healing in the animal model [19]. The study received prior approval from the Human Research Ethics Committee (ethical committee approval; Geneva ethical board; Switzerland; protocol 12–26). Written informed consent was obtained from the patient for publication of their individual details and accompanying images in this manuscript.

2.2. Study variables

The outcome of interest was the supraspinatus tear volume prior and 6 months after L-PRP infiltration healing. Furthermore, the number of patients with a loss of more than 50% tear volume were evaluated. Fifty percent of initial tear was chosen in order to assess whether radiologic differences were clinically relevant. Secondary outcomes included prior and 6 months after L-PRP infiltration visual analog scale (VAS) graded from 0 (no pain) to 10 points (maximal pain), SANE score [20], Constant score [21], and the number of patients reaching Constant score minimal clinically important difference (MCID). All the data was recorded by an independent observer (MG). The following baseline characteristics were also assessed prospectively prior L-PRP infiltrations: age, gender, type of work, dominant hand touched, tobacco use, alcoholism, diabetes, hypercholesterolemia.

2.3. Injection technique

The patient's own platelets were collected using the Recover System (GPS II-Plasmax-Platelet Concentration System; Biomet Biologics, Warsaw, IN, USA). This device uses a desktop-size centrifuge with disposable cylinders to isolate the platelet- and leukocyte-rich fraction from a small volume of the patient's anticoagulated blood drawn at the time of the procedure. A 60-ml sample of whole blood was collected from the uninvolved arm into two 30-ml syringes that contained 3 ml of sodium citrate. The platelet-rich fraction was prepared according to the instructions for the use of the Recover System. The latter device provides mean concentrations of platelets, white blood cells, PDGF-BB, TGF-β1, VEGF, EGF of 1,603,000/μl, 31.1×10^3/μl, 17 ng/ml, 120 ng/ml, 955 pg/ml and 470 pg/ml, respectively [22]. Approximately 5.5 ml of L-PRP was obtained for each patient. The L-PRP was then buffered to physiological pH using 8.4% sodium bicarbonate. No activating agent was used. The total time from blood aspiration to injection in the patients was about 30 min. No specialized equipment, other than the centrifuge to process the recover disposable, was required. All procedures were performed in the same office setting by a physician (KL) certified for blood management. One milliliter of L-PRP was injected directly into the supraspinatus interstitial RCT under ultrasound control.

2.4. Radiographic evaluation

The radiographic analysis was performed blindly and independently by two senior radiologists (KF and Dr Abed Kourhani). Tear volume was calculated by making the product of maximal tear volume in the 3 axis, divided by two. Intra-observer and inter-observer reliability were assessed with intraclass correlation coefficient.

2.5. Statistical analysis

No studies of L-PRP for interstitial RCT existed prior to the start of the current study on which a sample-size calculation could be

Table 1
Clinical characteristics and clinically relevant evolution of supraspinatus tendon tear size and Constant score.

	Age	Sex	Work	Dominant hand involved	Smoking	Constant MCID (10.4 points) reached	Tear volume > 50% evolution
1	44	M	Worker	Yes	No	Yes	Amelioration
2	51	M	Removal man	No	Yes	Yes	Pejoration
3	49	M	Teacher	No	No	Yes	Amelioration
4	55	M	Tinsmith	Yes	No	Yes	Amelioration
5	53	M	Physicist	No	No	Yes	Stable
6	48	F	Housewife	Yes	No	Yes	Stable
7	47	M	Policeman	Yes	No	Yes	Stable
8	47	F	Gardner	Yes	Yes	No	Stable
9	54	F	Housewife	No	Yes	Yes	Improvement
10	46	M	Cleaner	Yes	No	Yes	Stable
11	54	M	House painter	No	Yes	Yes	Improvment
12	58	M	Engineer	Yes	Yes	No	Stable
13	44	F	Swimming coach	Yes	No	Yes	Improvment
14	57	F	Office worker	Yes	No	Yes	Improvment
15	49	F	Office worker	Yes	No	Yes	Improvment
16	45	M	Computer scientist	No	No	Yes	Improvment
17	39	M	Office worker	No	No	Yes	Improvment
18	54	F	Housewife	Yes	No	Yes	Improvment
19	59	F	Office worker	No	Yes	No	Improvment
20	46	F	Cleaner	Yes	No	Yes	Stable
21	41	M	Office worker	Yes	No	No	Improvment
22	18	F	Student	No	No	Yes	Improvment
23	33	M	Fireman	No	No	Yes	Pejoration
24	42	M	Seller	Yes	Yes	Yes	Stable
25	56	M	Cook	Yes	No	Yes	Stable

based; therefore, the sample size of the current study was chosen by convenience. Each patient presented separately, and clinical characteristics are listed and analyzed with descriptive statistics. Tear volume consensus between the two radiologists was obtained as following: if intra-observer differences were >10%, experts had to do a third analysis and a median result was chosen. In case of interobserver difference, consensus was made between the two experts. For global sample pre and post L-PRP comparisons, p values were calculated with paired Wilcoxon rank test. Two-tailed *P* values less than .05 were considered statistically significant. A number of patients reaching a supraspinatus tear diminution of >50%, as well as Constant score MCID were calculated. Fifty percent decrease volume of initial tear was chosen in order to assess whether radiologic differences, revealed with Wilcoxon rank test, were clinically relevant.

3. Results

Of the 28 included patients, 3 dropped out the study, one because he underwent supraspinatus surgical repair in the 6 months following injection, and the 2 others were lost at follow-up. Therefore, the study sample at baseline consisted of 25 patients (Table 1). Patients sample included 15 males (60%) with a mean age of 48 ± 8.9 (range, 18 to 59), having a broad panel of professional activities (Table 1). In 15 of the 25 patients (60%), dominant shoulder was involved. Seven of the 25 (28%) patients were active smokers. No patients were diabetic, alcoholic or suffer from hypercholesterolemia. For radiologic evaluation of tears size, intra-observer reliability was excellent, with intraclass correlation coefficients of 0.99 and 0.98 for each senior radiologist. Inter-observer reliability was also excellent, with intraclass correlation coefficients of 0.98. Tear volume diminution (Fig. 1) was statistically significant ($P = .004$), as highlighted in an illustrative case (Fig. 2). Twenty patients had a diminution of their supraspinatus tear, of which 14 had a >50% diminution (Table 1). Four patients had an augmentation of their supraspinatus tear, of which 2 had a >50% augmentation (Table 1). Constant score amelioration was statistically significant ($P < .001$), as well as SANE score amelioration ($P = .001$), and EVA amelioration ($P < .001$) (Fig. 3). Twenty-one of the 25 (84%) patients reached MCID Constant score amelioration (Table 1).

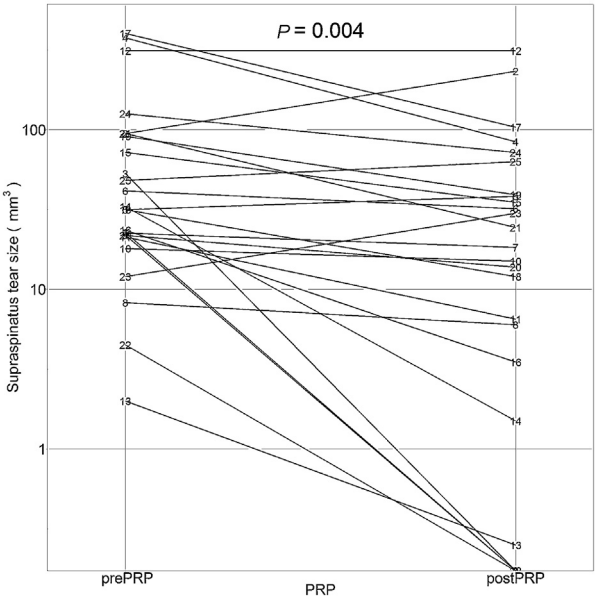

Fig. 1. Supraspinatus interstitial tear size evolution prior and after PRP infiltration. Graph is performed with tear size logarithm for clarity. *P* value was calculated with Wilcoxon test on non-transformed data.

4. Discussion

Biologic properties of the aging tendon are determinant factors and it seems that the healing rate could not be improved so far. Recently, attention has turned to the biology of tendon healing as a means to improve the outcome of such injuries. Biologic treatment strategies using growth factors may have a potential benefit in rotator cuff treatment. Among other things, an increase of tenocyte proliferation, as well as maturation and production of the brickets of the natural insertion, may be induced by stimulation

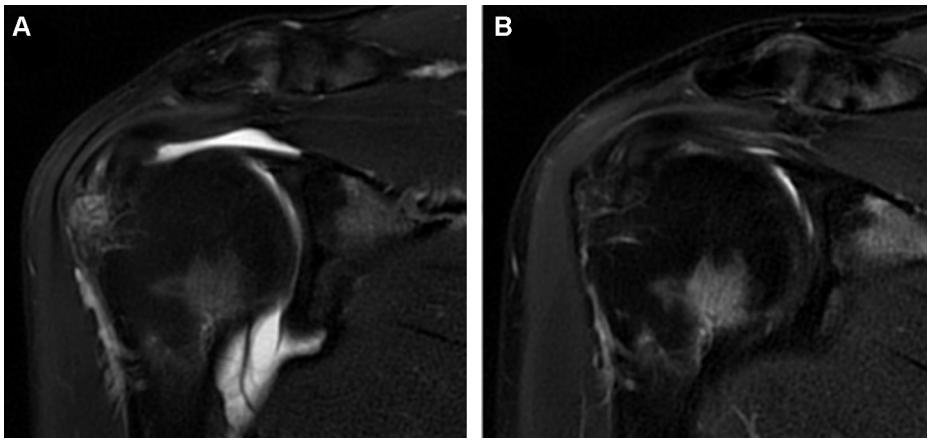

Fig. 2. Right shoulder MRA of a swimmer that had chronic pain. (A) The native coronal T2 FATSAT view revealed an interstitial rotator cuff lesion in contact with the greater tuberosity, which presents an edema. Six month after L-PRP injection, the patient was pain free. The same sequence demonstrated a decrease of the size of the lesion and of the bone edema (B).

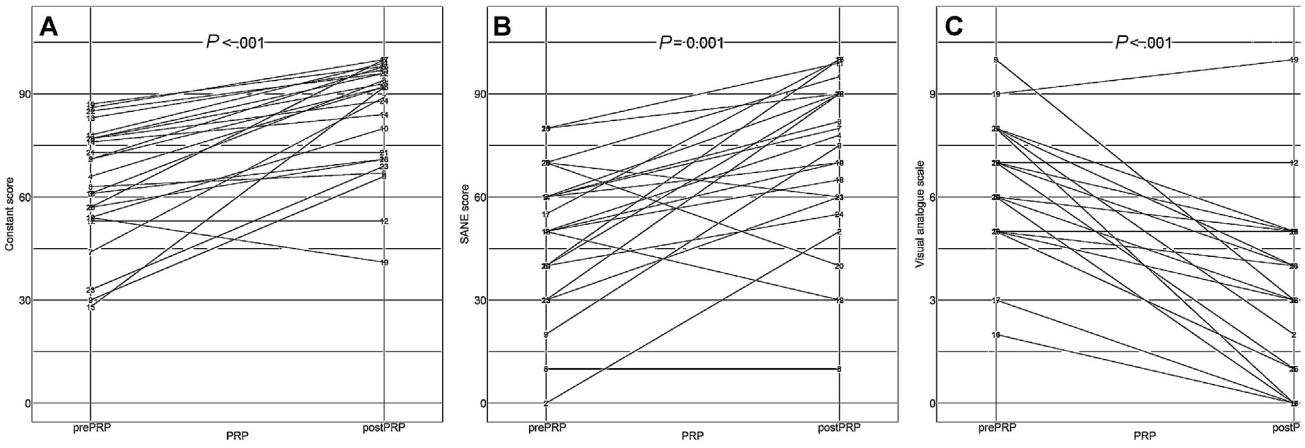

Fig. 3. (A) Constant score, (B) SANE score and (C) VAS evolution prior and after PRP infiltration.

of growth factor concentrates [23]. There remains ongoing controversy regarding of its clinical efficacy, as in vivo studies failed to demonstrate an improvement after PRC therapy associated with rotator cuff repair [13–15]. Nevertheless, the findings of the current prospective study show a structural, as well as clinical, improvement in interstitial RCT treated with L-PRP injection. Such radiological amelioration following L-PRP injections have already been noted in other anatomic areas [10–12], but not in RCT. We believe that the demonstrated positive effect in the current study is related to injection of growth factors in a confined space. Effectively in previous studies, PRC was deposited in a non-confined space and could have been flushed rapidly after application.

Several experimental in vitro and in vivo therapy methods have already been developed for biological improvement of the cuff reinsertion in order to enhance healing [24,25]. Unfortunately this seems, in the aforementioned studies, to have been accomplished through an increase of scar tissue production instead of forming a physiological tendon-to-bone insertion. Our study did not confirm the latter finding; we observed that after 6 months of the first injection, either the tendons were cured, tendon-to-bone insertions had a normal signal at MRA (Fig. 2), or simply persistent lesions were without any evidence of anarchic scar tissue formation.

Treatment strategies are controversially discussed in partial RCTs, which are frequent in young overhead athletes [26,27]. However, most of these athletes are not symptomatic [26,27]. NSAIDs medication and a potential combination with local anesthetic and steroid injections were used. The results of this study indicate that L-PRP may become in the future part of the therapeutic arsenal of partial RCTs, as it has been proven that PRC has less deleterious effects in and around tendons than steroids [28–30].

4.1. Limitations

This study has numerous limitations. First, we did not have group control. This prevents us to spontaneously analyze the rate of healing. However, the existing literature that describes RCT evolution, illustrates a trend of tendon tear progression, even if some cases of spontaneous healing are present [31–34]. We consequently believe that the latter is mostly related to injection. Then, we had a small sample size and 3 patients dropped out. This may have biased our results. Moreover, one could argue that the needling of the tendon might also be responsible for tendon remodeling. Therefore, further studies with more group control are necessary. Lastly, the optimal type and concentration of PRC is still unclear [35]. Platelet rich concentrates (PRC) are classified into four different categories dependent on the polymerization and 3-dimensional properties of the matrix and on the leukocyte content [36]. Because leukocyte rich-fibrin (L-PRF) and leukocyte poor fibrin (P-PRF) have a solid 3-dimensional matrix, their treatment options are reduced to open surgery as they cannot be injected after the polymerization process. Conversely, leukocyte rich-plasma (L-PRP) or leukocyte poor plasma (P-PRP) are injectable as they are in a liquid consistency. Even if L-PRP is more pro-inflammatory than P-PRP, it remains not

clear whether this potential inflammation has an impact on tendon healing [35].

5. Conclusion

We observed a statistically significant and clinically relevant effect on RCT size and clinical parameters after L-PRP infiltration. In clinical practice, such an important improvement of supraspinatus interstitial RCT with conservative management is uncommon, therefore, intratendinous L-PRP infiltrations could have been beneficial. This encouraging result should pave the way toward future randomized studies in order to formally determinate whether L-PRP infiltrations could be an alternative to surgical treatment of interstitial RCT.

Authors' contributions

All authors meet criteria for authorship. Substantial contribution to study conception and design was performed by AL, and AS. Substantial contribution to data acquisition was performed by AL, FK, MG, LK, and AS. Substantial contribution to data analysis and interpretation was performed by AL, MZ, and AS. Manuscript drafting and revision for critically important intellectual content as well as final approval were performed by all authors. All authors read and approved the manuscript.

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Disclosure of interest

The authors declare that they have no competing interest.

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