Foot and Ankle Surgery 21 (2015) 178–181

Contents lists available at ScienceDirect

Foot and Ankle Surgery

journal homepage: www.elsevier.com/locate/fas

Long-term beneficial effects of platelet-rich plasma for non-insertional Achilles tendinopathy

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ARTICLE INFO

Article history:
Received 26 September 2014
Received in revised form 3 November 2014
Accepted 13 November 2014

Keywords:
Achilles tendinopathy
Non-insertional
Leukocyte-rich
Platelet-rich plasma
L-PRP
PRP
Blazina score
Long term
Follow-up
Clinical outcome

ABSTRACT

Background: The aim of this retrospective study is evaluating the long-term clinical outcome in patients affected by mid-portion Chronic Recalcitrant Achilles Tendinopathies (CRAT) treated with administration of single platelet-rich plasma (PRP).
Methods: A total of 83 tendons (73 patients, 59 males and 14 females; age 43 ± 17.5 years) affected by non-insertional CRAT were treated with single PRP injection. These were evaluated with the Victorian Institute of Sport Assessment – Achilles (VISA-A) questionnaire, Blazina score and satisfaction index at baseline at intervals of 3 weeks, 3 months, 6 months. Final follow-up was carried out at a mean of 50.1 months (range, 24–96).
Results: Baseline VISA-A was 45 ± 15. Results relative to the final follow-up improved significantly to a mean of 88 ± 8 ($p < 00.1$). Blazina was used for patients practicing sports (54 tendons out of 46 different patients): 37 tendons were grade IIIa, 11 II, and 6 IIIbis. Final follow-up Blazina scores improved for 45 grade 0, 5 I, 4 II ($p < 00.5$). Seventy-six tendons (91.6%) were rated as satisfactory and patients would repeat the treatment. Seven tendons (8.4%) were classified as unsatisfactory at the 6 months follow-up and underwent a second PRP injection. In addition to this, patients reported no Achilles tendon rupture.
Conclusions: The study shows beneficial effects and low complication rate following of single PRP injections on a large cohort of patients with mid-long-term follow-up. No cases reported Achilles tendon rupture, in contrast to literature, which described CRAT as one of the most common risk factors. The use of a single PRP injection can therefore be a safe and attractive alternative in the treatment of non-insertional CRATs.

1. Introduction

Non-insertional Achilles tendinopathies are typically over-use injuries that occur 2–6 cm proximal to the tendon insertion, region with a lower vascularization [1–3].

The pathogenesis of Achilles tendinopathy is not fully understood but probably related to poor vascularization and high blood demand during activity. This is a painful condition affecting mainly active middle-age adults and it is responsible of a severe reduction in physical performance and persistent pain [4,5]. Onset of symptoms is just the tip of the iceberg of a long process due to unknown factors such as injury, overuse and metabolic disorders. It is in practice an advanced failure of a chronic healing response [6].

This condition has always been difficult to treat for orthopedic surgeons, choices are multiple from conservative to surgery without unique consensus. As the pathogenesis is not clear, we do not know why and how any therapeutic modality work [7–9].

Since 2006 with Mishra et al. [10] and Sanchez et al. in 2007 [11] local administration of platelet-rich plasma (PRP) has become a *hot-topic* in treatment in tendinopathies resistant to conservative approach [12,13]. Platelet-derived growth factors provide a local regenerative stimulus in tendon healing [14]. To date, local administration of growth factors contained in PRP is an increasing and valuable way to treat tendinitis and in particular Achilles tendinopathies. There are many PRP formulations, which differ in terms of cell type content, platelet concentration, storage methods, activation methods and protocols for therapeutic application [15,16].

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http://dx.doi.org/10.1016/j.fas.2014.11.005
1268-7731/

Several clinical trials are available about the use of PRP in Achilles tendinopathies but literature data is controversial and there are only a few studies with mid–long-term follow-up demonstrating the stability of clinical outcome.

Our retrospective study aims at filling this gap via evaluating the long-term clinical outcome in a large sample of patients treated with single leukocyte-rich PRP (L-PRP) for healing of mid-portion chronic recalcitrant Achilles tendinopathies (CRAT).

2. Materials and methods

From 2006 to mid-2012 PRP injections were performed in 98 Achilles tendons of 85 different patients (13 bilaterally). All patients were affected by mid-portion chronic recalcitrant Achilles tendinopathies (CRAT) with a history of more than 4 months of Achilles pain and not responding to conservative treatment as NSAIDs, physiotherapy, TENS or laser therapy. MRI or ultrasound (US) was also performed as confirmation (Fig. 1).

2.1. Technique for preparing and administering leukocyte and platelet-rich plasma

L-PRP preparations occur from a venous blood sample and citrate anticoagulant in 10:1 proportion, for a final volume of 60 ml then processed by the GPS™ II Platelet Concentration System (Biomet Biologics®, Warsaw, IN). This system is designed to produce a consistent 8x baseline count while capturing over 80% of the available platelets within the sample [17]. The sample is centrifuged for 15 min at 3200 rpm. After withdrawing platelet-poor plasma (PPP), the buffy coat containing the majority of the platelets was shaken for 30 s. Six cc of PRP was then suctioned. We performed just one L-PRP administration both in the lesion location, intratendon and in the peritendon area, always in local or locoregional anesthesia, with patient prone and under US control.

2.2. Aftercare and evaluation

After the injection patients stayed 3 h supine then were discharged. They were asked to rest, no weightbearing and to use ice for the first 24 h, then ambulated for 7 days with crutches and partial weightbearing. After 3 weeks they started a rehabilitation program based on eccentric exercises. Progressive return to sport and daily activity was allowed after 3 months, in according to their clinical status. Criterions investigated were age, sex, contralateral side state and treatment received prior to PRP. We evaluated our patients with the Victorian Institute of Sport Assessment – Achilles (VISA-A) [18] questionnaire and the Blazina score [19] (Table 1) before they underwent PRP (baseline) and at 3 weeks, 3 and 6 months intervals. Final follow-up was at a mean of 50.1 months (range, 24–96), where patients were evaluated with VISA-A, Blazina functional score and satisfaction index (Fig. 2). Blazina score is a score limited to assessing the clinical index of the severity of tendinopathies. This ranges from grade I, when tendinopathy does not affect activity, to IV grade where there is a major functional damage and activity is not possible. VISA-A questionnaire is the most used and easy index of the severity of Achilles tendinopathies. The Satisfaction index was divided in three scores: satisfied, satisfied with reservation and dissatisfied. Kaplan–Meier analysis was also used, all tests with $p < 0.05$ were considered statistically significant.

Table 1
Blazina score system.

Blazina score	
Grade I	Pain after excercising does not affect athletic activity
Grade II	Pain at the beginning of physical activity that disappears after warming up and comes back after exercising
Grade III	Pain during and after exercise, which progressively affects athletic performance
Grade III bis	All athletic activities are stopped because of pain
Grade IV	Major functional damage

3. Results

Seventy-three patients (59 males and 14 females; age 43 ± 17.5 years; 3 type 2 diabetics) of 85 treated were assessed in the study for a total of 83 tendons (10 treated bilaterally). Others were not included because they were not available for the final follow-up. The final follow-up took place on average after 50.1 months (range, 24–96). At baseline, VISA-A score was 45 ± 15. At the final follow-up, this improved significantly to a mean of 88 ± 8, with a mean delta of 43 points ($p < 00.1$). In particular, patients at the 6 months follow-up reported a VISA-A of 84 ± 15 (Fig. 3).

Forty-six of these patients practiced sports recreationally or at agonistic level, 1 professionally (21 runners, 10 football, 8 tennis, 1 basketballs, 6 others sports players). 54 tendons of these patients (8 bilaterally) were classified with a Blazina score: 37 tendons were grade IIIa, 11 II and 6 IIIbis. At final follow-up Blazina score improved in 45 grade 0, 5 I, 4 II ($p < 00.5$) (Fig. 4).

Seventy (84.4%) tendons were rated by patients as satisfactory, 6 (7.2%) were rated as satisfactory with reservations: a total of 91.6% (76 tendons) of satisfied patients expressed positive view that going back they would have chosen again to opt for this treatment. Seven patients (8.4%, no bilaterally), 5 not practicing sports, were classified as unsatisfactory and did not reach acceptable healing (VISA-A 54 ± 9; Blazina IIIa) at the 6 months follow-up. For these patients with minimal or no improvement

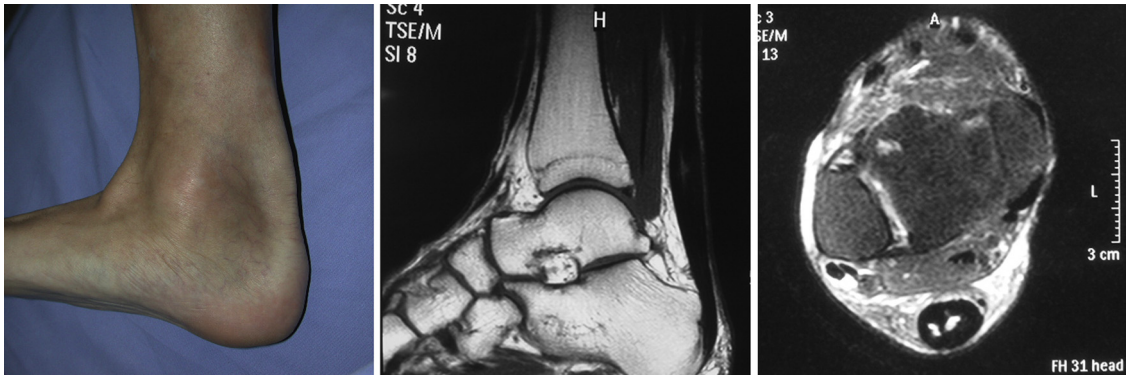

Fig. 1. A clinical and MRI case of CRAT.

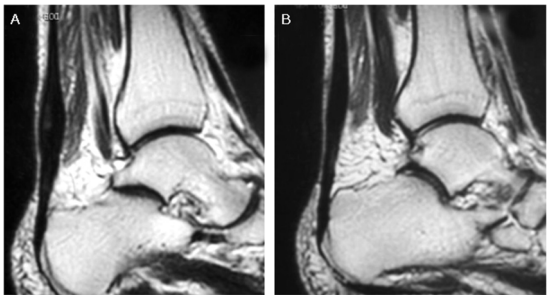

Fig. 2. MRI of a CRAT case successfully treated with leukocyte-rich PRP. (A) MRI at baseline; (B) MRI at 55 months of follow-up.

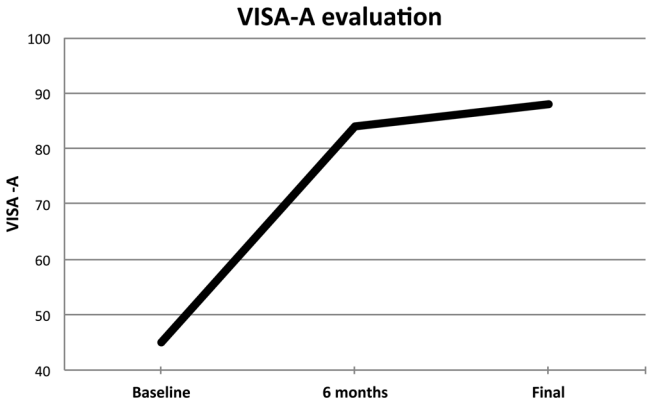

Fig. 3. VISA-A scores at baseline, 6 months and final follow-up.

(5 males and 2 females, age 55 ± 5.5 years, 2 type 2 diabetics) we performed a second L-PRP injection which took place after a mean of 12 ± 6 months. At the final follow-up (41 ± 20 months), after the second injection, VISA-A in these patients has been 77 ± 5 and all patients ranked grade I for Blazina. All athletes returned to sports within 6 months, 2 without reaching the same sport fitness level.

Complications due to the treatment such as infections, inflammations, edema or vasculo-nervous complication were not observed. In addition to this, patients reported no Achilles tendon ruptures.

4. Discussion

Our study shows a good clinical outcome within single L-PRP injections on a large cohort of patients with mid–long-term follow-up. Injection of PRP to Achilles tendon has proved safe as no complications have occurred. No patient reported Achilles tendon rupture, in contrast with existing literature data which identifies CRAT as one of the risk factors [20,21]. We hypothesize therefore that L-PRP could have a beneficial and protective role in Achilles tendon ruptures. Further studies are required to deepen analysis and detail and to further strengthen our findings.

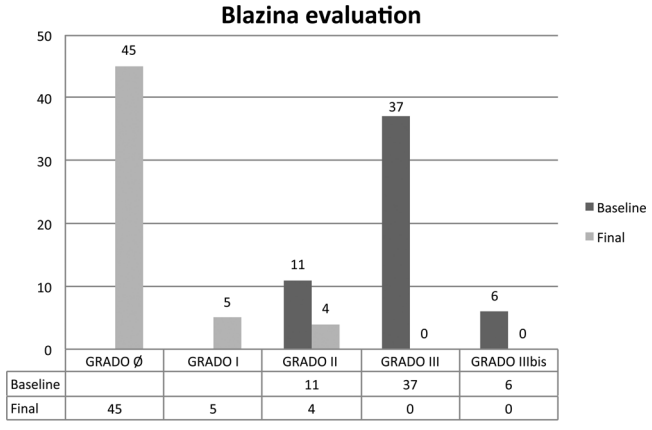

Fig. 4. Blazina ranked at baseline and at final follow-up.

PRP is an autologous preparation of concentrated platelets in a small volume of plasma, is safe, free of transmissible diseases and well accepted by patients and surgeons [22]. Recent clinical studies reporting a higher level of evidence fail to show consistent positive results for the use of various PRP [23] and to date no EBM support for the use of PRP. This could be due to a failure in standardization of procedures. A variety of different production methods for PRP have been published in literature or presented by medical companies [24]. This results in numerous PRP treatments being available, which differ in terms of number of platelets, white blood cell content, fibrin concentration and method of platelet activation [25]. Some authors define PRP as only platelets, whereas others note that PRP also contains increased concentrations of leukocytes, fibrin and some bioactive proteins [26]. For this reason, PRP was classified into pure platelet-rich plasma (P-PRP), leukocyte and platelet-rich plasma (L-PRP) and leukocyte and platelet-rich fibrin (L-PRF) [6]. Still, some authors prefer the term platelet-rich growth factors (PRGF) as they believe unique advantages of PRP are richness in growth factors [27].

Another crucial point in PRP standardization is its autologous origin: naturally, blood from one patient may have a very different composition from another, although blood from an individual can also vary greatly between each draw. Therefore, the final PRP is ultimately determined by the nature and characteristics of the patient's blood at the time of the draw [28].

Notwithstanding the above, the use of PRP in treatment of musculoskeletal injuries is backed mainly by good clinical outcomes, validated by numerous low-quality short-term follow-up trials [29]. The rationale of the treatment is to carry many growth factors and cytokines contained in platelet granules that are known to play a key role in hard and soft tissue repair [30–34]. PRP contains high concentrations of growth factors including transforming growth factor beta (TGF-B), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epithelial growth factor (EGF), hepatocyte growth factor (EGF) and insuline-like growth factor (IGF-I). These modulate the healing of bone, muscle and tendon through interactions with specific cells [35].

The first study focusing on the value of PRP in CRAT was Gaweda et al. [36] in 2010. He treated 15 tendons with significant improvement and functional recovery at 14 months of follow-up. Since Gaweda's assessment, numerous studies have taken place although almost all of them with short-term follow-ups.

Non-insertional Achilles tendinopathies are one of the most common tendinitis affecting both athletes and common people. NSAIDs, physiotherapy and Hyaluronic acid injections do not seem to have demonstrated any long-term efficacy. Eccentric exercise of the gastrosoleus complex was considered the only helpful treatment prior to surgery but it shows good results only in around 50% [22,37] of the cases. Operative treatments for patients where conservative management has proved ineffective for at least six months has been debated and not validated. In any case, operative treatment should be considered as last option only if other options have proven not effective.

5. Conclusion

In light of the above results, we can confirm that one injection of autologous leukocyte-rich PRP safely provides mid–long-term clinical benefits within treatment of CRAT. The symptoms showing

improvement and functional recovery are experienced over time in mid–long-term follow-up.

In conclusion, our study, notwithstanding many limitations as the lack of a control group and final imaging evaluation, is one of the firsts studies evaluating mid–long-term results in treating non-insertional Achilles tendinopathies with one single L-PRP injection.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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