

Are There Biologic Factors of Good Prognosis after a Platelet Rich Plasma (PRP) Injection for Tendinopathies ?

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Abstract

Background : The aims of this study were to evaluate the effect of a single PRP injection followed by a standardized reeducation protocol among patients suffering from different tendinopathies, but otherwise healthy, and to determine the biomarkers that constitute good prognosis factors, if any.

Methods : 48 patients suffering from different tendinopathies and refractory to conventional physiotherapy were treated with a single PRP injection. Prior to the injection, a blood sample was drawn and some biological parameters (glycemia, cholesterolemia,...) were measured. A pain assessment was then made using a Visual Analog Scale of pain (VAS) and a pressure algometer. The same assessment was carried out after 6 weeks and 12 weeks when possible.

Results : There is an overall significant improvement in VAS score at the end of the 12 weeks follow-up. However, no correlation was found between the evolution of the clinical scores and the biological parameters measured.

Conclusion: A PRP injection followed by a program of eccentric rehabilitation positively affects the algo-functional scores of patients with tendinopathies who were refractory to conventional physiotherapy, whatever the initial values of the measured biological parameters.

Keywords: Tendons ; Platelets Rich Plasma ; Biomarkers

Introduction

Tendinopathies represent a significant part of musculoskeletal injuries [1]. They are generally caused by microtraumae following a mechanical overload due to work or sport activities. Inflammation, like rheumatoid polyarthritis or spondylarthritis, can also result in tendon injury. Several factors can facilitate the onset of the tendinopathy, which can be either intrinsic or extrinsic [2]. Amongst the former, we can distinguish between those that can be altered (hyperurcemia, hypercholesterolemia, chondrocalcinosis, disthyroidis, degenerative rheumatism, infection,...) [3] and those that cannot (age, gender,...). Examples

of extrinsic factors include unadapted material, bad training planification, or usage of some drugs (quinolones, corticoids,...) [4]. Some patients are refractory to the traditional treatments (including physiotherapy, shockwaves, deep transverse massage, etc.) and thus need another option. Less invasive than surgery, Platelet-Rich Plasma (PRP) injection has become more and more popular over the last decades, particularly in sports medicine [5-7]. In this paper, in addition of presenting the data asserting the effectiveness of injections of reproducible PRP collected from an apheresis machine on different tendinopathies, we introduce another original contribution : the investigation of the possible correlation between several biomarkers and healing evolution to determine the factors of good prognosis, if any.

Material and Methods

Forty-eight patients (mean age = 49 y.o +/- 10 y.o, min = 26 y.o, max = 77 y.o. ; 15 women and 33 men) afflicted with different pathologies participated in this study after they gave their informed consent (lateral epicondylitis (n=20), medial epicondylitis (n=3), tendinopathy of the gluteus medius (n=1), patellar tendinopathy (n=6), calcaneal tendinopathy (n=14), and plantar fasciitis (n=4)). To be recruited, the patients have had to suffer from a chronic tendinopathy for more than 3 months and be refractory to the following classical treatments : non steroidal anti inflammatory drugs, electrotherapy, deep transverse massage, eccentric revalidation and shockwaves therapy. A clinical examination was carried out to confirm the diagnosis and to exclude any other pathology, including metabolic disease. After this first step, a blood sample was drawn and analyzed to quantify the presence of various metabolic biomarkers (glycemia, thyroid hormones, cholesterolemia, uricemia) which are considered to be risk factors of tendinopathies. The initial pain assessment was made using a Visual Analogic Scale (VAS) of pain and a pressure algometer (Commander Algometer, Tech Medical) prior to the PRP collection. The PRP collection and injection protocol used has already been described in previous

reports [8-10]. Briefly, the platelets are extracted using an apheresis machine (TEC.COM, Fresenius Kabi) which can lead to a reproducible platelet concentration of 850 000 units/microlitre, a value approximatively 4 times as high as in the whole blood [11]. 6 millilitres of this PRP were mixed with 300 microlitres of calcium chloride to activate the platelets. The injection was performed under ultrasound guidance and without local anaesthesia as it could decrease PRP healing effectiveness. The physiotherapy started 5 days after the injection, 3 times a week for 6 weeks [12]. The pain was reassessed 6 weeks and 12 weeks after the injection. For the statistical processing of these results, a Shapiro-Wilk test was made to evaluate the normal distribution of the data and a paired Welch test was used to compare the results of the VAS and the algometer at the different time points. Linear mixed effects models (nlme package, RStudio, Rstudio Inc.) were used to investigate the potential relationship between the biological parameters and the clinical evolution (evaluated by VAS and algometer scores).

Results

When combining the results for all the tendons, a significant decrease of the VAS score was noted after 6 weeks (VAS0 = 4.81, Δ VAS0-6 = -0.84 ; p = 0.007) and after 12 weeks (VAS0 = 4.81, Δ VAS0-12 = -1.1 ; p=0.01). The result of the algometer also improved significantly between the 6th and the 12th week (Algo6 = 52.8 N/cm², Δ Algo6-12 = 12.9 N/cm² ; p<0.05). Another way to look at the results is to observe that 70 % of the patients showed a positive effect following the PRP injection with a decrease of pain of at least 1 point on the VAS (Fig. 1). For 25 % of them, the decrease was at least 4 points. Independently, 40 % of the patients saw their algometer result increase by more than 30N/cm² by the end of the 12 week follow-up (Fig. 2). A tendon-specific analysis was also performed. Statistically significant results were only found for the groups of patients suffering from epycondylitis (Δ VAS0-12 = -1.69, p<0.005) and Achilles tendinopathy (Δ VAS0-6 = -1.96, p<0.005). The sample size of the other tendinopathies was too small to observe a statistically significant evolution.

A possible correlation between hypercholesterolemia and hyperglycemia and the evolution of VAS and algometer results was investigated (all the other biomarkers were in the normal range for all the patients). Such a correlation was not observed. Furthermore, no statistically significant differences in Δ VAS0-12 and Δ Algo0-12 were found after clustering the patients into two groups, one with normal and one with elevated cholesterolemia (Fig. 3) and glycemia (Fig. 4).

Discussion

This study quantitatively confirmed the effectiveness of a single PRP injection followed by an eccentric revalidation for patients suffering from various tendinopathies refractory to conventional treatments, as shown by the 23 % decrease in Δ VAS0-12 and 24 % increase in Δ Algo6-12. The tendon-specific results have too few data points to show statistical significance, but the trend observed is encouraging and confirms the results found in the literature. Indeed, in the case of epicondylitis, an algofunctional improvement was noticed as previously reported.

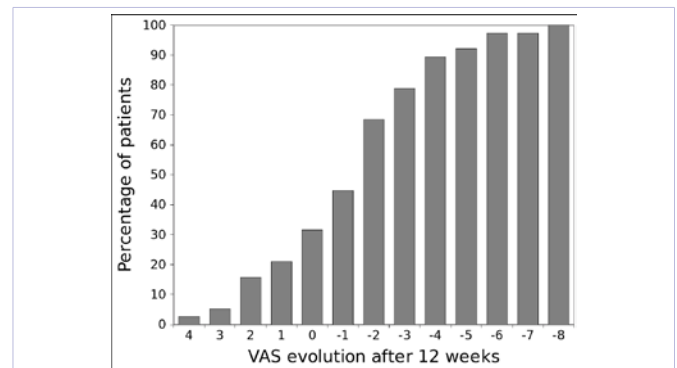


Figure 1: Cumulative histogram of the evolution of the VAS score for the 48 patients over the 12 weeks clinical trial. The pain decreased for 70% of the patients, 10% saw no difference and the pain increased for 20%.

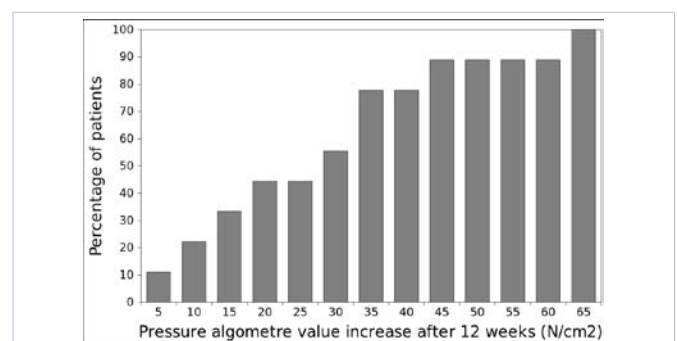


Figure 2: Cumulative histogram of the evolution of the algometer score for the 48 patients over the 12 weeks clinical trial. All patients saw an improvement of their score which reached 30 N/cm² for more than 50%.

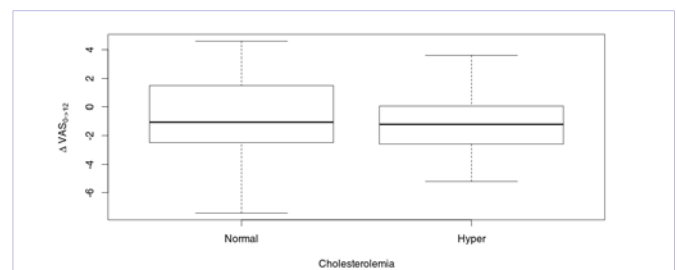


Figure 3: Evolution of the VAS score over the 12 weeks clinical trial with respect to cholesterolemia - whisker plot. 23 patients had a normal level and 24 presented hypercholesterolemia.

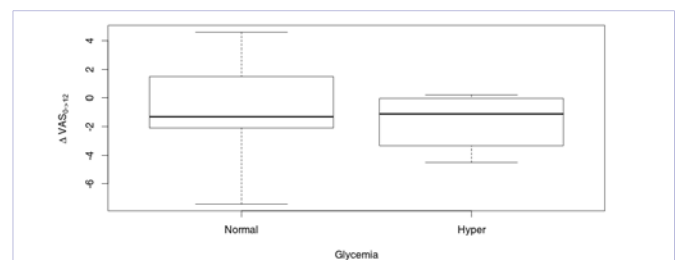


Figure 4: Evolution of the VAS score over the 12 weeks clinical trial with respect to glycemia - whisker plot. 28 patients had a normal level and 18 presented hyperglycemia.

[13, 14]. The follow-up in those studies lasted 24 weeks and 28 months respectively. As for Achilles tendinopathy, several other studies also demonstrated a decrease in pain following a PRP injection [15-17]. To the authors' opinion, the lack of significant results in the tendon-specific part of the present study is therefore due to the small number of patients recruited. Furthermore, no follow-up information could be obtained from several patients. Despite all the studies mentioned point in the same direction, it is difficult to compare them as the PRP collection protocols might be quite different. Indeed, the collection itself might be performed using laboratory or commercial machines, or also an apheresis machine. The amount of platelets will then vary according to the extraction method and is not repeatable in the case of the commercial technique [18, 19]. This study presents, to the best of the authors' knowledge, the first attempt to correlate biomarkers as factors of good prognosis to the evolution of the recovery. Hyperglycemia and especially type II diabetes, leads to a disorganization of collagen fibers, and an increase in tendons thickness and volume [20]; hyperthyroidism increases collagen catabolism and hypothyroidism leads to a decreased collagen metabolism [21]; hypercholesterolemia impairs the tendon extra cell matrix and thus alters its biomechanical properties [22] and finally, hyperucemia could cause an inflammation provoking the degeneration of the tendon tissue [23]. It might then be surprising that no correlation was found between the values of the biological markers and the evolution of the tendons healing evaluated by the VAS and the algometer. However, one has to distinguish between the correlation between the values of the markers and the susceptibility of developing a tendinopathy compared to the susceptibility of slower healing once the pathology has triggered. The former is out of the scope of the present report. From our results, it seems that the initial glycemia and cholesterolemia don't have any influence on the prognosis of the evolution of the tendinopathy. In a previous report [8], a young age of the patients (<30 years old) and a better strength of the quadriceps before infiltration were identified as good prognosis factors to recover from a jumper's knee while diabetes was a bad one [24].

Further studies should focus on comparing the effectiveness of the PRP treatment for different tendinopathies, which couldn't be established in the present study because of the relative small number of patients afflicted with different pathologies. The total number of patients was however sufficient to obtain statistically significant results regarding the effectiveness of a single PRP injection in the treatment of tendinopathies. Other good prognosis factors, like biomechanical ones, should be investigated too.

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