Reflections about the optimisation of the treatment of tendinopathies with PRP

Jean-François Kaux[1,2,3]
Marc Bouvard[4]
Christelle Lecut[5]
Cécile Oury[6]
André Gothot[5]
Mikel Sanchez[7]
Jean-Michel Crielaard[1, 2, 3]

[1] Department of Physical Medicine and Sports Traumatology, CHU Liège, Belgium
[2] Department of Pluridisciplinary Medicine and Sports Traumatology (SPORTS[2]), CHU Liège, Belgium
[3] Department of Motricity Sciences, University of Liège, Allée des Sports, Belgium
[4] Centre for Biology and Sports Medicine, Pau, France
[5] Laboratory Hematology Department, University of Liège, University Hospital Sart-Tilman, Liège, Belgium
[6] Laboratory of Thrombosis and Haemostasis, GIGA - Cardiovascular Sciences, University of Liège, Belgium
[7] Unidad de Cirugía Artroscópica, Vitoria-Gasteiz, Spain

Corresponding author:
Jean-François Kaux
Department of Physical Medicine and Sports Traumatology, CHU and University of Liège
Avenue de l'Hôpital, B35
4000 Liège, Belgium
E-mail: jfkaux@chu.ulg.ac.be

Summary

Background: **platelet-rich plasma (PRP) infiltration represents a recent therapy for chronic tendinopathies. However, in the literature, this treatment remains controversial.**
Purpose: **we suggest some ideas for improving this treatment.**
Methods**: these suggestions were based on a review of published studies and our clinical experience.**
Conclusion: **optimizing the technique for PRP collection is paramount. Different risk factors must be corrected before infiltration and chronic tendinopathies must be carefully selected. Finally, post-infiltration rehabilitation remains absolutely critical. Standardization of the use of PRP remains necessary in order to optimize the results.**

KEY WORDS: platelet-rich plasma, PRP, rehabilitation, optimization.

Introduction

Platelet-rich plasma (PRP) infiltration represents a recent therapy for chronic tendinopathies. Indeed, during degranulation, platelets release cytokines and growth factors (VEGF, PDGF, TGF-β, IGF-I, and HGF) that promote angiogenesis, tissue remodeling (bone, skin, muscle, tendon, etc.), and wound healing[1]. Most of the preclinical studies showed that PRP stimulates tendon healing process[2]. Thus, PRP could be an attractive therapeutic option for treating chronic musculoskeletal conditions, such as tendinopathy[3]. However, this treatment remains controversial[4]. Major difficulties in comparing and pooling clinical results stem from the fact that PRP is applied in different tendons (lateral epicondylitis, supraspinatus, patellar, Achilles…) and that outcome measurements vary between studies, even in those performed in the same tendon: e.g. epicondylitis, which is the most studied tendon, the variety of clinical scales makes comparisons difficult[4,5]. Based on the literature and our experience, we suggest some avenues for optimizing this treatment[6].

Preparing PRP

Result variability may be explained by a misknowledge about PRPs[7]. Depending on how they are obtained and prepared, PRPs (or Platelet-Released Growth Factors PRGF) present highly variable concentrations of platelets[8-10], erythrocytes and leukocytes. It is still necessary to optimize the techniques for obtaining and concentrating PRPs and standardizing the injection. Ideally, platelet concentration should be three to four times that of whole blood, i.e. between 600,000 and 900,000 platelets per microlitre[11-14]; a concentration higher than 1,200,000 platelets may, indeed, be unfavorable[14]. Ideally, a reproducible PRP (with identical platelet concentration) should be injected to all patients. Currently, only platelet collection using an apheresis machine enables these objectives to be easily achieved[15,16]. The presence of white or red blood cells could be ad-

verse to tissue healing process. It was demonstrated *in vitro* and animal studies that their absence limits the inflammatory response[17]. However, clinical positive effects of pure-PRP have not been demonstrated in controlled studies yet, and, in many clinical controlled studies, only a slight reduction of pain was obtained after a leukocyte rich-PRP injection. Moreover, it has been demonstrated that the anti-bacterial effect of PRP against *Staphylococcus aureus*, Staphylococcus *epidermidis*, *Propionibacterium acnes* and meticillin-resistant *Staphylococcus aureus* was not linked to the presence of leukocytes[18].

Finally, platelet activation is reduced postprandially[19]. Moreover, a gentle mastication is able to induce the release of pro-inflammatory components into the bloodstream, especially when patients have severe periodontal disease[20].

Thus, it would be preferable that patient should be fasting before preparing the PRP to reduce pro-inflammatory factors in platelet concentrate.

In addition, aspirin, corticosteroids and NSAIDs affect platelet functions and should be avoided at least during 10 days before blood collection[21-23].

Centrifugation speed should be set to a maximum of 900 rpm (100g), since a higher speed can lead to platelet activation and resulting decrease of platelet reactivity[21,24].

After blood collection, it is mandatory to prepare the PRP as soon as possible (ideally within 1 hour) to avoid undesired non-specific platelet activation[21,23,24]. The PRP is stable for about 3 to 4 hours at room temperature, but platelets can become refractory to agonist stimulation[21,23,24]. Usually, citrate (or ACD-A) anticoagulation is highly recommended because it better preserves blood and *ex vivo* platelet reactivity. In contrast, EDTA and heparin should be avoided due to decreased platelet reactivity leading to reduced release of growth factors[21,23-26].

Correcting tendinopathy risk factors

Before planning any PRP infiltration, it is essential to undertake a precise diagnosis backed up by research and to correct any metabolic factors (diabetes, hyperuricemia, hypercholesterolemia, dysthyroidism)[27]. PRP effectiveness may be compromised by medications including quinolones, corticoides (orally or by infiltration), or statins[27,28]. These families of drugs accelerate tendon degeneration, which may lead to rupture[28,29]. Finally, sports technical mistakes and technopathies should also be corrected as well as a control of the physical stresses (sports or work).

Indications for PRP infiltration

Patients likely to benefit from PRP infiltration must be selected: relevant indications (but still debated in literature) relate to chronic corporeal tendinopathies (patellar, Achilles) which are resistant to conservative therapies (including prolonged eccentric rehabilitation and shock waves), without any osseous impingement or luxation[30]. It is imperative to surgically correct any osseous impingements (Haglund deformity, subacromial impingement and a Bigliani type III acromion, Sinding-Larsen-Johansson sequelae, etc.) before envisaging any further PRP infiltration[30]. Enthesopathies (epicondylitis, jumper's knee, Achilles)may, in theory, benefit from PRP infiltration, although results remain less favourable, as with other treatments (such as shock waves), because of their particular histological structure[30]. For all inflammatory pathologies (e.g. enthesopathy in the context of a spondylarthropathy), it is crucial to treat the underlying inflammatory disease.

Therapeutic protocol

Although the product diffuses from the site of the injection[31], it is best to conduct the infiltration in the tendon lesion using ultrasound, while respecting aseptic precautions[32]. A local anaesthetic is not recommended as it compromises the therapeutic potential of PRP: the anaesthetic may effectively reduce local pH, which is responsible for the inhibition and reduction or absence of platelet degranulation[21,22,33]. It was thus more recommended to use a small needle (30G) to decrease pain[33]. Although PRP is naturally activated upon contact with denatured collagen, platelet pre-activation (e.g. by $CaCl_2$) promotes degranulation and thus the release of the growth factors involved in tissue healing[13]. A pH lower than than 7.7 inhibits platelet activation while a pH greater than 8.0 stimulates it. As the citrate used for the anticoagulation is slightly acidic, it is thus recommended to add a basic buffer like $NaHCO_3$ before injection[21].

After activation, 70% of the platelet growth factors are released from the α-granules within the first 10 minutes, and almost 100% have been secreted within the first hour[34].

Even though there is no general agreement on the volume to be injected, 3 to 6 mL of PRP could be injected in the tendon, depending on its caliber. It could be interesting to determine whether the injected volume of PRP could influence the healing process based on the «degenerative state» of the tendon. Likewise, whether we should modify the protocol in case of enthesopathy or middle substance tendinopathy has never been investigated.

Post-infiltration consequences are often painful and may justify the use of local cryotherapy and analgesics. NSAIDs are to be avoided for 21 days following the procedure, as they may inhibit the PRP effect[22,35]. Once the algesic period has passed, progressively intensive sub-maximum eccentric rehabilitation, combined with stretching, will 'guide' tendon healing[36]. In animals, active mobilization of the infiltrated tendon improves tendon healing[37]; eccentric rehabilitation is more effective than concentric work[38]. For the first four to six weeks post-infiltration, rest from sport is necessary to avoid any new intra-tendinous lesions occurring; only rehabilitation, below the

pain threshold, is permitted[16]. When sport is gradually resumed (reathletisation), any possible technique-related problems should be corrected and the tendon should be somewhat 'protected' using 'functional' orthoses (e.g. patellar brace) or 'strapping'[39].

In our series on the use of PRP to treat jumper's knee, we have observed that younger patients respond more effectively to treatment, most probably because of their greater healing potential[16,40]. Those suffering from jumper's knee for less than 10.5 months make the greatest progress[40]. Patients initially presenting with better quadricipital isocentric results during eccentric contraction at 30°/s and concentric contraction at 60°/s make better progress[16]. Moreover, patients presenting a significant reduction in pain after three months continue to progress positively up to one year later[40]. The three-month assessment looks at the effect of PRP infiltration and allows for a discussion to take place on the indication for a second PRP infiltration in the event of partial improvement to the tendinous symptoms[41]. Indeed, it was demonstrated that it was not useful to carry out 2 closely-timed infiltrations[42]. Surgery should be discussed in the absence of any improvement[40].

In case of several applications, the refrigeration or lyophylisation of platelet could be performed[43,44]. However, after PRP freezing-thawing, platelets are lyzed and a platelet lysate is obtained[44]. It has been demonstrated that platelet lysate increase the growth rate of mesenchymal stem cells[45].

Conclusion

PRP is a recent but controversial treatment for chronic tendinopathies. Standardization will be important to compare results and advance progress in the field, but it seems likely that more knowledge is awaited before proper standardization can be achieved. The first stage includes selecting the correct therapeutic indications and correcting the risk factors for tendinopathies. Subsequently, improving the techniques for obtaining PRP is crucial, as the injection protocol. Finally, post-infiltration rehabilitation remains absolutely necessary.

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