



Platelet-rich plasma application in the management of chronic tendinopathies

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Platelet-rich plasma (PRP) may represent a new therapeutic option for chronic tendinopathies. Platelets release various cytokines and growth factors which promote angiogenesis, tissue remodeling, and wound healing. We made an extended literature review of the use of PRP in chronic tendinopathies : epicondylitis, rotator cuff, patellar and calcaneal tendinopathies, and plantar fasciitis.

Medline, Embase and Google Scholar were used (until July 31, 2012). Clinical studies on PRP and tendinopathies published in English and French language peer-reviewed journals were included. Articles with a high level of evidence were given special consideration.

Despite the proven efficacy of PRP on tissue regeneration in experimental studies, there is currently scanty tangible clinical evidence with respect to its efficacy in chronic tendon disorders. The few studies that have been performed appear unlikely to be comparable. Randomized controlled studies with appropriate placebo groups are needed to determine the real effectiveness of PRP for treating chronic musculoskeletal injuries.

Keywords : platelet-rich plasma ; PRP ; tendinopathy ; growth factors ; plantar fasciitis.

INTRODUCTION

Platelets have known roles in coagulation, inflammatory processes, and immunity modulation. Moreover, during degranulation, platelets release various cytokines and growth factors (vascular en-

dothelial growth factor, platelet-derived growth factor, transforming growth factor-B, insulin growth factor-I, and hepatocyte growth factor) which promote angiogenesis, tissue remodeling, and wound healing (3). In addition, platelets can reduce painful symptoms by an unknown mechanism which is apparently dependent on the release of proteases with analgesic properties (2).

Thus, platelet-rich plasma (PRP) may represent a new therapeutic option for chronic tendinopathies. PRP is easy to prepare, relatively low cost, and can be administered in a minimally invasive manner. Furthermore, to date, no study on the use of PRP has reported any side effects.

PRP is obtained by centrifuging autologous blood to obtain a concentration of platelets (3-10 times that of whole blood). For this reason, different PRP

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preparation techniques cannot provide a consistently identical final product ; the latter varies both in volume and platelet, lymphocyte, and erythrocyte concentration (23,24). According to most authors, white blood cells adversely affect wound healing through the release of proinflammatory factors responsible for extracellular matrix degradation (20,33). In addition, erythrocyte lysis releases free radicals that harm tissue structures (40). Ideal PRP should contain the lowest possible amounts of white and red blood cells. However, there is currently no international consensus on this issue. PRP can be used in several different forms, the most common being the injectable form and in fibrin gel which has been used in tendon repair with or without associated surgery. PRP can be activated by the addition of thrombin or calcium citrate prior to injection, or it can be activated in situ by endogenous collagen.

PRP was removed from the doping drugs list of the World AntiDoping Agency since 2011.

MATERIALS AND METHODS

The electronic databases Medline, Embase and Google Scholar were searched (until July 31, 2012). Selected literature was limited to English and French language peer-reviewed journals. The key-words and their synonyms used have allowed for a systematic research. They consisted of synonyms for “tendon”, “tendinopathy”, “platelet”, “platelet-rich plasma” and “growth factors”. In Medline, we used existing MeSH (Medical Subject Heading) alone or in combination. In Embase and Google Scholar, we used the same terms as in Medline. Studies with a high level of evidence were considered preferentially. As it is a recent treatment, there are currently few studies with a high level of evidence. Therefore, articles with a low level of evidence were also included in this review of the literature. A total of 43 articles were selected, including 28 clinical papers on the use of PRP in tendinopathies.

RESULTS

The tendon capacity for healing and regeneration is slow. Growth factors released by platelets promote tenocyte proliferation. Other properties of platelet growth factors have been demonstrated, such as stimulation of angiogenesis. PRP has been

shown to stimulate and accelerate tissue regeneration in many animal models (rats, horses, etc.), particularly following Achilles tendon ruptures (5,21). According to some authors, optimal tissue quality requires the application of appropriate mechanical loads in addition to PRP (22,42). PRP should be considered for chronic tendon injuries (> 3 months). Indeed, the goal is to initiate an acute inflammatory reaction that quickly moves on to the proliferative phase involving collagen synthesis, which is necessary for appropriate tendon healing. PRP should therefore not be used for acute tendinitis or inflammatory injuries of the tendon (i.e. tenosynovitis), nor in case of conflict (i.e. Haglund disease).

Epicondylitis

The first clinical study assessing the effect of PRP on lateral epicondylitis compared to a control group (local anaesthetic infiltration) was published by Mishra *et al* (29). Two small groups (15 and 5 subjects, respectively) underwent an eccentric rehabilitation program (with elastic bands) after infiltration. After 8 weeks, the authors reported pain regression in both populations but significantly higher pain reduction in the PRP group (60 versus 16%). The pain reduction within the PRP group was 81% and 93% after 6 months and 24 months, respectively. After two years, 94% of the PRP-treated patients had returned to sports and/or professional activities. Unfortunately, the control patients were only followed for 8 weeks.

Peerbooms *et al* (31) confirmed these favourable results in a controlled randomized double blind study in a larger population (51 subjects treated with PRP versus 49 control subjects treated with corticosteroid infiltration). After one year, the pain and the algo-functional score were significantly improved in the PRP group, whereas local corticosteroid effectiveness vanished after 12 weeks. These results were confirmed in a longitudinal study with a 2-year follow-up (18).

Another prospective randomized double blind study comparing two injections (blood versus PRP) in 150 patients with chronic lateral epicondylitis showed similarly improved algo-functional scores

for both treatments after 6 months (9). These negative results were confirmed in another randomized controlled trial (28 subjects) comparing an infiltration of 3 mL autologous blood to 3 mL PRP under ultrasound guidance (41). The results of PRP infiltration were better than those of autologous blood on short-term (6 weeks) pain. In the longer term (3 and 6 months), the difference was no longer significant, but symptom improvement was greater with PRP. These two studies raise several questions regarding PRP quality, effective platelet concentration, and the possible presence of erythrocytes and lymphocytes (20,22,23,33,40).

Rotator cuff tendinopathy and rupture

In a personal observational series of 80 cases of tendinopathy, Frey (15) reported a favorable progression in 17 patients with rotator cuff tendinopathies who received PRP infiltration under ultrasound guidance.

An *in vitro* study on tenocytes harvested from rotator cuff tendons demonstrated that PRP actually stimulates cell proliferation and extracellular matrix synthesis (19).

A 24-month longitudinal observation of arthroscopic rotator cuff sutures reported a lasting reduction of pain and favorable mobility progression in 14 patients (36). A second randomized controlled study of 53 patients (26 in the PRP group and 27 in the control group) showed that pain in the first month after surgery was lower in the PRP group, and the 3-month algo-functional scores were also better (37). However, these scores evolved similarly in both groups after 6, 12, and 24 months, with no observed differences by magnetic resonance imaging (MRI). The authors noted a positive effect of PRP on external rotation strength recovery in patients with minor or moderate rotator cuff injuries. Similar results were reported for cuff sutures using an autologous fibrin membrane (28).

Neither the Constant score nor MRI taken after arthroscopic rotator cuff suture (small and medium lesions) and PRP injection improved in 88 patients randomly divided into two groups (7). Algesic and functional progression of the shoulder was not analyzed at an earlier stage, so it was not possible to

assess the effect of earlier rehabilitation. Finally, a prospective randomized study (79 patients) did not show any positive effect of applying a PRP matrix during cuff suturing compared with a control group (simple suture) (38).

Patellar tendinopathy

A prospective 4-month follow-up of eight high-level athletes with chronic patellar tendinopathy who received PRP infiltration under ultrasound demonstrated significant improvements in algo-functional scores and MRI tendon appearance (43). Moreover, a return to sports activities was possible after 12 weeks.

Similar results were observed in 20 athletes with symptomatic chronic patellar tendinopathy who were treated with three injections of PRP (25); all athletes were able to return to competition at their former level. The authors emphasize the protocol standardization for post-infiltration rehabilitation (rest and ice between the first two injections; stretching and light activity between the second and third injection; after one month, strengthening and progressive return to sports activities), stressing the importance of complementing the PRP injection with a mechanical stimulus.

Filardo *et al* (14) followed 15 athletes with symptomatic patellar tendinopathy refractory to conventional conservative treatment whose symptoms had been evolving for an average of 2 years. They compared them to a "control" population with moderate tendinopathy of 6 months duration, who had received a single conventional kinesiotherapy treatment. The subjects received three weekly injections of PRP. Clinical evaluation at 6 months revealed no significant difference, although the progression of the PRP group appeared better than the control group. This difference may be related to a recruitment and selection bias: the patients were actually two inhomogeneous populations. The authors concluded that patients with patellar tendinopathy refractory to conventional conservative treatment evolve as favourably as those with less severe pathology.

A case report of an athlete suffering from patellar tendinopathy for 9 months concluded that an

injection of PRP under ultrasound guidance could be an effective and inexpensive treatment (6).

A prospective study lasting 18 months compared a group of 14 patients who had already received treatment (corticosteroids or ethoxysclerol and/or surgery) with 22 patients who never received infiltrative or surgical treatment (17). All received prior eccentric rehabilitation, stretching, and eccentric work following the injection. After 4 weeks, patients were allowed to gradually resume sports or recreational activities. Improvement was noted in both groups in terms of pain during activities of daily living and algo-functional scores, but the improvement was more pronounced in patients who did not receive treatment prior to PRP infiltration.

In a personal study, 20 patients with superior patellar tendinopathy refractory to conservative treatment, who had not undergone treatment for at least one month, received PRP infiltration in the affected area without local anaesthesia (*submitted manuscript*). After 6 weeks, we observed improved algo-functional scores and reduced pain during physical tests, however without significant performance improvement. This trend continued for 3 months. No improvement was observed on ultrasound or MRI.

In a prospective randomized controlled study, PRP improved wound healing at the donor site (patellar tendon) during surgery for reconstruction of the anterior cruciate ligament (10).

Achilles tendinopathy

PRP stimulates and accelerates the tendon healing process following Achilles tendon damage in animal models (4,21,26) and humans (39); however, the literature is less clear regarding chronic tendinopathy.

Promising results were reported in a series of 14 patients (non-controlled) with chronic tendinopathy of the middle portion of the Achilles tendon refractory to conservative treatment (16). Following PRP infiltration and eccentric work, all patients reported decreased pain and had improved algo-functional scores and echo-Doppler images after 18 months.

The only randomized controlled prospective and double blind study is less encouraging (13). The

effect of PRP infiltration was compared to that of isotonic saline in two groups of symptomatic patients (n = 54) for over 2 months. They also performed eccentric activities for 3 months following PRP injection. After 24 weeks, the algo-functional scores, patient satisfaction, and return to sports activities were significantly improved in both groups. The slight superiority of PRP compared to saline was not significant. Similar findings were made after one year (11). The authors did not demonstrate any significant ultrasound differences regarding tendon structure or neovascularisation (12). Some patients who had not received any eccentric treatment before study inclusion may have caused a selection bias (8,27). Indeed, these subjects could have improved symptoms from a single eccentric rehabilitation in the absence of any infiltration. Alternatively, the injection could cause local bleeding that could initiate a healing process (34). A change in pressure-volume related to the presence of saline solution could explain the decrease in the neovascularisation and the pathological neo-innervation (34). The procedure, which was relatively invasive for a control group, could have led to a better placebo effect associated with greater expectation on the part of the patient (34). The PRP quality may not have been optimal; in fact, the final product contained a non-negligible number of red and white blood cells capable of negatively affecting the healing process (20,22,23,33,40).

Finally, a 2-year longitudinal follow-up of 10 patients with corporeal Achilles tendinopathy reported a modest improvement in function without any MRI changes (30).

Plantar fasciitis

Plantar fasciitis is defined as irritation of the fascia sheathing the tendons which are responsible for maintaining the foot arch. Although it is not a true tendinous structure, the symptoms and treatment are relatively similar; we will therefore briefly discuss this condition.

Only two studies on PRP injections in plantar fasciitis have been published. A prospective study by Ragab *et al* (36) (25 patients followed for 10 months) showed excellent results for pain (88%

improvement) and favorable functional progression (60%), which were associated with various favourable ultrasound changes (thickness and signal intensity of the plantar fascia). Aksahin *et al* (1) did not observe significantly different outcomes after PRP or corticosteroid infiltration after 3 weeks and 6 months, respectively, in 60 patients (2 groups of 30 subjects) with plantar fasciitis refractory to conservative treatment. A multicenter, randomized controlled study is currently underway (32).

DISCUSSION AND CONCLUSION

By releasing different platelet growth factors, PRP may be used as a new therapeutic option for chronic tendinopathies (2,3). Its ease of preparation, relatively low cost, and minimal invasiveness are arguments in its favour. Furthermore, PRP is not associated with any side effects. Despite the proven efficacy of PRP on tissue regeneration in experimental studies, there is currently little tangible clinical evidence to support its efficacy in chronic tendon disorders. The few studies that have been performed appear unlikely to be comparable; they have used different PRP preparations with varying qualities, different injection methods and different protocols (24). We think that the ideal PRP would not contain any red and white blood cells which could hinder the healing process, due to their pro-inflammatory action (20,33). A general agreement on the platelet concentration needed and the PRP quality is required. Randomized controlled studies with appropriate placebo groups are needed to determine the real effectiveness of PRP in the management of chronic tendinopathies.

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