Current evidence and indications for Prolotherapy with Platelet Rich Plasma in chronic musculoskeletal conditions

Introduction

Platelets have known roles in coagulation, inflammatory processes, and immunity modulation; they also have "restorative" properties. Indeed, during degranulation, platelets release different cytokines and growth factors (VEGF, PDGF, TGF-B, IGF-I, and HGF) that promote angiogenesis, tissue remodelling (bone, skin, muscle, tendon, etc.), and wound healing [1].

PRP is obtained by centrifuging autologous blood to obtain a concentration of platelets, usually between 3 and 10 times that of whole blood, depending on the isolation method [2]. For this reason, different PRP preparation techniques cannot provide a consistently identical final product, but there is currently no international consensus on this issue [3].

Overall, PRP could be an attractive therapeutic option for treating chronic musculoskeletal conditions, such as tendinopathy, plantar fasciitis, osteoarthritis, and nonunion.

The use of PRP for the treatment of tendinopathies

Tendons do not have a high metabolic index. Growth factors released by platelets promote tenocyte proliferation, stimulate angiogenesis and have analgesic properties, thus it could stimulate and accelerate tissue regeneration in animal models [4, 5]. In addition to PRP, optimal tissue quality requires the application of mechanical loads [6, 7]. PRP should be considered for tendinopathies for more than 3 months. Indeed, the goal is to initiate an acute inflammatory reaction that quickly moves on to the proliferative phase that involves collagen synthesis, which is necessary for appropriate tendon healing. PRP should therefore not be used for acute tendinitis or tenosynovitis.

For ***lateral epicondylitis***, studies assessing the effect of PRP compared to a control group reported significantly better outcomes (on pain and function) in the PRP group [8, 9]. These results were confirmed up to a 2-year follow-up [10]. It is important that groups underwent an eccentric program after infiltration. However 2 randomized controlled trials comparing an infiltration of autologous blood to PRP showed similarly improvement in middle term [11, 12].

To our knowledge no studies have studied the effect of PRP in ***rotator cuff tendinopathy***. However, long term observation of arthroscopic rotator cuff suture with adjunction of PRP showed that pain in the first month after surgery was lower in the PRP group [13, 14, 15]. No differences by MRI were observed. These results contrast with other studies which did not show any positive effect of applying PRP during cuff suturing compared with a control group [16, 17].

For ***patellar tendinopathy,*** series have shown significant improvements of algo-functional scores [18, 19, 20], and MRI appearance [21]. Even if these good result had been evolving for an average of up to 2 years [22], most of these studies needed 3 injections of PRP [21, 22]. In our study, 20 patients with superior patellar tendinopathy refractive to conservative treatment, who had not undergone treatment for over a month, received PRP infiltration in the affected area without local anesthesia [23]. After 6 weeks, we observed improved algo-functional scores and reduced pain during physical tests (without significant performance improvement). This trend continued for 3 months. No significant changes were observed on ultrasound or MRI.

Finally, for ***Achilles tendinopathy,*** results are controversial. Even if, observational series showed a decreased pain and improved algo-functional scores after PRP infiltration and echo-Dopler images [24], the only randomized controlled and double blind study (PRP infiltration was compared to that of isotonic saline, followed by eccentric activities) did not show any difference between the 2 groups after 24 weeks [25] and 1 year [26]. The authors did not demonstrate any significant ultrasound differences for tendon structure or neovascularization [27]. However, this studies is subject of methodological bias.

The use of PRP for the treatment of plantar fasciitis

Only two studies on PRP injections (vs corticosteroid infiltration) have been published. One with excellent results for pain and favorable functional progression which were associated with various favorable ultrasound changes after infiltration of PRP [28], and one which did not observe different outcomes after PRP or corticosteroid infiltration [29].

PRP treatment for osteoarthritis

Osteoarthritis is a degenerative phenomenon of the cartilage with complex, multifactorial pathophysiology. The healing potential of this type of injury is very poor. There are a multitude of conservative pharmacological treatments that are palliative rather than curative that can be used to delay the eventuality of a joint replacement. PRP could serve a new therapeutic alternative for traumatic and degenerative cartilage defects.

Sanchez et al. were the first to compare three PRP injections with hyaluronic acid as part of a study of a retrospective cohort in 30 subjects with gonarthrosis [30]. At 5 weeks, they observed a significant improvement in pain and algo-functional questionnaires for patients who received three PRP injections.

The same observations were made in different prospective studies comparing three PRP injections to hyaluronic acid in moderate cases of gonarthrosis [31-36]. Indeed, the PRP patient groups showed significant improvements in pain and algo-functional scores after a follow-up period of up to 1 year. They also emphasize the absence of side effects associated with this treatment.

A cohort study (144 patients) comparing the effect of two different PRP preparations for gonarthrosis cases also reported significant clinical improvement compared to baseline in both groups, despite the fact that one of the two techniques initially produced more pain and swelling

[37]. However, the best results were observed in younger patients with a low degree of cartilage damage.

In a written debate on the indication for knee arthroplasty versus therapy via PRP injection in cases of gonarthrosis, it appears that the two options seem reasonable in a 60-year-old patient with moderate symptoms who wishes to continue skiing [38]. Because PRP infiltration therapy is less costly, less invasive, and less risky than knee arthroplasty, it could be considered as a first line treatment. In the event of patient dissatisfaction regarding pain control and improved knee function, arthroplasty can then be considered.

Finally, in a cohort study (6-month follow up) of 40 patients with severe hip osteoarthritis, Sanchez et al. observed significant improvements in pain and algo-functional scores after three injections of PRP under ultrasound guidance [39].

PRP treatment for nonunion

A fracture will normally fuse, and nonunion is the absence of fusion between bone fragments. This produces pain and abnormal movements of varying degrees. The efficacy of percutaneous PRP injection under fluoroscopic guidance to treat nonunion remains unclear and controversial [40-42]. However, it seems that this technique could produce encouraging results and provide a less invasive alternative to open bone-grafting techniques [40].

Conclusion

By releasing different platelet growth factors, PRP may be used as a new therapeutic option for chronic musculoskeletal injury. Its ease of preparation, relatively low cost, and minimal invasiveness are arguments in its favor. Despite the proven efficacy of PRP tissue regeneration in vitro, there is currently little tangible clinical evidence for chronic tendon disorders, plantar fasciitis, osteoarthritis, or nonunion. 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.

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