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# Injections of Platelet-Rich Plasma (PRP) for the treatment of sports injuries: a review

## Abstract

Acute soft-tissue lesions and chronic overuse injuries in the sports medicine field are very frequent and, in most cases, difficult to treat. Tissue repair in musculoskeletal lesions is often too slow and sometimes incomplete for a given athlete. Many bioactive proteins and growth factors, amongst others, influence healing processes. Basic research and animal studies are promising, but evidence-based studies examining the treatment of human musculoskeletal lesions by Platelet-Rich Plasma (PRP) are still lacking. Nevertheless, such treatment is increasingly used in sports medicine clinical practice and much is expected of growth factor injections. The aim of this non-exhaustive review is to analyze the existing literature published in the fields of sports medicine. The results of this analysis do not permit us to recommend the systematic and generalized use of Platelet-Rich Plasma injections in the management of sport injuries. High-quality studies are needed to provide scientific evidence about effectiveness of these injections.

## Résumé

Les lésions aiguës des tissus mous, de même que les lésions de surcharge sont fréquentes en médecine du sport, et dans la plupart des cas, difficiles à traiter. Lors de lésion musculo-squelettique, la réparation tissulaire est souvent trop lente, et parfois incomplète chez certains athlètes. Beaucoup de protéines bioactives et de facteurs de croissance, entre autres, influencent le processus de guérison. La recherche fondamentale et animale est prometteuse, mais il manque encore des études basées sur l'évidence, dans le traitement des lésions musculo-squelettiques humaines au moyen de Plasma Riche en Plaquettes (PRP). Toutefois, de tels traitements sont de plus en plus utilisés en pratique clinique de médecine du sport. Le but de cette revue de littérature non exhaustive est d'analyser les études publiées dans le cadre de la médecine du sport. Les résultats de cette analyse ne permettent pas de recommander l'utilisation systématique et généralisée d'injections de plasma enrichi en plaquette dans la prise en charge de lésions sportives. Des études de haute qualité sont souhaitables afin d'amener des évidences scientifiques sur l'efficacité de telles injections.

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## Introduction

Acute and chronic musculoskeletal injuries are common during physical activities, are frequently problematic for an athlete, and always represent a therapeutic challenge for the clinician. Tissue healing after such injuries may be slow and sometimes incomplete. Nevertheless, optimal treatment for these injuries is mandatory and should be as safe, quick and cost-effective as possible, in order to restore athletes' pre-injury level in sports participation.

Physiologically, the healing of an injury progresses in overlapping phases and is characterized by a cascade of events triggered by the injured tissues. The three classic phases are: inflammation, proliferation and remodeling.

There are several treatment strategies with which to address musculoskeletal injuries. One novel approach is intra-lesion, autologous blood injection. Several products are available: Autologous Conditioned Serum (ACS), Platelet-Rich Plasma (PRP), Plasma Rich in Growth Factors (PRGF) and other derivatives. The large variety of products speaks for their different possible compositions with diverse biological effects. Other variables such as modalities of PRP activation, presence or not of white blood cells, local anesthesia or not, use of non-steroidal anti-inflammatory drugs, post-injection rehabilitation protocols, and many others, are confounding factors in studies, explaining the diversity of the experimental, but most of all clinical results [1, 2].

PRP is a simple and minimally invasive means of obtaining the concentration of autologous growth factors. It is defined as

a fraction of blood plasma, containing higher concentration of platelets than normal plasma, and consequently, a source of growth factors. Blood platelets consist of fifty to eighty alpha granula per unit. Each granula has more than thirty bioactive proteins, including platelet-derived growth factor (PDGF), transforming growth factor (TGF-Beta), vascular endothelial growth factor (VEGF), fibroblastic growth factor (FGF), epidermal growth factor (EGF), and insulin-like growth factor 1 (IGF-1). The different effects these factors have on human tissues have been extensively discussed in numerous papers [3, 4, 5].

PRP is neither considered as medication, nor as a therapeutic substance. Hence, the rules of its application remain vague. Furthermore, its use is no longer banned by the world anti-doping agency, regardless of the chosen application procedure.

Basic research and animal studies on the subject are relatively promising. Nevertheless, there is still ample discussion about the effectiveness of platelet-rich plasma injections for the treatment of human, acute or chronic, musculoskeletal injuries. This paper provides a critical, but not exhaustive, overview of the effect of platelet-rich plasma injections on tendon, muscle or ligament lesions, in human in-vivo investigations.

## Methodology

To assess current evidence for autologous plasma injections in the management of not surgically treated musculoskeletal injuries, a

literature search using EMBASE and MEDLINE databases was conducted. The key words were “autologous conditioned serum OR platelet-rich plasma” AND “soft tissues-muscle-ligament-tendon injuries”. All titles were checked for the presence of a reference to autologous plasma injections. At this time of selection, we identified 22 studies for human trials. Two persons read the articles and selected the studies considered methodologically acceptable following the Judet criteria.

As a particular focus was paid on human investigations we were interested in the quality of these trials. Among all identified human trials, only seven articles reached an evidence level type I or II (three studies referred to anterior cruciate ligament and four other were concerning tendon injuries). The quality of these studies was evaluated with the Pedro Scale. The quality ranged between 6/10 and 9/10 points. Given the paucity of high-level evidence-based articles (level I and II) concerning soft tissue injuries, we finally decided to check the references of recent literature reviews on the subject. However, no additional article could be identified.

### PRP in human chronic tendinopathies

Chronic tendinopathy is one of the most frequent lesions in musculoskeletal, sports injuries. Tendon problems are reputed to represent 30 to 50 % of all sports injuries in both professional and hobby athletes. Chronic tendinopathy is characterized by pain and tendon weakness. Its origin is multifactorial. The repetition of micro traumas due to exercise can lead to degenerative intra-tendon lesions, micro ruptures, and sometimes to poor healing [6]. Histo-pathologically, these lesions present non-inflammatory cell proliferation (in particular fibroblasts), vascular hyperplasia (neo-vascularization), and disorganized collagen fibers, without any sign of inflammation [7, 8].

In the tendon area, only a very few randomized controlled trials have been conducted in humans. Most of the studies are either cohort studies or case series. In this critical, non-exhaustive review, we focus on the three tendons most frequently affected in sports lesions: the Achilles tendon, patellar tendon, and tendons around the elbow (“epicondylitis”). These also happen to be the structures for which the PRP effect has been most investigated, as summarized in the main reviews on this topic [5, 9].

#### *Achilles tendinopathy*

Only one double-blind randomized controlled trial exists on this topic. PRP injections were compared with a saline isotonic solution in 54 patients that presented symptoms for at least two months. Concurrently, the subjects were admitted to a three-month-long, eccentric exercise program. As a result of the treatment, pain decreased, and functional scores, such as VISA-A, improved significantly in both groups. Even if results in the PRP group were somewhat higher, no statistical significance was found after six months between the 2 groups. There was also no difference in patient satisfaction or in the time taken to return to sport. Importantly, no relevant side effects were identified. The limitations of this study were the unique injection of the PRP, limited follow-up time, the relatively old age of the participants, and the lack of a control group without an eccentric program [10].

The same investigators subsequently extended the follow-up to one year, without finding any supplementary PRP benefit. Localized bleeding caused by the injecting syringe might have triggered the tissue healing process. A positive response could also be due to a placebo effect, as invasive procedures lead to higher expectancy of good results. Finally, in both groups, ultrasound showed that tendon structure and neo-vascularization improved significantly, without any group differences after six and twelve months. One of the main reasons for the absence of group differences is certainly the fact that standardized eccentric exercise training has already been shown to improve actual tendon structure [11].

Another article, a prospective case series with fourteen patients, showed a significant improvement of functional scores for up to

eighteen months after PRP injections. Echography further confirmed an improvement of structural anomalies. Nevertheless, the absence of a control group does not permit any final conclusion [12].

#### *Patellar tendinopathy (jumper's knee)*

Only three articles of moderate quality (level of evidence III and IV) investigated knee extensor lesions in a recent review on the subject [13].

The first study was performed on eight elite athletes in 2007. Participants received a single injection of PRP and were observed for four months, but only seven patients received a follow-up examination. Nevertheless, the authors found a significant improvement of the VISA score and of the radiological aspects in magnetic resonance (tendon abnormal signal and pre-insertion edema) [14].

The second article, a pilot study, included twenty athletes who experienced recurrent patellar tendinopathy symptoms, over a twenty-month period. Participants received three PRP injections within one month. Pain was evaluated on a visual analog scale, sports activity on the Tegner scale. Results showed a significant improvement at six months, compared to baseline. At the end of the study, most athletes returned to the same competition level as before. No relevant side effects were noted, except for pain at the time of injection. The rehabilitation protocol after the infiltration was systematically structured, an element underscored by the authors as a key factor for the success described. These investigators claim that such standardization should be a pre-requisite for all future studies. This study confirms the importance of the combination of growth factors and mechanical stimuli [15]. The third study followed 15 patients with a jumper's knee resistant to conservative treatment. Participants' symptoms lasted for a mean of 24 months. All received multiple PRP injections. This population was then compared to 16 controls with moderate tendinopathy symptoms (mean duration of symptoms: six months), who had been admitted to a classical physiotherapy treatment program. Follow-up took place after six months. No difference in pain, patient satisfaction with management and time to return to sport was observed between both groups. However, the 2 groups were not randomized and the characteristics (severity and duration of symptoms) of the control group were not comparable with those of the intervention group. Those limitations should be taken into account when interpreting the study's results. Nevertheless, patients with refractory jumper's knee, resistant to conventional treatment, may respond to PRP injections as positively as patients with less severe pathologies and classically treated [16].

Recently, a prospective study evaluates the influence of previous treatments on the effectiveness of PRP injections in 36 patients with chronic patellar tendinopathy. Assessment was done before and after injection of PRP using the VISA-P questionnaire and a VAS pain scale. The first group (14 patients) had been treated with cortisone, ethoxysclerol and/or surgical treatment before the injection, while the second group (22 subjects) had not received such treatments. It was found out a statistically significant improvement in both groups at 18 months, but larger in the group without previous treatments. Thus, this study opens the question about a relationship between prior treatment and efficacy of PRP injections [17].

#### *Elbow Tendinopathy*

Since 2003, only a few single case studies and case series reports were published on epicondylopathy, with encouraging results [5].

A prospective, pilot, cohort study investigated the effect of PRP infiltration in 15 patients with chronic elbow tendinopathies. PRP was administered under local anesthesia. The test group was compared to a control group of five patients receiving local anesthesia only. The patients were observed for 24 months. Unfortunately, by week eight, all of the small control group participants left the study because of the persistence of pain. At that time, 60% of the subjects who had been injected with PRP, but only 16% of those not treated with PRP, showed a significant decrease of pain. At six months, 80% of patients in the PRP group still showed a decrease in pain, and 93% at 24 months [18].

These findings were confirmed in a recent, randomized, double blind controlled trial that included 51 patients in a PRP group, and 49 patients in a group that received local infiltrations of corticosteroids. Pain (VAS) and a functional score of the upper extremity (DASH score) improved significantly compared to baseline values in both groups without any significant difference between groups during the first weeks after injections. From week 12, pain decreased and DASH significantly improved in the PRP group only, and for up to one year. This confirms the potentially early effect of corticosteroids in insertion injuries during the first weeks after injection, but maybe also their subsequent, negative influence on the tendon healing process [19].

Recently, a double-blinded, randomized trial investigated two types of blood injections. A group of 150 patients with elbow symptoms resistant to conventional treatment received either PRP injections or autologous conditioned plasma. The injections were repeated twice and both groups were compared. Unfortunately, there was no placebo control group. The authors of this study planned a follow-up after six months. In both groups, they reported marked reduction in pain and increase in function, but without any significant difference between groups. This raises the question of which concentration of platelets and growth factors is the best. "Less might be better", and the fact that the tissue healing response could be saturated after a certain concentration of growth factors locally should be taken into account [20].

### PRP in acute human ligament injuries

The complex process of normal tissue healing is only partially known. In addition, the temporal expression of cells and molecules during spontaneous healing has been barely studied and thus, the timing for optimal PRP administration is not yet known.

A recent systematic review identifying articles with the keywords "PRP" and "ligament" included only three human studies on ACL reconstruction which fulfilled criteria for an evidence level I or II. No statistically significant differences with regard to clinical outcomes, tunnel widening, and graft integration have been identified between control and PRP groups [21].

In general, studies on ACL reconstruction focus more on the osteo-integration of ACL grafts and less on the graft itself. However, a prospective, single-blinded MRI study has recently shown a 48% reduction in the time needed to present a complete, homogeneous graft signal with PRP injection versus controls, after surgical ACL reconstruction [22].

As this article should particularly help primary care physicians and sports medicine specialists in the clinical decision making we kept attention on conservative treatment of ligament injuries. Recently, a published case report evaluated the effect of two consecutive injections of a preparation rich in growth factors (PRGF) on an acute rupture of the medial collateral ligament of the elbow of a judoka. The authors reported an early return to full contact training at 3 months after injury and faster MRI recovery images at 6 weeks follow-up, compared to "classical" MRI outcome of those injuries [23].

### PRP in acute human muscle injuries

Physiologically, muscle injuries undergo distinct but overlapping healing phases, and the proper timing of PRP application is still unclear. The speed of recovery depends on the severity of the lesion, the treatment applied after injury, and the patient's ability to heal soft tissue lesions. At the time of trauma, myofiber ruptures and capillary lesions result in hematoma that fills the gap, with the release of cytokines and growth factors. The inflammatory phase thus starts from the first day on, involves a number of inflammatory responses and after one week, leads to the regenerative process. During this time and up to four to six weeks, the muscle gap is progressively replaced by fibrotic tissue which provides early support for new muscle tissue, involving in particular fibroblasts.

Capillary neo-formation occurs to reestablish the nutrition of the area. The proliferation and differentiation of muscle precursor cells then permit the fusion of differentiated cells, leading to the formation of new, multinucleated myotubes. After week three, the remodeling phase begins, leading to the increase of the muscle's functional capacities. Thus, the most important issue in muscle regeneration could be to prevent the development of fibrosis, thereby avoiding the apparition of a fibrotic tissue scar. PRP, with its high TGF-Beta1 level, might be deleterious to muscle healing by inducing fibrotic, muscle scar formation, possibly leading to increased risk of re-injury [24].

No randomized controlled studies conducted in humans could be identified and only three other studies were performed on small samples with only few valuable controls. Therefore, statistical power to support clinical evidence in humans is generally weak, due to this lack of methodologically robust studies.

The first description in humans did not strictly use PRP, but rather autologous conditioned serum (ACS). Eighteen professional athletes suffering from muscle strains were treated by ACS muscle injection and compared with 11 athletes with similar injuries and previously treated by Actovegin or Traumeel injections. Primary outcome was the time to return to competitive sport. The study reported a significant reduction in return-to-field days (16 versus 22), but presented numerous limitations: small sample size, non-blinded, atypical controls, variable injury sites, absence of long-term follow-up [25].

Two other case reports were published. The first one by Loo and al. presented a 35-year-old male bodybuilder with an adductor longus strain injury confirmed by echography. A weekly intramuscle injection for three consecutive weeks permitted the return to competitive training only one week after the last injection. Nevertheless, there were no details about the grade of injury, additional treatments, and follow-up [26].

The second paper described a 42-year-old active male with a sudden history of grade II medial hamstring muscle strain (semi-membranosus), confirmed by an MRI scan. PRP was injected once in the muscle, with an ultra-sound guided technique. Seventeen days after injury, the athlete had full ROM, was pain-free during muscle contractions and was able to perform all his recreational sporting activities. MRI performed at the same time revealed complete resolution of the signal enhancement, which was clearly different to the usual MRI outcome, with a signal intensity remaining positive for at least six weeks after injury. Long-term follow-up at twelve months did not reveal any negative outcomes [27].

### Conclusion

The role of PRP in tissue healing could open a new field in sports medicine, but a significant amount of research is still needed to understand the effect of PRP on the regenerative and healing processes of a given soft tissue.

Many basic science or animal studies assessed the effect of PRP on the musculoskeletal system during the last decade. In general, results are promising. However, this is not yet the case for human studies, especially in the area of sports medicine. Only a few human studies could be identified and a paucity of RCTs providing level I or II evidence for the efficacy of this intervention method exists. Furthermore, several questions remain unanswered. First of all, there is no consensus about the PRP preparations. A large diversity exists without knowing which one to adopt as the clinical best practice. There are no recommendations concerning the number of injections that should be administered, a single one or serial injections. We further do not know if pre-injection anesthetic affects the outcome. No standardized procedure for the administration of the injections exist (ultrasound guidance or not for example) and no precise information about ideal timing to administer PRP, depending on the lesions. A comprehensive rehabilitation planning is actually unavailable, in terms of what kind of activities should be permitted or avoided and during how much time.

However, studies agree on the absence of side effects or complications, albeit with limited duration of follow-up.

An analysis of the existing literature in human research reveals a weak evidence for the effect of PRP applications in soft tissue injuries. At this time, robust studies, with a good methodological quality and representative sample size are urgently needed and should be conducted. The authors are however confident that new studies will emerge in the near future.

Primary care physicians and sports medicine specialists should, with respect to current medical ethics, be cautious with the use of PRP to treat athletic or sporting injuries. Nevertheless, this field of treatment seems promising in the arsenal of non-operative management of sport injuries and particularly the cost-benefit ratio could be in favor of such procedures.

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