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PROTEIN-RICH PLASMA: FROM BENCH TO TREATMENT OF ARTHRITIS (S CHOATE AND J TOKISH, SECTION EDITORS)

Platelet-Rich Plasma: Review of Current Literature on its Use for Tendon and Ligament Pathology

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Abstract

Purpose of review Platelet-rich plasma (PRP) contains numerous growth factors and cytokines that potentially offer an alternative treatment modality to assist in the healing of multiple musculoskeletal issues. The purpose of this review was to examine the latest literature on the use of PRP for various ligament and tendon pathologies.

Recent findings Recent literature has shown moderate- to high-quality evidence that PRP can have positive clinical effects in certain conditions such as lateral epicondylitis and rotator cuff tendinopathy. Prospective studies have shown that it can also be useful in the treatment of patella tendinopathy.

Summary In summary, we found PRP to have variable success in ligament and tendon pathology; however, it should be considered a viable option in chronic musculoskeletal disease that has failed other treatments. Patient selection, duration of symptoms, and combining with other modalities such as physical therapy should all be taken into consideration in treatment with PRP.

Keywords Platelet-rich plasma · PRP · Tendinopathy · Ligament · Biologics

Introduction

The use of biologic therapy in the treatment of various musculoskeletal pathologies has increased significantly over the last 10 years. Specifically, platelet-rich plasma (PRP) has been an increasingly popular treatment for clinicians, especially for its potential in treating tendinopathy and degenerative cellular diseases. The history of PRP in the clinical setting began as early as the 1980s when it was found to be effective in blood loss during cardiac surgery [1, 2]. Its effect on bone was then examined in the field of dentistry for its regenerative properties on bone maturation and formation [3, 4]. In time, its use in musculoskeletal medicine has grown, and its role in tendon and tissue healing has been heavily investigated [5].

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What is PRP?

The term platelet-rich plasma is defined as an autologous blood sample that has a platelet concentration above that contained in normal baseline blood plasma [6, 7]. Although there is great appeal in using a patient's own blood as opposed to more common treatments such as steroids or anesthetics, there is inherent variability in both the preparation and the concentration of platelets [6]. Generally, the preparation of PRP involves obtaining autologous whole blood from the patient followed by a 1–2 step centrifugation process to separate plasma from red blood cells and leukocytes [8]. The method of isolation include the type of collecting tube and centrifuge speed, which both play a role in the final concentration of platelets and leuokocytes in the PRP preparation [6, 9]. Two varieties exist, with regard to leukocyte concentration: leukocyte-poor versus leukocyte-rich PRP [6]. Although leukocytes are important in wound healing and facilitating tissue repair, there is the possibility that it may induce an undesirable inflammatory response at the site of injection [6]. Unfortunately, there is not sufficient in vivo evidence to suggest which preparation method is the most ideal; however, understanding that there are several methods in obtaining and preparing PRP is essential.

This centrifugation process allows extraction of several isolated cell and growth factors in a much higher concentration. The biologic components of PRP are essential in the healing of tendon and cartilage, which are inherently difficult to heal naturally due to poor blood supply [10]. Platelets, one of the main components in PRP, help mediate the release of several growth factors that are essential in the healing process. These include platelet-derived growth factor (PDGF), transforming growth factor (TGF-β), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and insulin-like growth factor (IGF) (Table 1).

The abovementioned growth factors are essential for the three phases of healing: inflammation, proliferation, and remodeling. The proposed benefit of PRP is that it allows for the patient's own blood to provide a high concentration of growth factors to promote healing in both non-operative and operative sites that have limited healing capacity due to blood supply. This matrix serves as scaffold for sustained release of growth factors that drive chemotaxis and angiogenesis [11, 12]. This review will examine the most recent literature on the use of PRP for tendon and ligament pathology.

Basic science support of PRP on tendon/ligament injury

The use of PRP in the clinical setting is based on previous in vitro studies exploring its effect on tendons and ligaments. In tendon, PRP has been shown to induce tendon cell proliferation along with induction of angiogenic factors [13, 14]. Anitua et al. examined PRP on human tenocytes in culture and found significantly higher quantity of VEFG and hepatocyte growth factor produced by tenocytes once exposed to PRP [14]. Along with tenocytes, tendons also contain tendon stem/progenitor cells (TSCs) which make up about 5% of the adult tendon cell population [15]. Multiple in vitro studies have shown platelet-rich clot releasate (PRCR) to induce rabbit TSCs to differentiate into active tenocytes [15, 16]. Autologous PRCR was also shown to inhibit the differentiation of mice TSCs into nontenocyte lineages [17]. PRP has also shown to have anabolic effects on tendon cells by increasing the total collagen synthesis in tenocytes [16, 18]. One in vitro study showed that while platelets increased the expression of collagen type I, the addition of leukocytes induced higher collagen type III gene expression while lowering type I [18]. This is important as a high collagen type III/I ration may indicate fibrosis and reduce the strength of a healing tendon [15]. Despite this potential drawback, the presence of leukocytes has shown to have protective effects against infection. Itravia et al. compared two PRP preparations (leukocyte-poor vs. leukocyte-rich) and found that both preparations significantly decreased bacterial growth compared to whole blood [19].

PRP for ligament injury is also based on several basic science studies that support application of growth factors increasing collagen synthesis and enhancing healing [20, 21]. Early studies of PRP on animal medial collateral ligament showed enhanced healing and strength in the early stages of an acute injury [22, 23]. It has also been shown useful in intra-articular ligaments, such as the anterior cruciate ligament (ACL). Fleming et al. used collagen-platelet composites (CPC) in ACL reconstruction in a porcine model and found those with CPC had a higher load to failure with significantly reduced anteroposterior laxity [24]. These basic science studies help support the use of PRP for tendon and ligament healing in the in vivo setting.

Clinical application and outcomes

Tendinopathy

Rotator cuff tendinopathy

The use of PRP in rotator cuff pathology has come with mixed results in the literature. Early studies on augmenting rotator cuff repair with PRP have been inconsistent with regard to clinical outcomes [25, 26]. A meta-analysis by Zhao et al. reviewed eight randomized controlled trials comparing arthroscopic rotator cuff surgery with and without PRP augment and found no significant difference in re-tear rate or constant score between groups [26]. However, that meta-analysis was limited in study numbers and patients. A more recent meta-analysis by Hurley et al. examined over 18 randomized controlled studies comparing PRP or platelet-rich fibrin (PRF) to arthroscopic repair alone [27•]. Their study included over 1147 patients and found that PRP had significantly decreased rates of incomplete tendon healing for small-medium and medium-complete tears [27•]. They also found a significant decrease in visual analog scores at 30 days and final follow-up compared to the control group [27•].

Verhaegen et al. examined the use of PRP as an augment to arthroscopic needling of calcific deposits of the rotator cuff [28]. In a randomized controlled fashion, they examined whether using PRP would augment the healing process of the rotator cuff after a defect is created with a needling technique [28]. They found that regardless of PRP, all patients improved significantly after surgery, with no difference in rotator cuff defects observed on ultrasound during interval assessments at 3 and 6 months or on MRI during final follow-up at 1 year [28]. Carr et al. had similar results when he examined the use of PRP with arthroscopic acromioplasty for chronic rotator cuff tendinopathy [29]. The role of PRP for conservative treatment has shown significant improvement compared to dry needling in a randomized controlled trial [30]; however, when compared to steroid in a randomized

Table 1 Biologic molecules in platelet-rich plasma [11, 12]

Molecule	Source	Function
PDGF	Platelets, macrophages	Chondrocyte chemotaxis, MSC proliferation, angiogenesis, chondrogenesis
VEGF	Platelets, macrophages, neutrophils	Angiogenesis, endothelial migration
TGF-β	Platelets, macrophages	MSC and fibroblast proliferation, production of collagen, re-epithelialization
EGF	Platelets, macrophages, plasma	Re-epithelialization, organization of granulation tissue
FGF	Platelets	Endothelial proliferation, angiogenesis, collagen production
IGF	Plasma	Cell proliferation, production of proteoglycan, collagen
MMPs	Macrophage, Neutrophils	ECM turnover, tissue remodeling, and recruitment of proliferative cells

PDGF, platelet-derived growth factor; *VEGF*, vascular endothelial growth factor; *TGF-β*, transforming growth factor-β; *EGF*, endothelial growth factor; *FGF*, fibroblast growth factor; *IGF*, insulin-like growth factor; *MMPs*, matrix metalloproteinases.; *ECM*, extracellular matrix

control trial, PRP did not show significantly different results after 6 months [31].

Patellar tendinopathy

Patellar tendinopathy, otherwise known as Jumper's knee, is characterized by chronic pain in the patellar tendon as a result of overuse. PRP has become a common non-surgical intervention for Jumper's knee in recent years [32–35]. Liddle et al. performed a systematic literature review assessing the clinical outcomes of patients undergoing PRP injection and found that overall patients had significant improvement in pain and function, with up to 81% of patients able to return to their pre-symptom level of activity [32]. Studies however have been inconsistent. Gosens et al. found that only 22% of their study population were able to return to their pre-symptomatic activity [33].

A small study comparing PRP with physical therapy alone to physical therapy alone did not show a significant difference between cohorts at 6 months [36]; however, compared to extracorporeal shockwave therapy, PRP had a significant impact on pain and function [37]. The number of PRP injections has also been shown to have an effect on the outcome of the treatment, with two injections found to improve outcomes significantly more than a singular injection. Zayni et al. reported significantly greater improvement in pain and function for patients who received two injections versus one [33], a result corroborated in a 2018 meta-analysis by Andriolo et al. [38•]. Along with chronic patellar tendinopathy, PRP appears to be useful for patellar healing after graft harvesting in ACL reconstruction [38•, 39]. In a randomized controlled trial, Cervellin et al. found that patients who had PRP applied to the patellar tendon donor site following ACL reconstruction experienced a significant decrease in knee pain and improved function at 1 year [38•]. This finding, however, has not been consistent in the literature [40]. Walters et al. recently performed a randomized control trial examining the use of PRP in reducing kneeling pain at the donor site of ACL reconstruction [40]. Their study found no difference in kneeling pain at interval follow-up between patients who received PRP versus placebo [40].

Achilles tendinopathy

The Achilles tendon is a conjoined structure composed of the tendinous regions of the superficial posterior compartment musculature [41]. The tendon resists forces up to 12× body weight during exercise and is amongst the strongest in the body [42]. Despite its robust structure, it is also amongst the most frequently ruptured tendons in the lower extremity and accounts for 20% of major tendon injuries [43]. The healing potential of this tendon is variable for unclear reasons. Anatomic studies conducted in the 1950s identified a watershed region within the mid-substance of the tendon that was thought to create a relative ischemic zone susceptible to injury; however, more recent studies challenge this notion [41]. Due to its relative noninvasiveness and minimal risk, platelet-rich plasma injections are being investigated with hopes of improving tendinopathy outcomes.

A recent systematic review conducted by Di Matteo et al. sought to evaluate the available literature with hopes of better clarifying the clinical potential of PRP in Achilles tendinopathy [43]. While the majority of the 12 reviewed studies were level IV evidence, one randomized double-blinded prospective trial was reviewed [43]. In their 2010 study, de Vos et al. compared saline injection to PRP injection in adult patients who had been suffering from mid-substance Achilles tendinopathy for at least 2 months [44]. Results indicated a uniform increase in the mean Victorian Institute of Sports Assessment-Achilles questionnaire score in both groups; however, there was no significant

difference in pain or functional outcome between PRP and normal saline [44].

A more recent randomized double-blinded prospective trial corroborated and expanded these results. Boesen et al. focused on comparing high-volume methylprednisolone injection (HVI), PRP, and sham injections in 60 adult males with mid-substance Achilles tendinopathy for at least 3 months [45]. In addition to injections, each participant underwent standardized eccentric exercises through a focused rehabilitation program [45]. Results were promising, showing statistically significant improvement in function and pain in both the PRP and HVI group compared to sham injections, although the greatest increase was found in the HVI group [45].

Lateral epicondylitis

Lateral epicondylitis is a degenerative tendinopathy of the common attachment of the wrist extensor muscles at the lateral epicondyle of the humerus [46]. Treatment modalities include rest, behavior modification, physiotherapy, bracing, anti-inflammatory medications, and surgery for recalcitrant cases [47]. While these therapies can be useful in managing acute and chronic cases, the poor biological healing potential of native tendon has led to an increased interest in biologic augmentation with PRP [48].

Several recently published studies have compared PRP to other therapies, including operative and non-operative interventions [49•, 50, 51•, 52]. In a meta-analysis of level 1 randomized controlled trials examining the use of PRP in ligament and tendon injuries, the study authors found that PRP was significantly more effective at reducing pain (VAS) compared to various controls in both short-term (< 6.5 months) and long-term (> 1 year) follow-up periods [48].

The onset and persistence of therapeutic efficacy is an important consideration for patients and clinicians when considering different interventions. Two recent reports have demonstrated how PRP compares to corticosteroid injections over time in patients with lateral epicondylitis [49•, 50]. Ben-Nafa et al. found in their systematic review that PRP has slower therapeutic onset but longer lasting clinical effects in contrast to corticosteroids [50]. The authors concluded that no significant adverse effects were associated with peritendinous PRP administration and noted that clinical improvement lasted up to 2 years for PRP recipients [50]. There were also no evidence of subcutaneous atrophy or hypopigmentation with PRP, which are known complications of corticosteroid [53]. These results are consistent with the findings of a meta-analysis by Mi et al. who describe progressive improvement in VAS and disability of function scores for PRP compared with corticosteroid injections leading up to a 1-year follow-up [49•]. Early comparative assessments favored corticosteroids or was insignificant, while after 6 months, both clinical outcome measures significantly favored PRP patients [49•]. As previously mentioned, the type of PRP injection is also important to note, since lateral epicondylitis often does not heal due to its poor vascularity and inability to induce an inflammatory response. A leukocyte-rich PRP injection was found to be helpful in Mishra et al.'s study and yielded better long-term results compared to an active control group of local anesthetic injection and dry needling [51•].

Surgical techniques are also available for patients suffering from lateral elbow tendinopathy, particularly for refractory cases. A 2017 study reported on postoperative pain and functional outcome results over 2 years in patients who received either PRP injections or arthroscopic lateral elbow debridement [52]. Mean baseline VAS was 7.6 (95% CI 7.0–9.1) in the PRP group and 9 (95% CI 8.6–9.4) in the arthroscopy group [52]. The mean VAS declined significantly compared to baseline in both cohorts by 1 year; however, at 2 years follow-up, the mean VAS increased to 7.1 (95% CI 6.8–8.9) in the PRP group while only marginally increasing to 2.1 (95% CI 1.6–2.9) in the arthroscopy group [52]. The authors concluded that while both procedures were safe and accepted by patients, arthroscopy is superior to PRP in long-term pain and functional outcomes [52].

Ligament pathology

Ulnar collateral ligament

Injury to the medial ulnar collateral ligament (MUCL) occurs as a result of extraneous valgus loads and is common in overhead-throwing athletes [54]. A fully torn ligament or one that has not responded favorably to conservative treatment will be treated surgically; however, success rates have varied from 83 to 90% for a return to play by 9–12 months post-surgery [54]. A case study by Hoffman et al. detailed the outcome of an MUCL reconstruction in a 25-year-old professional pitcher that was augmented with a dermal allograft reconstituted in PRP and mesenchymal stem cells [55]. The authors found that their patient was able to return to pitching by 4 months post-op [55].

Alternatively, partial UCL tears are often treated without surgery. Conservative management usually includes rest, bracing therapy, and oral medication. Recently, there has been great interest in the potential role of PRP injection as well. Podesta et al. followed the progress of 34 throwing athletes being treated for partial thickness tears of the UCL with a single PRP injection [56]. They found that 30 of the 34 athletes were able to return to the same level of play or higher at an average of 12 weeks [56]. A similar study conducted by Dines et al. retrospectively evaluated the progress of 44 baseball players being treated for partial UCL tears with PRP injections [57]. They found that 32 of 44 had good to excellent results with a return to play by 12 weeks [57]. In a larger case

series, Deal et al. conducted a case series on 25 athletes with grade 2 MUCL tears that were treated with two injections of leukocyte-rich PRP [58]. The study found that 22 of 25 were able to return to play, with 20 of the 22 demonstrating a fully reconstituted MUCL on MRI [58]. Despite these various case reports, there are no available randomized controlled trials examining the effectiveness of PRP on MUCL and it is still unclear whether PRP expedites return to play in the conservative management of UCL injuries.

Anterior cruciate ligament

The ACL is vital to the stability of the knee and its rupture requires surgical intervention to restore this functionality. A systematic review by Figueroa et al. regarding ACL repair with the aid of PRP showed variable results in terms of clinical outcomes, bone tunnel healing/widening, and graft maturation [59]. As previously mentioned, studies have shown PRP to be useful with postoperative pain and healing of the harvest site [38•]. Unfortunately, with regard to tunnel healing and widening, PRP has shown little to no effect [60, 61]. Only one study concluded that PRP produced a statistically significant increase in the amount of tunnel cortical bone compared with no PRP at 2.5 months (36.2% vs. 22.5%) and that this difference was sustained at the 6-month mark (67.1% vs. 53.5%) [62].

Vogrin et al. performed a randomized controlled trial augmenting their ACL reconstruction with PRP and found there to be a statistically significant improvement in anteroposterior knee stability in the PRP test group [63]. However, they found no difference in healing at the intra-articular portion of the ACL on MRI at 12 months [63]. Magnussen et al. compared the use of PRP in addition to allograft ACL reconstruction, and found no difference in patient outcomes at 2-year follow-up whether or not PRP was used [64]. The use of PRP may show more promise in partial tears. A systematic review by Di Matteo et al. included two studies of PRP used for partial ACL tears, which showed that between 70 and 84% of patients return to previous level of activity without surgery [65]. Initial research regarding the use of PRP to treat ACL injuries shows promise in terms of its ability to help induce cell growth for various grafts; however, there is not sufficient research to conclude the best composition of PRP injections to induce the maximal amount of healing.

Conclusion

The use of biologics to improve soft-tissue healing is an ever-growing interest within the field regenerative sports medicine. PRP is derived from an autologous sample prepared to isolate elevated concentration of growth factors and cytokines in order to create a healing environment and reduce inflammation. Multiple basic science and in vivo animal studies support the use of PRP in tendon and ligament pathology. Although some clinical evidence supports its use in management of rotator cuff and patellar tendinopathy, studies examining efficacy in the treatment of ligament injuries such as ulnar collateral and anterior cruciate ligament are limited and inconclusive. Additional clinical studies are needed with higher level of evidence; however, PRP remains a viable conservative treatment measure with low risk of complication or adverse reaction. Etiology may a play role when choosing the type of PRP injection, such as leukocyte-rich versus leukocyte-poor. Acellular pathologies such as lateral epicondylitis may benefit more from leukocyte-rich PRP, which may help induce an inflammatory response to promote healing. PRP is yet to become the standard of care; however, with further studies in understanding the optimal candidate; it may be a much more common practice in the future.

Compliance with ethical standards

Conflict of interest Dr. Mazzocca is a consultant for Arthrex, Inc. and has received financial support from the biomechanics lab. All other authors declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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