Use of Platelet-Rich Plasma for Patellar Tendon and Medial Collateral Ligament Injuries: Best Current Clinical Practice

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Abstract

Platelet-rich plasmas (PRPs) are complex molecular therapies prepared from the patient's own blood through minimal manipulation. Clinical studies examining the efficacy of PRPs to manage patellar tendinopathy and medial collateral ligament (MCL) injuries have been reviewed. We found three controlled trials, two of them randomized, and seven case series in the management of patellar tendinopathy. In addition, three other randomized studies showed that PRPs help to regenerate the patellar tendon harvest site for anterior cruciate ligament reconstruction and to reduce patellar donor site morbidity. On the other hand, the use of PRP in MCL injuries is reported in a single case study. Seven of the 11 studies used leukocyte and PRP which was buffered in four studies. Seven of the 11 studies applied two or three injections. Given the heterogeneity of PRP protocols and the paucity of high-quality data, the most effective approach to guide clinical decisions regarding patellar tendinopathy cannot be deduced from the present published studies.

Keywords
- tissue regeneration
- signaling proteins
- biological therapy

Patellar tendinopathy (PT), also named jumpers knee, is an overuse injury characterized by activity-related anterior knee pain, most often showing lesions at the inferior pole of the patella, even though the midzone, paratenon, tibia tubercle or superior pole can also be affected.

PT is common among professional and recreational athletes[1] involved in sports with high demand of the knee extensors, in particular volleyball and basketball.[2] In this context, intrinsic risk factors such as patellar shape[3] and athlete's age, or extrinsic risk factors involving playing at high level competition, hours of training per week, and training errors among others make athletes vulnerable to PT.[4] So far, most research involves professional and recreational athletes. The personal and economic burden of PT is high, because swelling and pain impairs performance with loss of function (jumping and kneeling), often leading athletes to abandon their career.[5]

Several nonoperative treatment modalities can be used to manage PT, including a variety of injectable substances with different mechanisms of action such as corticoids, polidocanol or platelet-rich plasma (PRP). The effect of high volume injections to mechanically modify the tissue has been explored both in chronic PT[6] and recalcitrant medial collateral ligament (MCL) injuries.[7] In addition, physical therapies (mainly eccentric training) and extracorporeal shock wave therapy (ESWT) are used. While some evidence supports the efficacy of eccentric exercises, not enough data demonstrate the effectiveness of polidocanol injection or ESWT.[8] Their efficacy may depend on the phase of PT. Here, we review the available data on the efficacy of PRP injections in the management of PT.

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Typical histopathological features of PT include collagen bundles separated by mucoid tissue, increased cellularity, extensive neovascularity, as well as clefts in collagen, and occasionally necrotic fibers suggesting microtears.[9] From a molecular point of view, alterations in the mechanical environment, that is, disintegrated collagen fibers and loss of cell attachment, modify the microenvironment[10] and affect a range of biological processes. The latter may be molecularly described as a dysregulation of inflammatory and angiogenic molecules, including prostaglandin E2, interleukin 6, interleukin 6 receptor, cyclooxygenase 2, vascular endothelial growth factor, oncostatin M, leukemia inhibitory factor, connective tissue growth factor[11] as well as unbalanced anabolic/catabolic mediators.[12] In this context, PRP therapy, a multimolecular approach influencing inflammation, angiogenesis, and cell metabolism,[13] is increasingly used to manage pathological tendons both in the upper and lower limb[14] with variable efficacy between tendons.

PRP therapies are easy to implement, and are considered safe because they are prepared through minimal manipulation of the patients' own blood. But elucidating the effect of these therapies on patient outcomes requires careful analysis of PRP products and protocols, and methodological characteristics of the study to identify the most promising approaches. In this review, we examine clinical studies exploring the efficacy of PRP injections in PT and MCL injuries, seeking to identify under what conditions PRP works.

Methods

We searched for peer-reviewed original articles in the PubMed and Web of Science databases using the following keywords, and their different combinations: "platelet-rich plasma," "jumpers' knee," "patellar tendon," "patellar tendinopathy," and "medial collateral ligament" from January 2003 to January 2014. We also searched the authors own personal files. Only articles published in English were reviewed.

Study Selection and Data Collection

We have included all clinical studies, that is, case series, controlled nonrandomized and controlled randomized studies.

Extraction of data consists of study design, patient population, intervention, that is, type of PRP formulation, volume and number of injections and interval between injections, control treatment, outcome measurements, follow-up, and the reported results.

Results

Platelet-Rich Plasma Injections in Patellar Tendinopathy

PRP injections to manage PT were reported in a total of 226 patients, including three controlled studies[15–17]and eight case series studies[18–25] (►**Table 1**). Two randomized clinical trials, one including 23 patients,[15] and the other,[16] 46 patients, have been published recently (2013–2014). In a randomized controlled trial (RCT) comparing one leukocyte and PRP (L-PRP) injection ($n = 9$ patients) and eccentric exercises with dry needling and eccentric exercise ($n = 12$ patients), Dragoo et al[15] showed significant improvement in clinical outcomes, in visual analog score (VAS) and Victoria Institute of Sport Assessment-patellar (VISA-P) at 12 weeks after treatment. Three patients failed treatment in the dry needling group and were rescued with PRP; their outcomes at the 26 week time-point were lost. Thus, the study is biased because patients were no longer in the treatment group they were allocated. Moreover, at 26-week follow-up the number of patients was low and there were no differences between dry needling ($n = 9$) and the PRP injection ($n = 9$). The authors interrupted recruitment because of clinically significant differences in favor of the PRP group at 12 weeks. However, these differences vanished over 26 weeks.

Two randomized clinical trials,[16] each involving 46 patients, have compared two injections of pure PRP with ESWT. Clinical outcomes, as assessed by VAS, VISA-P, and Blazina scores, showed greater improvement at 6 and 12 months in the PRP group, and the percent of responders was significantly higher in PRP than in the ESWT group.[16] Given evident differences between experimental and control treatment these studies were blind merely for the outcome assessor.

In a nonrandomized controlled study, Filardo et al[17] showed that three injections of L-PRP 1 week apart were superior to physiotherapy as assessed by the Tegner activity score at 6 months. In this study, subjects treated with PRP had previously failed physiotherapy treatment.

Eight case series,[18–25] with a variable number of patients ranging from 5 to 43, have been published. Two[24,25] of these case series included both Achilles and PT.

Regarding procedural factors, most studies (6/8) used L-PRP[19,21–25]; the number of injections varied from a single injection (four studies),[21,23–25] two injections with 3 weeks interval (one study),[24] to three injections with 2 weeks interval (two studies).[17,18] All studies but one used the ultrasound (US) guidance for PRP delivery.[17] The VISA-P, a standardized and validated score that allows follow-up of chronic symptoms, was used in all studies except the study by Filardo et al.[17]

Several studies evaluated the structural changes after treatment.[23–25] Volpi et al[23] reported structural improvement in 80% of the treated tendons, as assessed by magnetic resonance imaging (MRI) at 3 to 4 month posttreatment, while Ferrero et al[24] reported significant changes in tendon thickness, reductions in hypoechoic areas, and decrease in intratendinous vascularity at 6 months posttreatment, but no changes at 20-day follow-up.

The effect of previous treatments and length of disease was examined in a prospective study involving 36 patients treated with one injection of buffered L-PRP.[21] Although, VAS and ADL (pain during daily activities) scores improved in both groups, patients with previous treatments (ethoxysclerol, cortisone and/or surgical treatment) did not show significant changes in VISA-P over time.

Whether the effects of PRP injections lasted or not was examined by Filardo et al[17] in a 4-year follow-up study including 42 male patients and 1 female patient. The VISA-P

Table 1 Platelet-rich plasma in the management of patellar tendinopathy

Patellar tendon (conservative management)				
Study (year) (Level of evidence)	**Study design, *N* (patient population)**	**PRP (volume)**	**Intervention/ outcome measurements**	**Follow-up/results**
Dragoo et al (2014)[15] (Level I)	RCT, $N = 23$	6 mL L-PRP (Plt: 4–8x WBC: 6x), buffered pH: 7.4 No exogenous activation	Single injection PRP + eccentric vs. US-guided dry needling + eccentric/ VISA-P, VAS, Tegner, Lysholm, SF12	12, 26 wks/VISA-P at 12 wks, VAS, Tegner, Lysholm, SF12 at 12 and 26 wks. Better PRP group at 12 wks but not at 26 wks. PRP accelerates the recovery but effect banishes over time No adverse effects
Vetrano et al (2013)[16] (Level I)	RCT, $N = 23$ per group Athletes, chronic > 6 mo recalcitrant	2 mL pure PRP Plt: 3–5x	Two PRP injections, biweekly, US-guided vs. ESWT/VAS, VISA-P, Blazina scale	2, 6, and 12 mo/VISA-P and VAS, PRP better at 6 and 12 mo, no differences at 2 mo; Blazina PRP better at 12 mo; PRP higher success rates (% responders) at 12 mo
Filardo et al (2010)[17] (Level III)	Nonrandomized study, PRP, $N = 15$ vs. physiotherapy $N = 16$ (matched for age, sex, and sport level) Chronicity > 3 mo and recalcitrant to conservative and surgical treatment only in PRP the group	5 mL L-PRP Blood bank: (Plt: 6x; WBC: ?) Activated Ca^{2+} mEq/ dose	Three blind injections/ biweekly + physical therapy Comparator: physical therapy/EQ-VAS, Tegner score	6 mo/No significant improvement in PRP group for EQ-VAS and pain level. Significant improvement in PRP group for Tegner score (+ 39 vs. 20%)
Charousset et al (2014)[18] (Level IV)	Case series, $N = 28$ athletes, 17 professional, 11 semiprofessional PT refractory	6 mL pure PRP (Plt: > 2x)	Three US-guided injections/VISA-P, VAS, Lysholm	2 year/21 athletes returned to presporting levels at 3 mo 57% patients recovered structural integrity, 7 treatment failures
Filardo et al (2013)[19] (Level IV)	Case series, $N = 43$, chronic	5 mL L-PRP Blood bank: (Plt: 6x; WBC: ?) Activated Ca^{2+} mEq/ dose	Three US-guided injections biweekly/ VISA-P, Blazina, EQ-VAS, Tegner, US	4 y/VISA-P increased over time, 80% were satisfied and resume previous sport activities
van ArK et al (2012)[20] (Level IV)	Case series, $N = 5$ patients, 6 tendons/ athletes, symptoms for over 12 mo VISA-P < 80, US hypoechogenicity, recalcitrant to at least 12 wks eccentric training	2–3 mL P-PRP Plt: 1.7x (ACP, Arthrex)	Single US-guided injection + physical therapy VISA-P, VAS during daily activities, functional test	6 mo/5/6 tendons showed an improvement of at least 30 points on the VISA-P after 6 mo
Gosens et al (2012)[21] (Level IV)	Case series $N = 36$, subgroups: refractory $N = 14$ vs. nonrefractory $N = 22$. Resistant to conservative and surgical treatment	3 mL L-PRP (Plt: 4–8x WBC: 6x), buffered pH: 7.4 + bupivacaine/no activation	Single blind injection, one skin portal, and five penetrations of the tendon VISA-P, ADL, VAS	18 mo/clinical improvement in refractory and non-refractory patients, better results in the last group

(*Continued*)

Table 1 (*Continued*)

Patellar tendon (conservative management)				
Study (year) (Level of evidence)	**Study design, *N* (patient population)**	**PRP (volume)**	**Intervention/ outcome measurements**	**Follow-up/results**
	$N = 14$, resistant but no injections, no responders to eccentric			
Kon et al (2009)[22] (Level IV)	Case series $N = 20$ males Refractory tendinopathy	5 mL L-PRP Blood bank: (Plt: 6x; WBC: ?) Activated Ca^{2+} mEq/ dose	L-PRP and rehabilitation three injections, 2 wk interval between injections/Tegner, VAS, SF-36	6 mo/significant improvement in all scores after 6 mo. Six men complete recovery, eight men marked improvement, two men showed mild improvement and four men no improvement
Volpi et al (2007)[23] (Level IV)	Case series $N = 8$ Young athletes, third proximal recalcitrant tendinopathy since at least 1 y	3 mL L-PRP (Plt: 4–8x WBC: 6x) buffered pH: 7.4/no activation	Single blind injection + rehabilitation/ VISA-P, MRI	4 mo/VISA improvement (91%)/ reduction in irregularity in 80% of treated tendons (MRI, 4 mo)
Ferrero et al (2012)[24] (Level IV)[a]	Case series 28 patellar tendons in 24 patients Competitive and recreational athletes, resistant to conservative treatments	Blood bank: 6 mL L-PRP Plt: 5x WBC: 6x/ thrombin activation	US-guided two injections and scarifications (3 wks interval)/ VISA-P, US/6 mo	VISA-P improvement at 6 mo/reduction in hypoechoic areas and tendon thickness after 6 mo. Intratendinous vascularity increased at 20 d and 6 mo
Volpi et al (2010)[25] (Level IV)[a]	Case series, patellar ($N = 13$ tendons), nine athletes, other recreational	3 mL L-PRP (Plt: 4–8x WBC: 6x) buffered pH: 7.4 no activation	PRP and rehabilitation Single US-guided injection	VISA-P, MRI//24 mo/ Improvement in VISA-P (+ 37) and reductions in abnormalities in 80% of treated tendons (MRI). The improvement of clinical symptoms is maintained for at least 2 y following treatment. Improvement less marked in Achilles

[a]Achilles and patellar tendon examined in the same study.
Abbreviations: ESWT, extracorporeal shock wave therapy; L-PRP, leukocyte-rich PRP; MRI, magnetic resonance imaging; Plt, platelets; PRP, platelet-rich plasma; PT, patellar tendon; RCT, randomized controlled trial; US, ultrasound; VISA-P, Victoria Institute of Sport Assessment-patellar; VAS, visual analog score; WBC, white blood cells; SF-12, health survey 12 questions; SF-36, health survey 36 questions.

score was significantly higher 4 years after the treatment and 80% of patients resumed their sporting activities thus were satisfied with the treatment. Results were worst in patients with bilateral PT, and in those with longer history of the pathology.

Use of Platelet-Rich Plasma Fibrin to Regenerate Patellar Tendon Harvest Site

PRP can enhance tissue regeneration in acute conditions as illustrated at the patellar tendon harvest site. The patellar tendon is often used for ACL reconstruction because of earlier bone to bone healing (►**Table 2**), mechanical qualities of the tissue, and ACL compatible size and shape. However, harvest site morbidity is reported in more than 40% of patients, including anterior knee pain, patellar stiffness, and loss of range of motion.[26] Common sequelae are increased patello-femoral joint compression and late chondromalacia of the patella, and in some cases patellar fracture.

Three RCT[27–29] have assessed the impact of filling the patellar harvest site with PRP Cervellini et al[27] sutured PRP into the patellar harvest site in an RCT involving 40 patients, 20 per group. There were no differences in VAS scores at

Table 2 Platelet-rich plasma treatment of patellar tendon harvest site

Study (year) (Level of evidence)	Number of patients PRP	Outcome assessments/ follow-up	Results
Cervellin et al (2011)[27] (Level I)	RCT $N = 40$, 20 received PRP PRP applied to patellar and tendon bone plug harvest site L-PRP (GPS) $CaCl_2$ and thrombin	VAS, VISA/12 mo	VISA-P higher in PRP group, no differences in postoperative VAS $> 70\%$ of bone gap filled: 85% in PRP vs. 60% controls N/S
de Almeida et al (2012)[28] (Level I)	RCT $N = 27$, $N = 12$ receive PRP Platelets 7.65x leuko-depleted clotted with autologous thrombin prepared after $CaCl_2$ addition to a PRP aliquot	MRI at 6 mo, isokinetic tests VAS, functional questionnaires, Lysholm, IKDC, Kujala and Tegner/6 mo	Patellar tendon gap significantly smaller in PRP group. VAS lower in PRP group. All groups improved except for Tegner. No differences between groups. No infections or inflammatory complications
Seijas et al (2013)[29] (Level I)	RCT, PRP $N = 23$; control $N = 20$ Pure PRP, 1–3x, $CaCl_2$ activated	Maturity degree, vascularity (Ohberg scale) Doppler US-assessment/4, 8, 16, 24, 36, 48, and 96 wks	Differences in maturity degree at 16 mo, no differences at other time-points. No differences in vascularity

Abbreviations: IKDC, International Knee Documentation Committee; L-PRP, leukocyte-rich PRP; MRI, magnetic resonance imaging; N/S, not significant; PRP, platelet-rich plasma; PT, patellar tendon; RCT, randomized controlled trial; US, ultrasound; VISA-P, Victoria Institute of Sport Assessment-patellar; VAS, visual analog score.

12 months, but the VISA-P score was higher in the PRP group. In another RCT,[28] 12 patients were treated with 20 to 40 mL of PRP, and compared with 12 patients in whom the donor harvest site was left untreated. At 6 months, the area of the patellar area treated with PRP was significantly smaller than the untreated area, as assessed by MRI. In addition, postoperative VAS scores were lower in the PRP group. A faster healing of the donor harvest site treated with PRP was also confirmed in another RCT performed by Seijas et al.[29]

Use of Platelet-Rich Plasma in Medial Collateral Ligament Tears

The MCL along with the anterior, posterior, and lateral cruciate ligaments are critical to maintain knee stability. Most often, MCL injuries occur as part of more complex knee injuries. At present, only a case report[30] has been reported in an isolated Grade III MCL injury (Hughston classification). The athlete received three injections of L-PRP with 1-week interval and was followed-up for 16 months. The football player resumed sports activities at day 18, and full competition at day 25.

Discussion

The quality of the presently available evidence is insufficient to guide clinical decisions about PRP administration in PT because of the reduced number of controlled studies (three studies, of which two were RCTs). Despite that, the present published evidence mostly shows positive outcomes after PRP management of PT. In case series, most patients treated with PRP with positive results were refractory to other conservative management. Implementation of PRP treatment seems reasonable before considering arthroscopic or surgical treatments. Of note, symptom exacerbation after PRP (or PRP + fat cells) treatment has been reported in three cases.[31] Adverse reactions to PRP treatment can be very informative. Two of these patients had bilateral PT; one of them (a collegiate swimmer) received PRP mixed with abdominal fat in both knees while the second one (a professional volleyball player) received 3 mL of buffered L-PRP in each knee. The other patient (a high school basketball player) received two injections of pure PRP with 1-week interval.

The best PRP formulation and treatment regimen cannot be deduced from the present state of the art.[32] In fact, the PRP formulation, the volume and number of injections, and whether injections are associated or not to tendon needling may influence outcomes. In PT, as in other tendinopathies,[14] the most commonly used PRP formulation is L-PRP (seven vs. four studies). However, two of the three RCTs performed till date used two pure PRP injections, 1 or 2 weeks apart, with good results.

The optimal number of injections is controversial. More than one injection produces apparently more lasting results.[19] This has sense from a biological perspective, since a single injection may be insufficient to induce sufficient cell migration, activation of local tendon fibroblasts, and enough synthesis of extracellular matrix proteins, to reverse cell apoptosis and the mucoid degeneration that has developed over months to years. Because the conditions of the host

tissue may constrain the therapeutic response, it seems reasonable to speculate that the number and volume of injections should be tailored to each patient taking into account the severity of the injury, and the clinical response. Thus, appropriate treatment algorithms including demographic, clinical, and perhaps genetic polymorphisms data (associated to disease vulnerability) may help in identifying responders to PRP therapies.

Whether PRP is a palliative treatment or induces true regenerative changes in the tendon itself should be ascertained. Theoretically, if tendon regeneration is to be achieved through PRP injections, a long-lasting response is expected to accompany structural changes. Clinical and structural changes are not concomitant, but both long-lasting clinical effects and structural changes in the patella have been reported. In addition, the association of physical therapy to PRP injections may improve clinical and structural outcomes.[33,34]

The phase of PT in which the patient should be treated with PRP is unclear. In fact, whether PRP is indicated for refractory tendinopathy or as a prior indication is arguable. Better results after a single L-PRP injection were found in nonrefractory patients, compared with recalcitrant patients in whom the condition was chronic.[21] From these data, we may deduce that refractory patients need additional injections of PRP. Indeed, a 3-year follow-up case series study emphasizes the potential importance of a second PRP injection in painful tendon tears unresponsive to a single injection.[35]

A recent cross-sectional retrospective survey gathered outcome data from different tendons treated with PRP. In this study involving a total of 180 patients, 106 patients were treated for PT and more than 80% of patients who received one or two injections and 76% of those who received three injections reported moderate-to-complete resolution of symptoms.[36]

In an acute injury context, in particular when grafting patellar tendon to reconstruct the ACL, the use of PRP fibrin to fill the hole left after graft harvest is clinically relevant.[27–29] From a biological point of view, the PRP fibrin provides the necessary biological cues and structural support for cell activities (migration, proliferation, and extracellular matrix synthesis) and tissue regeneration.[37] Preclinical research involving bilateral resection of the central half of patellar tendon[38] showed enhanced mechanical properties of the PRP treated site at 12 weeks.

The value of PRP injections for managing MCL injuries is under-researched. In fact, only one case report has been published.[30] Preclinical studies, mainly performed in rabbits, showed enhanced healing of the MCL after pure PRP application.[37–39] At 20 weeks, the ultimate failure load of the regenerated ligament was 78% of that in healthy controls. In accordance, when PRP was injected in the MCL of healthy rabbits new collagen deposition was found.[40]

PRP is a promising biological intervention applicable in the clinical setting. However, more research is needed to determine the optimal formulation, volume of PRP, number of injections and interval between injection and associated physical therapy. Given the heterogeneity of PRP protocols and the paucity of high quality data, the most effective approach to guide clinical decisions regarding PT cannot be deduced from present published studies. It is mandatory to generate high quality evidences before recommending this treatment to our patients. To further advance in the field, we have to conduct well-designed clinical studies assessing the potential therapeutic effect of PRP.

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