Platelet-Rich Plasma Treatment for Ligament and Tendon Injuries

Justin Paoloni, MBBS, PhD, Robert J. De Vos, MD,† Bruce Hamilton, MBChB,*‡ George A. C. Murrell, MD, DPhil,§ and John Orchard, MBBS, MD¶*

Abstract: Platelet-rich plasma (PRP) is derived from centrifuging whole blood, has a platelet concentration higher than that of the whole blood, is the cellular component of plasma that settles after centrifugation, and contains numerous growth factors. There is increasing interest in the sports medicine and athletic community about providing endogenous growth factors directly to the injury site, using autologous blood products such as PRP, to potentially facilitate healing and earlier return to sport after musculoskeletal injury. Despite this interest, and apparent widespread use, there is a lack of high-level evidence regarding randomized clinical trials assessing the efficacy of PRP in treating ligament and tendon injuries. Basic science and animal studies and small case series reports on PRP injections for ligament or tendon injuries, but few randomized controlled clinical trials have assessed the efficacy of PRP injections and none have demonstrated scientific evidence of efficacy. Scientific studies should be performed to assess clinical indications, efficacy, and safety of PRP, and this will require appropriately powered randomized controlled trials with adequate and validated clinical and functional outcome measures and sound statistical analysis. Other aspects of PRP use that need to be determined are (1) volume of injection/application, (2) most effective preparation, (3) buffering/activation, (4) injection technique (1 depot vs multiple depots), (5) timing of injection to injury, (6) single application versus series of injections, and (7) the most effective rehabilitation protocol to use after PRP injection. With all proposed treatments, the doctor and the patient should weigh up potential benefits of treatment, potential risks, and costs. Based on the limited publications to date and theoretical considerations, the potential risks involved with PRP are fortunately very low. However, benefits remain unproven to date, particularly when comparing PRP with other injections for ligament and tendon injuries.

Key Words: platelet-rich plasma, PRP, ligament, tendon

(*Clin J Sport Med* 2011;21:37–45)

Submitted for publication February 14, 2010; accepted November 17, 2010.

From the *Sports Medicine, Aspetar, Doha, Qatar; †Department of Sports Medicine, The Hague Medical Centre, the Netherlands; ‡Qatar Orthopaedic and Sports Medicine Hospital, Doha, Qatar; §Orthopaedic Research Institute, St George Hospital, Sydney, New South Wales, Australia; and ¶Sports Medicine, University of Sydney, Sydney, New South Wales, Australia.

The authors report no conflicts of interest to disclose.

Corresponding Author: Justin Paoloni, MBBS, PhD, Sport Medicine, Aspetar, Doha, Qatar (e-mail: justin.paoloni@aspetar.com).

INTRODUCTION

Platelet-rich plasma (PRP) is derived from centrifuging whole blood, has a platelet concentration higher than that of whole blood,[1,2] and is the cellular component of plasma that settles after centrifugation. Platelet-rich plasma contains numerous growth factors, including transforming growth factor-β1, insulin-like growth factors 1 and 2, vascular endothelial growth factor (VEGF), basic fibroblast growth factor, and hepatocyte growth factor (HGF).[3] There is increasing interest in the sports medical and athletic community about providing endogenous growth factors directly to the injury site, through the use of autologous blood products, such as PRP, for facilitating early return to sport after musculoskeletal injury.[3] Despite this interest, and apparent widespread use, there is a lack of high-level evidence regarding randomized clinical trials assessing the efficacy of PRP in treating ligament and tendon injuries.[4–7]

Ligament and tendon injuries can be either acute or chronic, and in clinical practice, any treatment should be individualized to target specific pathology and diagnoses and generally be combined with other treatment measures, such as bracing or physiotherapy. Acute injuries involve tearing of collagen fibers, hematoma formation, and subsequent healing through inflammation, cellular proliferation, regeneration and repair, and remodeling processes.[8] Chronic ligament and tendon injuries are common with increasing age and sports participation, but there is still a lack of knowledge about the etiology and pathogenesis of these injuries.[9] These chronic injuries are associated with overuse and may involve degenerative processes. The degenerative processes of chronic injuries would include tendinopathy with collagen fiber disruption, mucoid degeneration, neovascularization, and absence of inflammation.[10] Chronic ligament injuries generally represent chronic instability from failure of acute ligament healing, often involve fiber stretching or tearing and joint laxity, and may have an inflammatory component.[11,12] As with acute muscle injury,[13] for acute ligament and tendon injuries, there may be an argument for the use of PRP to synergistically assist the inflammatory cascade and regenerative processes in healing injured tissue. With chronic injuries, particularly tendon injuries with no, or minimal, inflammatory component, the rationale for use of autologous blood products, including PRP, is less clear. However, as is recognized in treating ligament and tendon injuries, the healing pathways are extremely complex and not fully understood with regard to stimulatory, inhibitory, and regulatory influences on healing.[14] In this setting, it is difficult to conceptualize how delivering a bolus of growth

factors into an injured area could enhance healing when, presumably, these growth factors are, or will have been, acting on this injured region at some stage. In general, despite many basic science and animal studies and some small case reports on PRP injections for ligament or tendon injuries, there are few randomized controlled clinical trials assessing the efficacy of PRP injections, and the level of scientific evidence of efficacy is lacking.[7]

To better understand how PRP may assist in healing, we analyzed the existing evidence regarding PRP treatment for specific ligament and tendon injuries.

ACUTE LIGAMENT INJURY

There is basic science evidence that specific growth factors (in this case, platelet-derived growth factor) improve healing and mechanical strength in the early stages of animal acute medial collateral ligament (MCL) injury.[15,16] The greatest effect was seen with early PRP administration, within 24 hours, and there seemed to be a plateau in the dose–response effect.[16] Tendon or ligament cultured in PRP shows increased COL1A1:COL3A1 ratio and decreased matrix metalloprotease 13 expression, suggesting an enhanced tendon collagen type I production and decreased degradation. Furthermore, expression and growth factor concentration correlate with platelet concentration in PRP.[17] It has been noted that extra-articular ligaments, such as the MCL, have greater physiological wound site filling and increased presence of fibrinogen and growth factors when healing as compared with intra-articular ligaments, such as the anterior cruciate ligament (ACL), although the application of PRP to injured ACL can ameliorate these differences.[18] There is early improvement in load to failure, maximum load, and stiffness of porcine ACL suture repairs with the application of PRP[8] but no improvement in laxity, maximum tensile load, or linear stiffness with longer follow-up.[19]

A level 1[20] (Table 1) double-blind randomized clinical trial evaluated PRP application to the central aspect and the tunnels of bone-patellar tendon-bone allograft and found no statistically significant differences in inflammatory parameters, appearance of the graft in magnetic resonance imaging (MRI), or clinical evaluation using validated scores.[21] Another prospective clinical study showed that 3 months after ACL reconstruction using hamstring allograft, there was no difference in graft fixation, as measured by MRI Sharpey fiber integration in the fibrous interzone, with PRP delivered into the graft tunnels or combined treatment of PRP into the graft tunnels and PRP intra-articular injections at subsequent intervals of 2 and 4 weeks after surgery.[22] Single application of PRP into the femoral and tibial tunnels during ACL reconstruction using hamstring allograft did not affect clinical or functional outcome measures.[23] There was a significant difference in ACL graft density on computed tomographic scan in the PRP group compared with that in the control group, with the ACL density approximating that of the posterior cruciate ligament. One complication/side effect in the PRP group was a noted synovitic reaction with ACL hypertrophy and surrounding soft tissue reaction.

Despite basic science evidence of enhanced early healing of acute ligament injuries with PRP application, human randomized controlled trials (RCTs) have failed to show an effect, and thus, PRP single-application treatment cannot be recommended in combination with ACL reconstruction. There is a need for good quality RCTs to assess the efficacy of PRP injections in the treatment of acute extra-articular ligament injury, such as MCL injury or ankle ligament injuries (deltoid or lateral ligament complex).

ACUTE TENDON INJURY

In acute tendon injury models in animals, there is evidence that circulation-derived cells, such as macrophages and fibroblasts, are present in the early stages of tendon healing and decrease with time.[24] Healthy tendon or ligament tissue explants cultured in PRP showed increased COL1A1:COL3A1 ratios and decreased matrix metalloprotease 13 expression.[17] Platelet-rich plasma enhanced the number of fibroblasts in tendon, and the amount of collagen synthesis, in the initial stage after injury,[14] and in the longer term (24 weeks), equine studies show that there are increases in collagen, glycosaminoglycans, and DNA content; collagen organization; metabolic activity; improved load to failure; and elastic modulus.[25] Platelet-rich plasma has been demonstrated to increase the synthesis of VEGF and HGF within cultured human tendon cells and as such may provide both an angiogenic response and a cellular proliferative response.[26,27] Platelet-derived growth factor contributes to cell proliferation, whereas transforming growth factor-β1 increases collagen synthesis but inhibits cellular proliferation possibly through the increase in VEGF and reciprocal decrease in HGF in cultured human tendon cells.[26] There is evidence that single PRP injection significantly increased tendon force to failure, stiffness, and ultimate stress in the early stages of tendon healing in rats; however, this effect seems to abate with time in both patellar tendon[28] and Achilles tendon[29] injury models. Achilles tendon repair in a sheep model showed that surgical repair using a scaffold (in this case, a cross-linked acellular porcine dermal patch) was effective and that the addition of PRP fibrin matrix to the scaffold did not alter the repair process.[30]

In a case-controlled study of the surgical repair of Achilles tendon rupture, Sanchez et al[31] showed a significant improvement in the PRP adjunctive group for earlier ankle range of motion, early return to gentle running and to sports training, and decreased tendon cross-sectional area. This study used a fibrin scaffold in addition to PRP, but had small patient group numbers (N = 6), and suggests that randomized controlled clinical trials with large patient cohorts are required to assess the efficacy of this treatment. Very recently, a randomized clinical trial was performed on 30 patients with ruptured Achilles tendons. Before final skin suture, randomization was performed and 16 patients were injected with 10 mL of PRP, whereas 14 were not. The Achilles tendon Total Rupture Score, a validated patient-reported instrument for measuring outcome after treatment in patients with a total Achilles tendon rupture, was used as an outcome measure. At 1-year follow-up, there was no significant difference in heel raise index between groups, but the Achilles tendon Total

TABLE 1. Levels of Evidence from the Oxford Centre for Evidence Based Medicine, March 2009, Last Edited January 2010

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential Diagnosis/Symptom Prevalence Study	Economic and Decision Analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR" validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR" with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval"¡)	Individual inception cohort study with >80% follow-up; CDR" validated in a single population	Validating** cohort study with good“ ” “ reference standards; or CDR” tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts“ ”	All or none case-series	Absolute better-value or worse-value analyses “ ” “ ”
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; eg, <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR" or validated on split-sample§§§ only	Exploratory** cohort study with good“ ”“reference standards; CDR” after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	“Outcomes” Research; Ecological studies	“Outcomes” Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”	Expert opinion without explicit critical appraisal, or based on economic theory or “first principles”

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick, March 2009.

Notes

Users can add a minus-sign “-” to denote the level that fails to provide a conclusive answer because of
EITHER a single result with a wide Confidence Interval
OR a Systematic Review with troublesome heterogeneity.
Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

(*continued on next page*)

TABLE 1. (*continued*) Levels of Evidence from the Oxford Centre for Evidence Based Medicine, March 2009, Last Edited January 2010

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
"	Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)
"¡	See note above for advice on how to understand, rate, and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
" "	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
"¡"¡	Good, better, bad, and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
" " "	Good reference standards are independent of the test, and applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a Level 4 study.
" " " "	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (eg, using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, nonobjective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1-5 years chronic)

Grades of Recommendation
A: consistent Level 1 studies
B: consistent Level 2 or 3 studies ***or*** extrapolations from Level 1 studies
C: Level 4 studies ***or*** extrapolations from Level 2 or 3 studies
D: Level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation that has potentially clinically important differences than the original study situation.
Page last edited: January 3, 2010

Rupture Score was significantly lower in the PRP group, suggesting that PRP may have a detrimental effect.[32]

Overall, there is conflicting evidence of efficacy[20] in surgically repaired acute Achilles tendon ruptures. Furthermore, there is no evidence of PRP enhancement of fibroblast numbers occurring in acute tendon injury in humans.

CHRONIC TENDON INJURY

Chronic tendon injury, such as tendinopathy, frequently has histopathological features of collagen fiber disruption, mucoid degeneration, neovascularization, and absence of inflammation.[10] There is an absence of basic science studies on growth factors and PRP in chronic tendon injury models, but it is suggested that growth factors may be useful in treating tendinopathy due to effects on angiogenesis and collagen synthesis.[3,33,34] There is evidence that the effects of growth factors on collagen synthesis differ in intrasynovial and extrasynovial tendons.[35]

In one RCT assessing PRP injection in chronic tendinopathy, de Vos et al[36] used 4 mL of PRP injected in small depots in the degenerated area of the Achilles tendon under Doppler ultrasound guidance. This study showed no difference in outcome measures when compared with the placebo saline injection, although both groups improved approximately 21 points on the Victorian Institute of Sports Assessment-Achilles score (21.7 vs 20.5 for the PRP and saline groups, respectively, at the 6-month stage, n = 27 each group) and both groups had similar return-to-sport rates (57% for both groups at 12 weeks and 67% to 78% at 24 weeks with a slight but nonsignificant increased rate in the PRP group). In this study, patients were selected before they had started eccentric exercise therapy. One might speculate that PRP treatment is better indicated as an alternative for resistant

tendinopathy, which fails to respond to eccentric loading. Whether this specific patient group may benefit from PRP treatment needs further investigation. Another criticism of the above study is that the eccentric exercises may have overshadowed the possible beneficial effect of PRP.[37] From this study, one can conclude that the additive value of PRP injection to these exercises is limited.

In one of the few other human studies on tendinopathy, albeit uncontrolled, Kon et al[38] used three 5-mL PRP injections separated by 15 days each to treat patellar tendinopathy and showed a significant improvement in pain and physical function using health quality of life scales (SF-36 and EQ-VAS; N = 20). The scale of these improvements from baseline for pain and physical function was approximately 25 to 28 by the end of the 3-injection treatment series and 30 to 36 at the 6-month follow-up. This same research group[39] conducted a comparative study in 31 patients with chronic patellar tendinopathy. One group received 3 PRP injections with a rehabilitation protocol starting after the second and third injections, and the other group received only the stretching and strengthening exercises prescribed. The PRP was obtained using a double-spin centrifugation process. Patients were not randomized at baseline. In both groups, the VAS score (PRP group 26 points on a 0-100 scale) and the functional Tegner score (PRP group 2.9 points on a 0-10 scale) improved significantly after the 6-month follow-up. The authors reported no between-group difference in VAS score, but the improvement in Tegner score was higher in the PRP group. However, the statistical baseline difference in Tegner score between these groups was not reported. Another possible explanation for this difference might be that the response is amplified when a treatment is invasive and raises high expectations.

In the cohort study by Mishra and Pavelko,[40] a single (2-3 mL) injection of PRP was delivered in 5 small depots into the tender symptomatic area of either the medial epicondylar region or lateral epicondylar region (N = 15) to treat wrist flexor tendinopathy or wrist extensor tendinopathy, respectively. An unblinded cohort control group (N = 5, of which 3 patients dropped out of the study by 8 weeks to seek alternative treatment) had 2 to 3 mL of bupivacaine injected in a similar manner. The PRP group showed significant improvements in visual analog pain scores at all follow-ups and significant improvements in Mayo elbow scores at 8 weeks and at greater than 12 months (mean, 25.6 months; range, 12-38 months) relative to the small control group. The scale of these improvements from baseline for pain and physical function was an average improvement of 48 by visual analog scale (VAS) and 26 on the Mayo elbow scale at 8 weeks and 65 by VAS and 36 on the Mayo elbow scale at the 6-month follow-up. Interestingly, 1 of the 2 control cohort patients tested at 6 months was completely asymptomatic, with no pain and full function on Mayo elbow scale. Peerbooms et al[41] conducted an RCT comparing a single 1-mL PRP injection (n = 51) in multiple small depots in wrist extensor tendinopathy with a "gold standard" corticosteroid injection (n = 49) and showed significant decreases in pain and improvement in function at 6 months and 12 months in the PRP group. At 6 months with PRP injection, there was an average decrease in pain by VAS of 27 and an improvement in function as measured by DASH (Disabilities of the Arm, Shoulder, and Hand) outcome measure score of 70, and at 12 months, the PRP group showed average pain decrease on VAS of 45 and improvement in DASH function of 105. The main outcome measure in this study was a 25% reduction in VAS score or DASH outcome measure; statistical analysis used a "pre-established analysis plan" and did not seem to perform a between-group comparison of means. This is an unusual statistical analysis and makes the results difficult to interpret. In this study, the investigators also performed further interventions at periods between 2 and 6 months in 18 patients throughout the study follow-up period (in the PRP group, 3 patients had surgery and 2 patients had corticosteroid injections; in the corticosteroid injection group, 6 patients had surgery, 6 patients had PRP injections, and 1 patient had a second corticosteroid injection). The reasons for these interventions are not stated, there is no description of planned crossover in the methods section, and the data seem to have been analyzed on an intention-to-treat basis, with these patients' treatment being classified as "unsuccessful"; however, the between-group means of pain VAS and DASH scores were not statistically analyzed. Furthermore, the negative effects of corticosteroid injections and the markedly fair natural healing response on the longer term in wrist extensor tendinopathy have been described previously, making the between-group differences even harder to interpret.[42]

Randelli et al[43] reported a case series (N = 14) pilot study of PRP application in arthroscopic rotator cuff repair and showed decreased VAS of 18 at 4 weeks and 51 at 6 months and improved functional scores of 16 and 31 at 2-year follow-up (UCLA and Constant scores, respectively).

Gaweda et al[44] performed a case series in 14 patients (15 tendons) with chronic midportion Achilles tendinopathy. They injected 3 mL of PRP under ultrasound guidance into the hypoechoic area of the tendon. The patients had to use elbow crutches for 6 weeks, and in 6 cases, the injection and rehabilitation protocol was repeated. Normal activities of daily living were resumed between week 6 and week 12, and sports activities were discouraged. The Victorian Institute of Sports Assessment-Achilles score improved from 24 to 96 at 18 months follow-up ($P < 0.00005$), and the American Orthopaedic Foot and Ankle Society (AOFAS) scale (0-100) improved from 55 to 96 at 18 months follow-up. The authors also reported an improvement in qualitative gray-scale ultrasound characteristics. Fusiform thickening, peritendineum thickening, hypoechoic foci, and intrasubstance tears decreased in almost all cases at follow-up. There was a temporary increase in neovascularization until 3 months, and after that, the vascularity diminished in most patients. However, currently, we lack the knowledge of the natural progress of tendon structure disorganization and vascularity after a rehabilitation program.

It is difficult to compare these various studies due to marked methodological differences and particularly with regard to different tendinopathy sites and outcome measures used. It is impossible to compare tendon-specific scales with general health quality of life scales, but the magnitude of the response to any injection used in these studies is similar, whether single PRP or series of PRP injections. We may expect

TABLE 2. Human Clinical Trials on PRP in Ligament and Tendon Injuries, Description of the Type of Study, Level of Evidence, Results, and Relevant Comments

Authors	Diagnosis	Design	Results	Comments	Level of Evidence
Nin et al[21]	Ligament injury: ACL bone-patellar tendon-bone allograft	Prospective randomized controlled trial (n = 50 each group)	No difference inflammation, MRI, or clinical evaluation	RCT with appropriate statistical power, with 2-year follow-up, single PRP application, possible type 2 error	1b
Silva and Sampaio[22]	ACL hamstring allograft	Prospective randomized controlled trial (N = 10 each group)	No difference in MRI evaluation	Small RCT with 3-month follow-up only, single and multiple PRP application groups, possible type 2 error	1b
Ventura et al[23]	ACL hamstring allograft	Prospective randomized controlled trial (n = 10 each group)	No difference in clinical evaluation or functional scores. Increased ACL density on computed tomographic scan in PRP group, similar to density of posterior cruciate ligament	Small RCT with 6-month follow-up only, single PRP application, possible type 2 error. Computed tomographic scan is not commonly used to assess ACL	1b
Sanchez et al[31]	Acute tendon injury: Achilles tendon rupture	Case–control study (n = 6; control n = 6)	Significant improvement in earlier ankle range of motion, earlier return to gentle running and earlier return to sports, smaller cross-sectional tendon area on ultrasound	Case–control study with small numbers and 12-month follow-up (but only 6 months reported), single PRP application at surgery with fibrin scaffold	3b
Schepull et al[32]	Achilles tendon rupture	Prospective randomized controlled trial (n = 16 PRP; n = 14 control group)	No difference in functional measures (Achilles Tendon Total Rupture Score)	RCT with 12-month follow-up. Platelet-rich plasma–implanted bead application in depots proximal and distal to rupture	1b
de Vos et al[36]	Chronic Tendon Injury; Achilles tendinopathy	Prospective randomized controlled trial (N = 27 each group)	No difference in pain scores or functional measures (VISA-A)	RCT with appropriate statistical power but with only 6-month follow-up. Single PRP application in multiple depots under ultrasound guidance compared with saline injection. Saline injection into tendon is not commonly performed	1b
Gaweda et al[44]	Achilles tendinopathy	Case series (N = 15)	Significant improvement in functional measures (VISA-A and AOFAS)	Case series only with 18-month follow-up, single or repeated ultrasound guided PRP injections and rehabilitation	4
Kon et al[38]	Patellar tendinopathy	Case series (N = 20)	Significant improvement in quality of life scores (EQ-VAS and SF-36) and function (Tegner score)	Case series only with 6-month follow-up, 3 PRP injections into depots at intervals of 15 days, no guidance, quality of life scores	4
Mishra and Pavelko[40]	Elbow tendinopathy (wrist extensor tendinopathy or wrist flexor tendinopathy)	Case–control study (n = 15; control n = 5)	Significant improvement in pain (VAS) and function (modified Mayo score)	Case–control study with 24-month follow-up, single PRP application, no guidance. Different diagnoses (medial and lateral elbow tendinosis). Only 2 controls after 8 weeks and not followed after this, 1 control asymptomatic	4
Peerbooms et al[41]	Elbow tendinopathy (wrist extensor tendinopathy)	Prospective randomized controlled trial (n = 51 PRP group; n = 49 corticosteroid injection group)	Significant improvement in "successful outcomes" of decrease 15% in pain (VAS) and function (DASH scores)	RCT with appropriate statistical power but with 12-month follow-up only, single PRP application compared with single corticosteroid injection, unexplained crossover interventions, and unusual statistical analysis	1b
Filardo et al[39]	Patellar tendinopathy	Prospective randomized controlled trial (n = 15 PRP; n = 16 control group)	No significant improvement in PRP group with pain (VAS) and function (Tegner score)	Small RCT with 6-month follow-up only, 3 PRP injections, compared with exercise only group, possible type 2 error	1b
Randelli et al[43]	Complete rotator cuff tear	Case series (N = 14)	Significant improvement in pain (VAS) and function (UCLA and Constant scores)	Case series with 24-month follow-up, single PRP application at surgery. Joint-specific scores	4

AOFAS, american orthopaedic foot and ankle society; DASH, disabilities of the arm, shoulder and hand; UCLA, UCLA shoulder rating scale; VISA-A, Victorian Institute of Sports Assessment-Achilles.

TABLE 3. Patellar Tendinopathy and Platelet-Rich Plasma Series of 3 Injections: Results From Case Series by Kon et al[38] and Pilot Randomized Controlled Study by Filardo et al[39]

	Complete Recovery, n (%)	Marked Improvement, n (%)	Mild Improvement, n (%)	No Improvement, n (%)
PRP group (n = 20)[38]	6/20 (30)	8/20 (40)	2/20 (10)	4/20 (20)
PRP group (n = 15)[39]	5/15 (33)	6/15 (40)	2/15 (13)	2/15 (13)
Control group (exercise only) (n = 16)[39]	4/16 (25)	4/16 (25)	5/16 (31)	3/16 (19)

There were no significant between-group differences in pain scores, functional measures, or patient satisfaction or time-to-recovery rates in the study by Filardo et al.[39]

pain to decrease from baseline by 18 to 48 on VAS at 4 to 8 weeks and possibly up to 20 to 65 on VAS by 6 months. One study suggests that the improvement from PRP may be sustained for 12 months.[40]

SIDE EFFECTS

In all human clinical studies on PRP in ligament and tendon injuries, there were a total of only 248 patients (70 ACL injury, 22 Achilles tendon rupture, and 156 chronic tendinopathies in multiple sites, including Achilles tendinopathy, patellar tendinopathy, wrist flexor tendinopathy, wrist extensor tendinopathy, and rotator cuff tendinopathy) who were treated with PRP application/injection. In these studies, it was reported that there was 1 patient who had ACL graft hypertrophy with synovial reaction around the treated ACL,[23] 1 patient who had a marked pain response that lasted 3 weeks to PRP injected into patellar tendon,[38] and common but unspecified numbers of patients with local inflammation causing pain for 3 to 4 weeks after PRP injection for lateral epicondylosis.[41] In pooled studies of PRP use in ACL reconstruction, this represents a side effect rate of 1.4%, although there was a 10% rate in the study by Ventura et al.[23] In pooled studies of PRP injection for chronic tendinopathy, there is a side effect rate of at least 1.3%, although there was a 5% rate of side effects in the study by Kon et al.[38] Interestingly, only the study by Kon et al measured increased pain and stiffness after PRP injection; this was present in all subjects with a mean intensity of 6.1 of 10 for both pain and stiffness, and lasted between 1.5 and 2.1 days. Peerbooms et al[41] mention that this is a common reaction, but patient numbers are not specified, nor is the severity of the pain response.

DISCUSSION

Despite worldwide interest from the medical community, athletes, and the media[45] concerning PRP and the possibility of enhanced healing and earlier return to sport, there is no evidence in human clinical trails of the efficacy of PRP in treating ligament and tendon injuries. There is certainly a lack of scientific evidence of earlier, or more effective, return-to-sport rates with PRP injections compared with other inert injections. In fact, few randomized controlled clinical trials have found significant differences in clinical measures of efficacy, or MRI appearance of ligament healing in the short term, with the use of PRP in treating ligament and tendon injuries (see Tables 2–4).

It has been suggested that patients with refractory conditions, such as Achilles tendinopathy, who have failed physiotherapy and multiple nonsurgical modalities may be candidates for PRP injections.[7,46] However, there is currently no reason to consider PRP a more efficacious injection option than many other treatments, including polidocanol, autologous blood, normal saline, or glucose prolotherapy. These treatments are also often less expensive than PRP and may also be considered in the treatment algorithm, especially given the lack of efficacy in the only RCT on PRP in Achilles tendinopathy.[36] At best, in this setting, we may expect pain to decrease from baseline by 18 to 48 on VAS at 4 to 8 weeks and

TABLE 4. Tendinopathy at the Elbow and Platelet-Rich Plasma: Results From a Randomized Controlled Study on Wrist Extensor Tendinopathy by Peerbooms et al[41] Using 1-mL Peppering Technique Injection and a Case–Control Study on Combined Group of Wrist Extensor Tendinopathy and Wrist Flexor Tendinopathy Patients by Mishra et al[40] Using 3-mL Peppering Technique Injection

	Baseline VAS	VAS Decrease				
		4 Weeks (%)	8 Weeks (%)	12 Weeks (%)	26 Weeks (%)	52 Weeks (%)
PRP group (N = 51)[41]	70.1 (100%)	14.7 (21%)	23.2 (33.1%)	31.4 (44.8%)	37.5 (53%)	44.8 (63.9%)
Control group (cortisone injection) (N = 49)[41]	65.8 (100%)	21.6 (32.8%)	22.9 (34.8%)	21.6 (32.8%)	9.2 (14%)	15.7 (24%)
PRP group (N = 15)[40]	80.3 (100%)	33.9 (46%)	48.3 (60%)	—	—	74.6 (93%)
Control group (bupivicaine injection) (N = 5)[40]	86 (100%)	15 (17%)	3 patients withdrew; 1 of 2 remaining patients showed nil symptoms	—	—	—

There were no reported significant between-group differences in pain scores in the study by Peerbooms et al, but there was a significant difference in the number of PRP-treated patients who achieved >25% reduction in visual analog pain scores at 1 year (primary outcome measure with a "pre-established analysis plan").

possibly up to 20 to 65 on VAS by 6 months. It is interesting, but not altogether surprising, that the better clinical studies, including RCTs, often fail to detect significant differences with PRP use, whereas uncontrolled studies consistently detect significant differences. Although it is possible that there are no significant differences on RCTs due to type 2 error from underpowered studies, and there are few noted side effects from PRP use, this cannot be a justification for the use of PRP in ligament and tendon injuries. Evidence of efficacy and safety of PRP are lacking, and currently, PRP is on the World Anti-Doping Authority prohibited list 2010. Having stated this, there is no reason to completely discount PRP injections because some elements of PRP may have clinically useful effects on healing when delivered in the correct preparation, at the correct site, and at the correct time. This is the challenge to determine which aspects of any autologous injection are critical and optimal and to scientifically assess their efficacy. The use of injectable agents to specifically target a presumed area of abnormal healing response in chronic ligament and tendon injuries may be a more effective method of treating these sports injuries than the current nonsurgical methods, but efficacy and validity remain untested. In chronic injuries, selective growth factors, such as fibroblast growth factor or vascular growth factor inhibitor, could potentially be agents that enhance healing, or alter pain perception, when targeted to areas of tissue degeneration or neovascularization, respectively.[3,7] However, improving collagen synthesis and increasing vascularization might not be related to symptom reduction. Despite the fact that patients with tendinopathy have tendons with more disorganized collagen structure histopathologically, there is no relationship between the degree of ultasonographical tendon structure organization and the clinical outcome at a single point in time or in changes over time.[47] Therefore, one might speculate that other features are more important as a source of pain.

There are many manufacturers developing multiple commercial techniques for PRP and growth factor preparation and delivery, but as yet no body of scientific evidence that they work. The use of these agents is attractive in principle but may be driven more by commercial interests and media hype than by hard scientific evidence. Despite many basic science and animal studies and some small case reports on PRP injections for ligament or tendon injuries, there are few randomized controlled clinical trials assessing the efficacy of PRP injections, and none demonstrated scientific evidence of efficacy. It is imperative that scientific studies are performed to assess clinical indications, efficacy, and safety, and this will require appropriately powered RCTs with adequate and validated clinical and functional outcome measures and sound statistical analysis.[4–6] Other aspects of PRP use that need to be determined are (1) volume of injection/application, (2) most effective preparation, (3) buffering/activation, (4) injection technique (one depot vs multiple depots), (5) timing of injection to injury, (6) single application versus series of injections, and (7) the most effective rehabilitation protocol to use after PRP injection.

With all proposed treatments, the doctor and the patient need to weigh up possible benefits of the treatment, potential risks, and costs. Based on the limited publications to date and theoretical considerations, the potential risks involved with PRP are fortunately very low. However, benefits have not been proven to date, particularly when comparing PRP injections with other more inert substances, such as glucose or normal saline. Commercially available kits may be able to increase the concentration of PRP injections and therefore may be somewhat more likely to subsequently show benefits, but the cost of a specific kit may not be able to be justified currently in the absence of such studies. Although taking PRP from a simple centrifugation process is also not proven as a treatment to date, at least it can be undertaken as a low-cost and low-risk treatment option.

REFERENCES

1. Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? *Implant Dent*. 2001;10:225–228.
2. Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. *Plast Reconstr Surg*. 2004;114:1502–1508.
3. Molloy T, Wang Y, Murrell GAC. The roles of growth factors in tendon and ligament healing. *Sports Med*. 2003;33:381–394.
4. Mei-Dan O, Mann G, Maffulli N. Platelet-rich plasma: any substance into it? *Br J Sports Med*. 2010;44:618–619.
5. de Vos RJ, van Veldhoven PL, Moen MH, et al. Autologous growth factor injections in chronic tendinopathy: a systematic review. *Br Med Bull*. 2010;95:63–77.
6. Alsousou J, Thompson M, Hulley P, et al. The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery: a review of the literature. *J Bone Joint Surg Br*. 2009;91-B:987–996.
7. Foster TE, Puskas BL, Mandelbaum BR, et al. Platelet-rich plasma: from basic science to clinical applications. *Am J Sports Med*. 2009;37:2259–2272.
8. Murray MM, Spindler KP, Ballard P, et al. Enhanced histologic repair in a central wound in the anterior cruciate ligament with a collagen-platelet-rich plasma scaffold. *J Orthop Res*. 2007;25:1007–1017.
9. Maffulli N, Wong J, Almekinders LC. Types and epidemiology of tendinopathy. *Clin Sports Med*. 2003;22:675–692.
10. Khan KM, Cook JL, Bonar F, et al. Histopathology of common tendinopathies. Update and implications for clinical management. *Sports Med*. 1999;27:393–408.
11. Hayter CI, Guffre BM. Overuse and traumatic injuries of the elbow. *Magn Reson Imaging Clinic N Am*. 2009;17:617–638.
12. Yastrebov O, Lobenhoffer I. Treatment of isolated and multiple ligament injuries of the knee: anatomy, biomechanics, diagnosis, indications for surgical repair. *Orthopade*. 2009;38:563–580.
13. Hammond JW, Hinton RY, Curl LA, et al. Use of autologous platelet-rich plasma to treat muscle strain injuries. *Am J Sport Med*. 2009;37:1135–1142.
14. Kajikawa Y, Morihara T, Sakamoto H, et al. Platelet-rich plasma enhances the initial mobilisation of circulation-derived cells for tendon healing. *J Cell Phys*. 2008;215:837–845.
15. Hildebrand KA, Woo SL-Y, Smith DW, et al. The effects of platelet derived growth factor-BB on healing of the rabbit medial collateral ligament: an in vivo study. *Am J Sports Med*. 1998;26:549–554.
16. Batten ML, Hansen JC, Dahners LE, et al. Influence of dosage and timing of application of platelet derived growth factor on early healing of the rat medial collateral ligament. *J Orthop Res*. 1996;14:736–741.
17. McCarrel T, Fortier L. Temporal growth factor release from platelet-rich plasma, trehalose lyophilized platelets, and bone marrow aspirate and their effect on tendon and ligament gene expression. *J Orthop Res*. 2009;27:1033–1042.
18. Murray MM, Spindler KP, Abreu E, et al. Collagen-platelet rich plasma hydrogel enhances primary repair of the porcine anterior cruciate ligament. *J Orthop Res*. 2007;25:81–91.
19. Murray MM, Palmer M, Abreu E, et al. Platelet-rich plasma alone is not sufficient to enhance suture repair of the ACL in skeletally immature animals: an in vivo study. *J Orthop Res*. 2009;27:639–645.

20. Oxford Centre for Evidence-Based Medicine. *Levels of Evidence*. Oxford, United Kingdom: University of Oxford; 2009. http://www.cebm.net/index.aspx?o=1025. Accessed September 2010.
21. Nin JRV, Gasque GM, Azcarate AV, et al. Has platelet-rich plasma any role in anterior cruciate ligament allograft healing? *Arthroscopy.* 2009;25: 1206–1213.
22. Silva A, Sampaio R. Anatomic ACL reconstruction: does the platelet-rich plasma accelerate tendon healing? *Knee Surg Sports Traumatol Arthrosc*. 2009;17:676–682.
23. Ventura A, Terzaghi C, Borgo E, et al. Use of growth factors in ACL surgery: preliminary study. *J Orthop Traumatol*. 2005;6:76–79.
24. Kajikawa Y, Morihara T, Watanabe N, et al. GFP chimeric models exhibit a biphasic pattern of mesenchymal cell invasion in tendon healing. *J Cell Phys*. 2007;210:684–691.
25. Bosch G, van Schie HTM, de Groot MW, et al. Effects of platelet-rich plasma on the quality of repair of mechanically induced core lesions in equine superficial digital flexor tendons: a placebo-controlled experimental study. *J Orthop Res*. 2010;28:211–217.
26. Anitua E, Sanchez M, Nurden AT, et al. Reciprocal actions of platelet-secreted TGF-β1 on the production of VEGF and HGF by human tendon cells. *Plast Reconstr Surg*. 2007;119:950–959.
27. de Mos M, van der Windt A, Jahr H, et al. Can platelet-rich plasma enhance tendon repair? *Am J Sport Med*. 2008;36:1171–1178.
28. Lyras DN, Kazakos K, Verettas D, et al. The effect of platelet-rich plasma gel in the early phase of patellar tendon healing. *Arch Orthop Trauma Surg*. 2009;129:1577–1582.
29. Aspenberg P, Virchenko O. Platelat concentrate injection improves Achilles tendon repair in rats. *Acta Orthop Scand*. 2004;75:93–99
30. Sarrafian TL, Wang H, Hackett ES, et al. Comparison of Achilles tendon repair techniques in a sheep model using a cross-linked acellular porcine dermal patch and platelet-rich plasma fibrin matrix for augmentation. *J Foot Ankle Surg*. 2010;49:128–134.
31. Sanchez M, Anitua E, Azofra J, et al. Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. *Am J Sport Med*. 2007;35:245–251.
32. Schepull T, Kvist J, Norman H, et al. Autologous platelets have no effect on the healing of human Achilles tendon ruptures: a randomized single-blind study [published online ahead of print]. *Am J Sports Med*. doi: 10.1177/0363546510383515.
33. Chandra S, Esaki J, Marui A, et al. Angiogenic properties of sustained release platelet-rich plasma: characterization of in-vitro and in the ischaemic hind limb of the mouse. *J Vasc Surg*. 2009;50:870–879.
34. Mehta S, Watson JT. Platelet rich concentrates: basic science and current clinical applications. *J Orthop Trauma*. 2008;22:433–438.
35. Yoshikawa Y, Abrahamsson S-O. Dose-related cellular effects of platelet-derived growth factor-BB in various types of rabbit tendons in vitro. *Acta Orthop Scand*. 2001;72:287–292.
36. de Vos RJ, Weir A, van Schie HTM, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomised controlled trial. *JAMA*. 2010;303:144–149.
37. Creaney L. Platelet-rich plasma for treatment of Achilles tendinopathy. *JAMA*. 2010;303:1696.
38. Kon E, Filardo G, Delcogliano M, et al. Platelet-rich plasma: new clinical application. A pilot study for treatment of jumper's knee. *Injury.* 2009;40: 598–603.
39. Filardo G, Kon E, Della Villa S, et al. Use of platelet-rich plasma for the treatment of refractory jumper's knee. *Int Orthop*. 2009;34:909–915.
40. Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. *Am J Sport Med*. 2006;34:1774–1778.
41. Peerbooms JC, Sluimer J, Bruijn DJ, et al. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. *Am J Sports Med*. 2010;38:255–262.
42. Smidt N, van der Windt DA. Tennis elbow in primary care. *BMJ.* 2006; 333:927–928.
43. Randelli PS, Arrigoni P, Cabitza P, et al. Autologous platelet rich plasma for arthroscopic rotator cuff repair. A pilot study. *Disability Rehabil*. 2008; 30:1584–1589.
44. Gaweda K, Tarczynska M, Krzyzanowski W. Treatment of Achilles tendinopathy with platelet-rich plasma. *Int J Sports Med*. 2010;31:577–583.
45. Schwarz A. A promising treatment for athletes, in blood. *New York Times*. February 17, 2010:A1. http://www.nytimes.com/2009/02/17/sports/17blood.html. Accessed December 2010.
46. Sanchez M, Anitua E, Orive G, et al. Platelet-rich therapies in the treatment of orthopaedic sport injuries. *Sports Med*. 2009;39:345–354.
47. Khan KM, Cook JL, Maffulli N, et al. Where is the pain coming from in tendinopathy? It may be biochemical, not only structural, in origin. *Br J Sports Med*. 2000;34:81–83.