A Systematic Review of the Use of Platelet-Rich Plasma in Sports Medicine as a New Treatment for Tendon and Ligament Injuries

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Objective: To evaluate, through a systematic review of the current literature, the evidence-based outcomes of the use of platelet-rich plasma (PRP) for the treatment of tendon and ligament injuries.

Data Sources: A search of English-language articles was performed in PubMed and EMBASE using keywords "PRP," "platelet plasma," and "platelet concentrate" combined with "tendon" and then "ligament" independently. The search was conducted through September 2010.

Study Selection: Search was limited to in vivo studies. Nonhuman studies were excluded. Tissue engineering strategies, which included a combination of PRP with additional cell types (bone marrow), were also excluded. Articles with all levels of evidence were included. Thirteen of 32 retrieved articles respected the inclusion criteria.

Data Extraction: The authors reviewed and tabulated data according to the year of study and journal, study type and level of evidence, patient demographics, method of PRP preparation, site of application, and outcomes.

Data Synthesis: The selected studies focused on the application of PRP in the treatment of patellar and elbow tendinosis, Achilles tendon injuries, rotator cuff repair, and anterior cruciate ligament (ACL) reconstruction. Seven studies demonstrated favorable outcomes in tendinopathies in terms of improved pain and functional scores. In 3 studies on the use of PRP in ACL reconstruction, no statistically significant differences were seen with regard to clinical outcomes, tunnel widening, and graft integration. One study examined the systemic effects after the local PRP application for patellar and elbow tendinosis.

Conclusions: Presently, PRP use in tendon and ligament injuries has several potential advantages, including faster recovery and, possibly, a reduction in recurrence, with no adverse reactions described. However, only 3 randomized clinical trials have been conducted.

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INTRODUCTION

Initially introduced in maxillofacial and plastic surgery in 1990s,[1] platelet-rich plasma (PRP) has recently experienced a surge in clinical uses for various sport-related injuries due to potential healing properties on tendons and ligament injuries through the recruitment, proliferation, and differentiation of cells.

Sports-related soft tissue injuries represent a significant source of time lost from play for athletes and teams and a significant burden to society in terms of health care resources, personal disability, and activity restriction. In 2002, an estimated 15.8 billion dollars in total health care expenditures were used in the medical management of these injuries.[2]

Despite the lack of hard evidence through randomized clinical trials, the use of PRP in humans has increased significantly. The increase in recently published pilot studies has prompted our systematic review of the literature, exploring the current knowledge and indications for clinical use. The outcomes will be evaluated with emphasis on the effectiveness and safety of the current applications. The processes of PRP production and the various methods of application will be evaluated.

Basic Science

Platelet-rich plasma is a concentrate of platelets and associated growth factors (GFs), obtained through withdrawal and centrifugation of a sample of patient's own blood. Although the use of PRP varies greatly among studies, the retrieval of PRP from patients is relatively constant. The general protocol for preparing PRP requires the separation of blood components through 1 or 2 centrifugation steps. The first centrifugation step leads to the separation of red and white blood cells from plasma and platelets, and the second produces an increase in the concentration (3-fold to 5-fold) of platelets and GFs. This is followed by the exogenous or endogenous platelet activation (with bovine thrombin or $CaCl_2$) before application to the site of injury. There is little consistency among studies on the time between retrieval and application. Considering the coagulative properties of PRP and platelets,

this timing may have an effect on its activity and reparative potential. It also may be noted that allowing for solidification into a gel may keep the preparation localized but also eliminates its injectability, limiting the use to open surgical procedures.

Autologous platelet preparations have demonstrated the potential to modify the natural healing pathway of tendons and ligaments in several ways. The action is related to the increased concentration of GFs and bioactive proteins released by activated platelets (Table 1), which seem able to help the regeneration of tissues that otherwise have low healing potential,[3–7] potentially restoring biomechanical properties similar to normal tendons and ligaments.[8] The application of PRP amplifies the surge of chemical mediators to the microenvironment of the injured area, including platelet α-granule–derived factors. The increased concentration of platelets and GFs mimics the initial stage of the inflammatory response, characterized by the migration of neutrophils, monocytes, and macrophages to the site of injury under the guidance of the chemical mediators.[5,6]

These cytokines mediate the initiation of neovascularization, tenocyte proliferation, fibroblast proliferation, and further recruitment of inflammatory cells.[6,7] In addition to the stimulatory effects of PRP on reparative cells, there is evidence that PRP may also have an inhibitory effect on certain proinflammatory cytokines that may be detrimental to the early stages of healing, specifically through suppression of IL-1 release from activated macrophages.[9] This dual action of enhancing repair and minimizing tissue breakdown may allow local PRP application to accelerate the tissue healing process, leading to a wide range of potential applications and potential advantages for improved outcomes and faster recovery. However, additional studies must be completed to confirm these proposed benefits.

METHODS

A systematic review of English-language articles was performed using PubMed/Medline and EMBASE. Our literature search focused on the keywords "PRP," "platelet plasma," and "platelet concentrate" each combined with the keywords "tendon" and then "ligament." This resulted in 6 independent searches: PRP tendon, PRP ligament, platelet plasma tendon, platelet plasma ligament, platelet concentrate tendon, and platelet concentrate ligament. The search was conducted through September 2010 by 2 of the authors (D.W.T. and M.P.), and analysis of these articles was conducted by all the authors involved in the study. The reference list for each article reviewed was also searched for articles that met our inclusion criteria.

The articles found were pooled and subjected to inclusion and exclusion criteria that had been established before commencement of the review. Search was limited to in vivo application of PRP in tendon and ligament injuries. Articles with all levels of evidence were included. Nonhuman studies and articles that did not pertain to sports medicine (eg, dental ligament cells) were excluded. In trying to remain focused on the effect of the specific use of PRP, studies reporting tissue engineering strategies, where additional cell types (bone marrow) were combined with PRP applications, were excluded.

Data were reviewed and tabulated according to year of study and journal, study type, patient demographics, method of preparation (focusing on type of preparation, erythrocyte spin, pellet spin, activating agent, volume, baseline, and final count of platelet), site of application, and outcomes.

TABLE 1. GFs Released by Activated Platelets

GF	Function
TGF-β1	Matrix synthesis
PDGF	Stimulate angiogenesis, cell proliferation, mitogen for fibroblasts
bFGF	Proliferation of fibroblasts and myoblasts, angiogenesis
VEGF	Angiogenesis
EGF	Proliferation of epithelial and mesenchymal cells
IGF-1	Stimulate fibroblasts and myoblasts
HGF	Angiogenesis

bFGF, basic fibroblast growth factor; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor; PDGF, platelet-derived growth factor; TGF, transforming growth factor.

RESULTS

References to PRP in literature were found to vary depending on the methods of collection, preparation, or administration. Assorted terminology was used, including platelet concentrate, platelet plasma, preparation rich in GFs, collagen PRP, platelet-rich fibrin matrix, and collagen-platelet composites.

The search retrieved 13 human in vivo articles that met our criteria and are presented in Table 2. They focused on the application of PRP in elbow tendinopathy (3 studies), rotator cuff surgery (2 studies), Achilles tendon repair or chronic tendinopathy (3 studies), patellar tendinopathy (2 studies), and ligament [anterior cruciate ligament (ACL)] reconstructions (3 studies). In one of these, the authors studied the application of PRP in 2 different samples (patellar and elbow tendinopathies).[10]

We found only 3 prospective, randomized, double-blind studies (level 1), 3 were prospective cohort studies (level 2), and 7 were case reports or case-control studies (1 level 3 and 6 level 4).

Eight studies showed favorable outcomes after the use of PRP in rotator cuff surgery,[12,13] elbow tendinosis,[11,20] patellar tendinosis,[19] and Achilles tendon injuries (acute tear repair and revision surgery),[14,15] but only 1 was a randomized controlled trial and[20] another was a cohort study.[11] On the contrary, 1 prospective randomized study focusing on chronic Achilles tendinopathy showed no significant improvement after the treatment with PRP.[21] One study examined the systemic effects after PRP application for patellar and elbow tendinosis, showing no modification in the levels of circulating cytokines and GFs, including vascular endothelial GF (VEGF), except for a transitory decrease in epidermal GF (EGF).[10] In 3 studies (level 1 and level 2) on the use of PRP in ACL reconstruction, no statistically significant difference was seen with regard to

TABLE 2. Published Studies on PRP Clinical Applications and Their Outcomes

Authors	Site	Study Type and No. Patients	Purpose and Interval	Outcome Measure	Follow-up	Results
Banfi et al[10]	Elbow and patella tendinopathy	Laboratory cohort 4 patella and 1 elbow	Examine the systemic effects after PRP application in tendinopathies	Serum concentration of cytokines using ELISA assay	30 minutes before application, 3 and 24 hours after	No modification in IL-4, IL-6, IL-10, IL-1α, IL-1β, TNF-α, interferon γ levels VEGF (pg/mL) before, 140 (20-302); 30 minutes after, 123 (25-392); 3 hours after, 65 (26-232); 24 hours after, 119 (47-232) EGF (pg/mL) before, 130 (22-182); 30 minutes after, 85 (3-156); 3 hours after, 40 (3-153); 24 hours after 68 (7-153)
Mishra and Pavelko[11]	Elbow tendinosis	Controlled cohort study 15 PRP vs 5 control	Compare PRP injection vs bupivacaine/ epinephrine injection	VAS modified Mayo elbow score	4 weeks, 8 weeks, and 6 months	4 weeks: PRP patients reported a mean 46% improvement in pain and 42% improvement in Mayo elbow score compared with 17% and 20%, respectively, in the control group 8 weeks: PRP-treated patients reported a mean 60% improvement in pain and 52% improvement in Mayo elbow score compared with a 16% and 14% improvement in the control group 25.6 months: PRP-treated patients reported 93% reduction in pain
Maniscalco et al[12]	Rotator cuff	Case report	Evaluate the outcome of the application of commercial PRP membrane ("Cascade") after rotator cuff repair	Physical examination, Constant score, MRI	6 months	Reduction of pain and improvement of range of motion (Constant score, 96) MRI: complete integrity of the cuff under the membrane
Randelli et al[13]	Rotator cuff	Prospective case series N = 14	Evaluate the effect of intraoperative application of combined PRP and autologous thrombin on functional outcome	VAS, UCLA score, Constant score	Preoperation, 6, 12, and 24 months	24 months: 3 patients had achieved excellent results and 10 good according to the UCLA score; according to the Constant scores all final outcomes were excellent VAS score improved from 5.31 (±1.84) preoperation to 1.00 (±0.58) at the final follow-up UCLA score improved from 16.54 (±5.46) preoperation to 32.92 (±1.19) at the final follow-up Constant scores improved from 54.62 (±16.98) preoperation to 85.23 (±7.22) at the final follow-up

TABLE 2. (*continued*) Published Studies on PRP Clinical Applications and Their Outcomes

Authors	Site	Study Type and No. Patients	Purpose and Interval	Outcome Measure	Follow-up	Results
Sanchez et al[14]	Achilles tendon	Case-control study (N = 12)	Evaluate the effect of PRP injection and fibrin matrix in Achilles tendon repair	Time to full ROM, time to resuming gentle running, time to return to competition, Cincinnati sports activity scale, ultrasound evaluation	Twice in the first month, then every 4 to 6 weeks until 6 months, then at 9 months and 1 year	Time to full ROM: 7 weeks in the PRP group and 11 weeks in the control group Time to gentle running: 11 weeks in the PRP group and 18 weeks in the control group Time to return to training: 14 weeks in the PRP group and 22 weeks in the control group PRP-treated patients required 14 weeks to return to preinjury scores compared with 22 weeks required for the control groups Ultrasound: mean increase in callus diameter was 298 ± 90% in control and 499 ± 91% in PRP group
Sanchez et al[15]	Achilles tendon	2 case reports	Evaluate the effect of PRP application in the management of complications after primary surgical repair of Achilles tendon	ROM functional recovery MRI	Case 1: 11-month follow-up; Case 2: 5-year follow-up	MRI showed thickening of tendon in 1 case Both athletes were able to return to their sport (14 weeks to resume football training and 28 weeks to resume climbing) No recurrences
Orrego et al[16]	ACL reconstruction	Randomized control trial (N = 108 subdivided in 4 groups)	Evaluate the effect of PRP on healing of hamstring graft and on functional outcome	MRI	3 and 6 months	59% in the control group showed no tunnel widening, compared with 89% in the BP (bone plug) group and 81% in the PRP-BP group 67% in control group showed no interface between the graft and bone at the femoral tunnel, compared with 88% in the PRP group and 70% in the PRP-BP group At 6 months after the surgery, MRI findings of low-intensity (mature) graft signal in 100% of patients from the PRP group, compared with 78% of the control group
Silva and Sampaio[17]	ACL reconstruction	Prospective cohort study (N = 40)	Evaluate the effect of PRP on tendon-bone integration in ACL reconstruction with hamstring	MRI	3 months	No difference in MRI findings among groups with regard to tendon-bone integration

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TABLE 2. (*continued*) Published Studies on PRP Clinical Applications and Their Outcomes

Authors	Site	Study Type and No. Patients	Purpose and Interval	Outcome Measure	Follow-up	Results
Nin et al[18]	ACL reconstruction	Prospective, randomized, double-blind study 50 PRP vs 50 control	Evaluate the effect of PRP in ACL reconstruction using BPTB	IKDC score, MRI, inflammatory parameters	Mean follow-up of 24 months	No difference in IKDC score MRI: Mean diameter of the graft was 8 mm (5-12 mm) in the control group and 9 mm (5-12 mm) in the PRP group. Signal intensity of the graft showed a mean of 190 ROIs in the control group and 230 ROIs in the PRP group. On T2, the mean number of ROIs was 61 in the control group and 75 in the PRP group CRP 1 (mg/dL), 1.22 in control group vs 1.14 in PRP group; CPR 2 (mg/dL), 0.85 in control group vs 0.88 in gel group
Kon et al[19]	Patellar tendinopathy	Prospective case series (N = 20)	Evaluate the outcomes of PRP injection in the treatment of jumper's knee	Tegner, EQ-VAS, SF 36	6 months	Tegner score increased from a mean value of 4 to a mean value of 8 EQ VAS increased from a mean value of 58 to a mean value of 82 SF 36 (physical function) increased from a mean value of 56.7 to a mean value of 86.7
Peerbooms et al[20]	Elbow tendinopathy	Randomized clinical trial, 51 PRP vs 49 corticosteroid injection	Compare the effectiveness of PRP vs corticosteroid injection in the treatment of chronic lateral epicondylitis	VAS score, DASH score	1 year	VAS: improvement in 49% of corticosteroid group vs 73% of PRP group DASH: improvement in 51% of corticosteroid group vs 73% of PRP group
de Vos et al[21]	Chronic Achilles tendinopathy	Randomized clinical trial, 27 PRP injections and eccentric exercise program vs 27 saline injections and eccentric exercise program	Evaluate the outcomes of PRP injection in addition to an eccentric exercise program for the treatment of chronic Achilles tendinopathy	VISA-A	6, 12, and 24 weeks	VISA-A: After 24 weeks, mean improvement in PRP group was 21.7 points vs 20.5 points in the placebo group
Gaweda et al[22]	Noninsertional Achilles tendinopathy	Prospective case series, 14 patients (15 Achilles tendons)	Evaluate the effectiveness of PRP treatment in noninsertional Achilles tendinopathy	AOFAS score, VISA-A scale, ultrasonography, PDUS	6 weeks and 3, 6, and 18 months	AOFAS: mean improvement from 55 to 96 points VISA-A: mean improvement from 24 to 96 points Ultrasonography: normalization of peritendineum and tendon thickening, resolution of hypoechogenic lesions PDUS: increase in vascular impulses in peritendineum and surrounding area; early increase of vascular activity within tendon at 6 weeks and 3 months, decrease of vascular activity at 18 months

AOFAS, American Orthopaedic Foot and Ankle Society; DASH, disabilities of the arm, shoulder and hand score; ELISA, enzyme-linked immunosorbent assay; EQ-VAS, EuroQol visual analogue scale; IKDC, International Knee Documentation Committee; MRI, magnetic resonance imaging; PDUS, power Doppler ultrasonography; ROI, region of interest; ROM, range of motion; SF 36, Short Form (36) Health Survey; UCLA, University of California at Los Angeles; VISA-A, Victorian Institute of Sports Assessment-Achilles.

TABLE 3. PRP Preparation Protocols in Human Studies

Study	Type of Preparation	Erythrocyte Spin	Pellet Spin	Activating Agent
Banfi et al[10]	PRP solution	3200 RPM for 15 minutes	Not performed	Not specified
Mishra and Pavelko[11]	PRP solution	3200 RPM for 15 minutes	Not performed	None
Maniscalco et al[12]	Fibrin membrane	Not reported	Not reported	Not reported
Randelli et al[13]	Spray application of PRP solution	3200 RPM for 12 minutes	Not performed	Autologous thrombin
Sanchez et al[14]	Platelet-rich fibrin matrix and solution	460*g* for 8 minutes	Not performed	$CaCl_2$
Sanchez et al[15]	Fibrin membrane + PRP solution	640*g* for 8 minutes	Not performed	$CaCl_2$
Orrego et al[16]	PRP solution	3200 RPM for 15 minutes	Not performed	Thrombin and $CaCl_2$
Silva and Sampaio[17]	PRP solution	3200 RPM for 15 minutes	Not performed	Thrombin
Nin et al[18]	PRP gel	3000 RPM for 8 minutes	1000 RPM for 6 minutes	$CaCl_2$
Kon et al[19]	PRP solution	1800 RPM for 15 minutes	3500 RPM for 10 minutes	$CaCl_2$
Peerbooms et al[20]	PRP solution	Not reported	Not reported	None
de Vos et al[21]	PRP solution	RPM not reported, 15 minutes	Not reported	None
Gaweda et al[22]	PRP solution	2400 RPM for 10 minutes	3600 RPM for 15 minutes	Thrombin and $CaCl_2$

Study	Volume of Blood Drawn	Platelet Baseline Count	Platelet Final Count	Increase From Baseline
Banfi et al[10]	30 mL	Not reported	Not reported	Not reported
Mishra and Pavelko[11]	55 mL	Not reported	3.31×10^6/2-3 mL plasma	5.39×
Maniscalco et al[12]	Not reported	Not reported	Not reported	Not reported
Randelli et al[13]	54 mL	Not reported	Not reported	Not reported
Sanchez et al[14]	40 mL	$223 \times 10^3/\mu L$	$634 \times 10^3/\mu L$	3.10×
Sanchez et al[15]	80 mL	Not reported	Not reported	Not reported
Orrego et al[16]	67 mL	Not reported	Not reported	Not reported
Silva and Sampaio[17]	27 mL	Not reported	Not reported	Not reported
Nin et al[18]	40 mL	$178 \times 10^3/\mu L$	$837 \times 10^3/\mu L$	4.69×
Kon et al[19]	150 mL	Not reported	6.8×10^6/mL	6×
Peerbooms et al[20]	27 mL	Not reported	Not reported	Not reported
de Vos et al[21]	54 mL	Not reported	Not reported	Not reported
Gaweda et al[22]	8.5 mL	Not reported	Not reported	Not reported

RPM, revolutions per minute.

tunnel widening and graft integration[16–18] (Table 2). No studies reported adverse reactions.

The articles reported nonhomogeneous methods for PRP preparation (different volume blood drawn, different platelet separation system, different activating agent) and application (injection, PRP gel, PRP scaffold, PRP fibrin membrane) (Table 2). Studies used various activating agents, including autologous thrombin,[13] calcium chloride,[14,15,18,19] both,[22] and none at all.[11,20] Three studies did not specify the use of activating agents.[10,12,21] The method of application was another variable between studies, with PRP applied through injection in 7 studies, as fibrin membrane ("Cascade"; A.T. Grade, Milano, Italy) in 1 and as a spray or gel application in 2 (Table 2). In 2 other studies, the method of application was combined (PRP fibrin matrix and solution).

DISCUSSION

The application of PRP preparations in the management of soft tissue injuries has only been formally investigated in recent years, and results have been mixed. In several animal models, PRP has demonstrated clear benefits in terms of accelerated healing process,[23–30] whereas other studies have not been able to show a significant biomechanical benefit.[31,32]

Current Evidence in Human Studies

Platelet-rich plasma has advantages in the treatment of tennis elbow, as demonstrated by Mishra and Pavelko[11] and Peerbooms et al.[20] Additional preliminary studies have raised interest in PRP use for the treatment of jumper's knee, rotator cuff, and Achilles tendon repair, but additional randomized control trials are need to support these claims. Results in the treatment of Achilles tendinopathy have been conflicting. In 1 study in chronic cases, no improvement was shown,[21] whereas other authors report moderate benefits.[22] In ACL reconstruction, no effect was found on accelerating bone-tendon integration and preventing tunnel widening in hamstring and bone-patellar-tendon-bone (BPTB) graft,[16–18] although PRP seemed to accelerate the maturation process of the graft.[16] Presently, potential weaknesses can be found in many studies, related to small study groups, limited data, short-term follow-up, and lack of randomization. Only the studies by Nin et al,[18] Peerbooms et al,[20] and de Vos et al[21] were prospective, randomized, double-blind studies.

Anterior Cruciate Ligament Reconstruction

Two studies evaluated the effects of PRP on tendon-bone healing in ACL reconstructions with hamstring tendons.[16,17] Silva and Sampaio[17] evaluated the signal intensity of the fibrous interzone in the femoral tunnel and found that even

with the addition of PRP, the integration at the femoral tunnel was not complete at 3 months after the surgery and that graft stability was still provided by the fixation device. Orrego et al[16] also evaluated the healing process at 3 and 6 months, focusing on bone-tendon interface, widening of the femoral tunnel, and graft signal intensity, noticing no differences until 6 months after the surgery. Comparing postoperative imaging, 100% of magnetic resonance imaging from the PRP group showed a mature graft signal (low intensity), compared with 78% in the control group, leading to the conclusion that the use of PRP may have an enhancing effect on the graft maturation process. Conversely, no statistical differences were seen with regard to tunnel widening or bone-tendon interface.[16] The study by Nin et al[18] on the application of PRP in ACL reconstruction with BPTB allograft led to similar conclusions, showing that at 2-year follow-up, the use of PRP did not lead to discernable biomechanical effects. At this time, addition of PRP has not shown to confer any benefit over standard ACL reconstruction procedures.

Elbow Tendinopathy

Peerbooms et al[20] compared the application of PRP with corticosteroid injection in the treatment of lateral epicondylitis in a population of 100 patients, finding significantly improved outcomes in the PRP group with regard to pain and function. They also highlighted that initial benefits of corticosteroid injections gradually declined, whereas PRP patients progressively improved. This study confirms the results published by Mishra and Pavelko,[11] who also demonstrated a significant improvement in pain and elbow scores after PRP injection for chronic elbow tendinosis compared with a control group treated with bupivacaine/epinephrine injection. After 4 weeks, PRP-treated patients reported a mean 46% improvement in pain and 42% improvement in Mayo elbow score compared with a 17% and 20% improvement, respectively, in the control group. These improvements were maintained through 25 weeks at the time of publication; however, it should be noted that the patients were not blinded. Currently, there is more evidence for the use of PRP in treating elbow tendonosis than in treating other anatomical areas.

Achilles Tendinopathy and Tendon Repair

de Vos et al[21] published a prospective, randomized, clinical study focusing on the application of PRP to treat chronic Achilles tendinopathy. They showed that PRP injection associated to an eccentric exercise program does not lead to better functional outcomes and pain improvement compared with a control group treated with eccentric exercise and saline injection. On the other hand, Gaweda et al[22] reported a significant improvement in clinical scores and ultrasonographic parameters. Additionally, Sanchez et al[14] reported good outcomes after the use of PRP as augmentation in Achilles tendon surgery. The authors retrospectively studied the influence of fibrin matrices prepared from PRP in the repair of Achilles tendon tears in 6 athletes, describing better functional outcomes and an earlier return to training in the PRP group. In another study, they described the use of PRP scaffolds and liquid preparations simultaneously applied in 2 cases of complicated Achilles tendon repair (revision of infected tendon repair with tissue loss),[15] reporting good results with return to sports at an average of 21 weeks (14 weeks to resume football training and 28 weeks to resume climbing) and ultrasound findings of scar tissue filling the site of lesion. In 1 case, the follow-up was 5 years. Platelet-rich plasma application for Achilles tendinopathy and repair seems to still be controversial. Although preliminary studies have shown promise, randomized control trials are needed to further confirm these proposed benefits.

Rotator Cuff Repair

Two articles focused on PRP application in rotator cuff repair. A case report by Maniscalco et al[12] described the use of the "Cascade" membrane (A.T. Grade) as augmentation after suture of the supraspinatus tendon. The patient showed improved range of motion and reduction in pain. With no control group, these improvements cannot be credited to the use of the PRP membrane, and thus this study can only be used to support the safe use of the Cascade membrane. A prospective case series by Randelli et al[13] presented the results of the intraoperative application of PRP solution in combination with an autologous thrombin component after an arthroscopic rotator cuff repair. Similar to Maniscalco et al,[12] the authors described improvement in function and pain. Visual analog scale (VAS) scores did not show any difference between treated and control groups after 1 month, but after 6 months, VAS, University of California at Los Angeles shoulder rating scale, and constant scoring showed a significant improvement in PRP-treated patients. These improvements were again confirmed after 24 months, indicating that the effect of PRP may take longer than a month to have effect. As with the Achilles tendon, benefits of PRP in rotator cuff repair have shown promise, but randomized control trials are needed to confirm the promise these case studies have shown.

Patellar Tendinopathy

Kon et al[19] presented the results of a case series pilot study for the treatment of jumper's knee in 20 athletes, showing statistically significant improvements in Tegner, VAS, and Short Form (36) Health Survey scores at 6-month follow-up. To date, there has only been 1 study on PRP application in patellar tendinopathy. Additional studies with higher levels of evidence are required to support the use of PRP in this area.

Controversies

Currently, uncertainties exist regarding the systemic effect of PRP and also concerns about a possible local or systemic carcinogenic effect, related to the high concentrations of GFs.[33] A role as a promoter of carcinogenesis has been hypothesized for GFs, secondary to the promotion of the division and proliferation of the mutated cells; the anti-apoptotic capacity of insulin-like GF and VEGF has also been reported.[33–36] However, currently, no evidence exists in the literature of the neoplastic transformation related to the use of PRP. The only published article examining the systemic effects of local PRP application did not show a significant variation in the levels of circulating cytokines and GFs, except for a statistically significant decrease in EGF.[10] Continued demonstration of safety in human applications will also be

an important area of concern for future research to address. To date, no adverse events or deleterious effects on recovery or functional outcome have been documented.

Another controversy remains regarding the optimal dose, number, and interval of injections. All studies reviewed used different protocols for the PRP preparation and different formulations (Table 3). The use of thrombin and scaffolds has been proposed to promote platelet activation and conversion of fibrinogen to fibrin, increasing the time GFs are maintained within the area of application. Gel formulation with fibrin may decrease absorption and diffusion away from the injured area. So far, the use of scaffolds in human models has been limited to fibrin matrices[14] and membranes.[12] Because comparisons among uses of liquid/gel PRP, scaffolds, and matrices have not been published, it is difficult to determine if an additive effect exists. Additional studies on the benefits of using either collagen or fibrin matrices with PRP are needed to determine the effects of scaffold use.

Finally, clarification is required in respect of the rules of antidoping agencies for the use of PRP in elite and professional athletes. The World Antidoping Agency prohibits the use of individual concentrated GFs and the use of autologous blood intravenously (blood doping).[37] However, as of 2011, PRP is no longer prohibited for intramuscular use. Studies on the systemic effects of PRP focused on the performance advantages are necessary, but currently, there is no evidence of a performance-enhancing effect.

CONCLUSIONS

The use of PRP has several potential theoretical advantages, including faster recovery and improved functional outcomes in tendon and ligament injuries. To the athlete, these benefits will allow for earlier return to training and competition, improved immediate postinjury performance, and possibly a reduction in relapse.

However, despite some benefits demonstrated to date, it must be acknowledged that the uses of PRP in soft tissue applications are still weakly supported. Inferences regarding the potential benefits and safety of this new therapy must consider the low number of studies, low sample numbers, and levels of evidence.

Establishment of platelet therapy as a reliable, efficacious, and safe therapy in managing the pathology of tendons and ligaments will require the completion of high-quality clinical trials with long-term follow-up.

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