[Primary Care]

Platelet-Rich Plasma: Where Are We Now and Where Are We Going?

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Context: Platelet-rich plasma (PRP) may affect soft tissue healing via growth factors released after platelet degranulation. Because of this potential benefit, clinicians have begun to inject PRP for the treatment of tendon, ligament, muscle, and cartilage injuries and early osteoarthritis.

Evidence Acquisition: A PubMed search was performed for studies relating to PRP, growth factors, and soft tissue injuries from 1990 to 2010. Relevant references from these studies were also retrieved.

Results: Soft tissue injury is a major source of disability that may often be complicated by prolonged and incomplete recovery. Numerous growth factors may potentiate the healing and regeneration of tendons and ligaments. The potential benefits of biologically enhanced healing processes have led to a recent interest in the use of PRP in orthopaedic sports medicine. There has been widespread anecdotal use of PRP for muscle strains, tendinopathy, and ligament injuries and as a surgical adjuvant to rotator cuff repair, anterior cruciate ligament reconstruction, and meniscal or labral repairs. Although the fascination with this emerging technology has led to a dramatic increase in its use, scientific data supporting this use are still in their infancy.

Conclusions: The literature is replete with studies on the basic science of growth factors and their relation to the maintenance, proliferation, and regeneration of various tissues and tissue-derived cells. Despite the promising results of several animal studies, well-controlled human studies are lacking.

Keywords: platelet-rich plasma; tendinopathy; ligament injuries; muscle strain injuries; early osteoarthritis

Soft tissue injury is a major source of disability and health care expense, resulting in more than 1 million office visits per year in the United States.[4] In addition to health care expense, the societal cost of these injuries includes lost job wages and production. In competitive or professional athletes, this vocational loss may have extreme consequences. Soft tissue healing in vivo is often a slow, complicated, and incomplete process.[28] Our understanding of the contribution of growth factors (GFs) to the regulation of normal tissue structure and development, as well as tissue's response to injury, continues to evolve at a rapid rate. Coupled with this advancing scientific knowledge is the fascination with the potential impact of GF application on the healing of injured tissue. The ability to modulate or augment the healing process and expedite recovery times is a subject of vigorous scientific investigation.

Platelet-rich plasma (PRP) is a simple, efficient, and minimally invasive method of obtaining a natural concentration of autologous GFs.[2] Generation of PRP involves centrifugation of autologous blood to separate and extract the plasma and buffy coat portion of the blood, which contain high concentrations of platelets. PRP has established use in the fields of dentistry, dermatology, plastic and maxillofacial surgery, acute trauma, cosmetic surgery, and veterinary medicine.[12,28,36,38,53] The rationale for the widespread use of PRP in the healing process of such varied tissue types resides in the fact that platelets represent an easily accessible reservoir of critical GFs and other signaling molecules, including leukocyte-derived catabolic cytokines and fibrinogen, which may govern and regulate the tissue-healing process.[8,41,44] This milieu of bioactive molecules contributes to a well-orchestrated tissue-healing response to injury, which proceeds sequentially through the inflammatory, reparative, and remodeling phases of wound healing.[62]

The purpose of this review is to establish a foundation of knowledge related to the definition of PRP and to analyze the

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Table 1. Growth factors present in platelet-rich plasma.

Name	Acronym	Function
Platelet-derived growth factor	PDGF	Stimulates fibroblast production, chemotaxis, stimulates transforming growth factor–β1, collagen production, upregulation of proteoglycan synthesis
Transforming growth factor–β1	TGF-β1	Modulates proliferation of fibroblasts, formation of extracellular matrix, cell viability; increases production of collagen from fibroblasts, suppression interleukin 1–mediated effects on proteoglycan synthesis in cartilage
Basic fibroblastic growth factor	bFGF	Produces collagen; stimulates angiogenesis, proliferation of myoblasts
Vascular endothelial growth factor	VEGF	Promotes angiogenesis
Epidermal growth factor	EGF	Promotes cell differentiation, angiogenesis, proliferation of mesenchymal and epithelial cells

PRP results in preclinical and clinical studies to determine if the cumulative scientific evidence suggests efficacy of PRP and supports its use for the treatment of musculoskeletal injuries. A tremendous challenge to the interpretation and extrapolation of the available data lies in the variability of platelet and leukocyte concentrations among the various methodologies used in preclinical and clinical studies.

THE ROLE OF PLATELETS

Platelets are the first cell type to arrive at the site of tissue injury and are particularly active in the early inflammatory phases of the healing process.[62] They play a role in homeostasis, through cell membrane adherence, aggregation, clot formation, and release of substances that promote tissue repair and that influence the reactivity of blood vessels and blood cell types involved in angiogenesis and inflammation.[8,44] Platelets mediate these effects through degranulation, in which platelet-derived GF (PDGF), transforming GF-β1 (TGF-β1), vascular endothelial GF (VEGF), basic fibroblastic GF (bFGF), and epidermal GF (EGF) are released from alpha granules (Table 1).[21,23,38] Platelets also store antibacterial and fungicidal proteins, metalloproteases, coagulation factors, and membrane glycoproteins, which may influence inflammation by inducing the synthesis of other integrins, interleukins, and chemokines.[2] Dense granules in platelets store and release ADP, ATP, calcium ions, histamine, serotonin, and dopamine, which are active in tissue modulation and regeneration.[49] Platelet degranulation begins within 10 minutes of exposure to clotting cascade factors (such as thrombin) or, in their absence, contact to exposed basement membrane. The majority of GF secretion occurs within the first hour, although continued release occurs throughout the period of platelet viability (7 days).[38]

Although many GFs are associated with wound healing, PDGF and TGF-β1 appear to be 2 of the more integral modulators.[34] PDGF has activity in early wound healing (during the acid tide).[19,33] In vitro studies have shown that at lower pH (5.0), platelet concentrate lysate has increased concentrations of PDGF, with an increased capacity to stimulate fibroblast proliferation.[33] TGF-β increases the production of collagen from fibroblasts.[33,61] Its release (in vitro) is enhanced by neutral or alkaline pHs, which correspond to the later phases of healing.[33] Through modulation of interleukin-1 production by macrophages, PRP may inhibit excessive early inflammation that could lead to dense scar tissue formation.[66]

Insulinlike GF-I (IGF-I) has also been extensively studied for its ability to induce proliferation, differentiation, and hypertrophy of multiple cell lines. Separate analyses of GFs in PRP have shown significant increases in PDGF, VEGF, TGF-β1, and EGF, compared with their concentrations in whole blood.[21,23,38,56,64] However, there are conflicting results with regard to IGF-I, where the majority of studies reported no increase in IGF-I in PRP, compared with whole blood. There are also conflicting results regarding the correlation between the GF content and platelet counts in PRP.[21,23,38,49,64] The basis of these contradictions are not fully understood and may be related to variability in patient age, health status, or platelet count. Alternatively, differences in GF content and platelet count may be due to the various methods of processing, handling, and storing of samples, in addition to the type of assay performed. The diversity of PRP products should be taken into account when interpreting and comparing results and methods for generating PRP.

PRP IN ORTHOPAEDICS

The allure of PRP use in soft tissue injuries resides in the possible delivery of a physiologically natural balance/ratio of

GFs and other cytokines containing anabolic and catabolic functions in supraphysiologic concentrations directly into the site of injury to potentially optimize the healing environment.[3,15,41] Maintaining a natural ratio of GFs may allow maintenance of the body's homeostatic environment and theoretically provide an abundance of healing factors without disrupting their in vivo relationships. Equally appealing is its simplicity, low cost, availability, and absence of significant adverse consequences. The autologous nature of PRP eliminates the risk of immune rejection or disease transmission. Despite this nearly intuitive and enormous potential, well-conducted randomized controlled clinical trials are lacking (Table 2).

Several manufacturers have commercially available devices to produce PRP. The techniques used to generate the platelet concentrate products differ in the amount of whole blood, the use of anticoagulant (acid citrate dextrose), the time and speed of centrifugation, the final volume, and the number of platelets in the platelet concentrate. In addition, the application can vary, depending on the use of either bicarbonate, to buffer the acidic nature of PRP derived with acid citrate dextrose, or thrombin, to initiate the clotting cascade through degranulation of platelets.[15,37] A theoretical advantage of PRP gel administration may be the adhesive support that can confine the platelets and their GFs at the treatment site.[3]

According to the American Red Cross, PRP is greater than or equal to 5.5×10^{10} platelets per 50 mL. This translates to a two- to sevenfold increase in platelet concentration compared with that of whole blood. The normal human range of platelet concentration is 150 000 to 450 000 platelets per µL of whole venous blood.[18,40] Concentrations of platelets in PRP differ widely, ranging from 2.5 to 8.0 times the concentration of platelets found in whole blood.[16] Reportedly, the clinical benefit of platelet concentrates occurs more predictably when this fourfold increase in platelet concentration is achieved,[37] but substantial scientific evidence is lacking, and concentrates lower than this may prove to be clinically beneficial.

The importance of the leukocyte concentration in PRP is unclear. In an ex vivo study investigating the effects of PRP products on matrix synthesis in the flexor digitorum superficialis tendon, leukocyte concentration was positively correlated with collagen type III transcription (indicative of scar formation) and matrix metalloproteinases 3 and 13 (which degrade intact collagen fibers).[38] Leukocyte concentration was also negatively correlated with indicators of matrix synthesis, including the ratio of COL1A1 to COL3A1, cartilage oligomeric matrix protein, and decorin.[38] The clinical importance of leukocytes in acute or chronic tendinopathy is presently unknown, but leukocyte concentration should be considered and reported in preclinical and clinical studies. Further investigation is still needed to determine the most efficacious platelet concentration and appropriate additives to produce the optimal PRP preparation. An important step toward determining an optimal PRP preparation is adoption of a standardized nomenclature for PRP products to accurately reflect platelet and leukocyte concentrations.[18]

There is a lack of animal and clinical studies to demonstrate the potential of PRP in soft tissue repair. Application of PRP for musculoskeletal injuries is relatively new, and accumulation of data to support Level 1 clinical studies will take time. Individual functions of GFs tested in vitro may not accurately represent their in vivo function, because the interrelations among the numerous GFs may be such that they require the symbiotic presence of other GFs to properly modulate their effects.

PRP FOR TENDINOPATHY

In tendinopathy, the essential pathology includes chronic microscopic tears occurring in hypovascular tendon tissue. These tears heal by scar formation rather than the normal vascular and inflammatory-driven tendon-healing pathways.[14] Modulation of bioactive factors in the diseased tendon may increase the potential for tendon healing.[43] Individual in vitro GFs in PRP have been shown to increase type I collagen synthesis and tenocyte proliferation, including TGF-β1, PDGF, VEGF, and EGF.[29,34,61,67] When exposed to PRP, tendon matrix synthesis is enhanced in cultures of isolated tenocytes and in ex vivo tendon explant cultures.[16,38,56]

Animal studies have suggested positive effects of PRP on tendon repair—namely, improved repair with abundant tendon callus and increased force to failure.[5,63] Injection of PRP into areas of tendon injury in animal models enhances the contribution of circulation-derived cells to tendon healing in the early phases of tendon healing.[27]

Some clinical evidence supports the translational application of PRP in tendinopathy in Level 4 studies. In a cohort study conducted by Mishra and Pavelko,[42] 93% of the patients reported reduction in epicondylar pain at a 2 year follow-up after receiving a single PRP injection. Kon et al[31] prospectively followed 20 patients with patellar tendinosis who presented with pain and dysfunction for an average of 20 months. Three PRP injections at 15-day intervals were delivered into the diseased tendon. Statistically significant improvements in SF-36 Health Survey, visual analogue scale, and sporting activity (using Tegner score) were realized at 6-month follow-up. Most recently, a Level 1 randomized controlled trial suggested that PRP treatment for chronic Achilles tendinopathy did not improve patient pain or activity, compared with a saline control.[17] Unfortunately, the platelet or leukocyte counts in the PRP treatment were not reported, nor was patient age, lesion size, or chronicity of the condition.

The use of PRP as an adjuvant to surgical repair of rotator cuff and Achilles tendon tears has been tested.[24,50,54] Athletes undergoing Achilles tendon repair augmented with PRP intraoperatively recovered range of motion earlier, had fewer wound complications, and resumed training activities earlier than did those treated with surgical repair alone.[54] Rotator cuff repairs augmented with PRP resulted in significant improvement over a 24-month period (based on visual analogue scale, UCLA, and Constant scores), as well

Table 2. Outcomes of clinical trials using platelet-rich plasma (PRP).

Pathology	Epicondylar pain[42]
Patient number	Group 1: bupivacaine, 5; Group 2: PRP, 15
Mean follow-up period (months)	25.6
Volume of injection	2-3 cc of PRP
Number of injections	1
Outcomes	Mayo score*: initial, 50.3; 6 months, 86.3. Mean pain score*: initial, 80.3; 6 months, 15.07. *$P = .0001$.
Study level and comments	Level 2, cohort study. Three-fifths of bupivacaine patients withdrew from study, preventing analysis. PRP patients reported a 93% decrease in pain. Conclusion: PRP reduced pain from elbow tendinosis and should be considered before surgery.
Pathology	Rotator cuff[50]
Patient number	14
Mean follow-up period (months)	24
Volume of injection	Not applicable
Number of injections	1 injection
Outcomes	Visual analogue scale*: initial PRP, 5.64; 2-year PRP, 1.00 ± 0.58. UCLA*: initial PRP, 16.54 ± 5.46; 2-year PRP, 32.92 ± 1.19. Constant*: initial PRP, 54.62 ± 16.98; final PRP, 85.23 ± 7.22. *$P = .001$.
Study level and comments	Level 4, case series; 13 patients were seen at follow-up. Conclusion: PRP is safe and effective for treatment of the rotator cuff and produces results that are consistent over time.
Pathology	Achilles tendon (plasma-rich growth factor)[54]
Patient number	Group 1: plasma-rich growth factor, 6; Group 2: control, 6
Mean follow-up period (months)	Group 1: 32; Group 2: 50
Volume of injection	4 cc of plasma-rich growth factor
Number of injections	1 injection after repair
Outcomes	Time (weeks) of improvement: Return of ankle motion*: control, 11 ± 3; plasma-rich growth factor, 7 ± 2. Return to running*: control, 18 ± 3; plasma-rich growth factor, 11 ± 1. Return to training*: control, 21 ± 3; plasma-rich growth factor, 14 ± 0.8. *$P < .05$.
Study level and comments	Level 3, case control. Conclusion: Plasma-rich growth factor may be a new option for enhanced healing and functional recovery.
Pathology	Achilles tendon[17]
Patient number	Group 1: PRP, 27; Group 2: saline, 27
Mean follow-up period (months)	24
Volume of injection	4 cc of PRP

(continued)

Table 2. (continued)

Number of injections	1 injection
Outcomes	Composite pain and activity score, mean improvement from baseline: PRP, 21.7; saline, 20.5. Improvement between groups nonsignificant.
Study level and comments	Level 1, randomized control trial. Conclusion: In treating Achilles tendinopathy, PRP, when compared to saline, does not result in greater improvement in pain or activity.
Pathology	Anterior cruciate ligament reconstruction[57]
Patient number	50
Mean follow-up period (months)	3
Volume of injection	3 cc of PRP
Number of injections	1 injection
Outcomes	Magnetic resonance signal intensity: PRP demonstrated no differences within femoral tunnels following anterior cruciate ligament reconstruction, compared to controls.
Study level and comments	Level 3, cohort control. Conclusion: The use of PRP or thrombin does not appear to accelerate tendon integration.
Pathology	Jumper's knee[31]
Patient number	20
Mean follow-up period (months)	6
Volume of injection	5 cc of PRP
Number of injections	3 Injections
Outcomes	Functional improvement*: before therapy, 56.7; end of therapy, 82.0. Pain improvement*: before therapy, 35.7; end of therapy, 63.8. *$P < .05$.
Study level and comments	Level 4, case series. Conclusion: Short-term results show reduced pain and a return to activity when PRP is used to treat jumper's knee.
Pathology	Lateral epicondylitis[20]
Patient number	28
Mean follow-up period (months)	9.5
Volume of injection	2 cc of PRP
Number of injections	1 Injection
Outcomes	Average pain score: preinjection, 7.8; postinjection, 2.3. Average Nirschl stage: preinjection, 6.5; postinjection, 2.0. No statistics performed.
Study level and comments	Level 4, case series. Of 28 patients, 22 report complete pain relief even during strenuous activity. Conclusion: Encouraging results to address lateral epicondylitis.
Pathology	Anterior cruciate ligament reconstruction[47]
Patient number	N, 108; Group 1: control, 27; Group 2: PRP, 26; Group 3: bone plug, 28; Group 4: PRP + bone plug, 27

(continued)

Table 2. (continued)

Mean follow-up period (months)	6
Volume of injection	6 cc of PRP
Number of injections	1 injection
Outcomes	Mature graft magnetic resonance imaging signal in femoral tunnel at 6 months: Group 1, 21 of 27 (78%); Group 2, 26 of 26 (100%)*; Group 3, 25 of 28 (89%); Group 4, 25 of 27 (93%). *P = .036. International Knee Documentation Committee, 6 months postoperatively: all groups, > 89% reported excellent and good outcomes (nonsignificant). Lysholm, 6 months postoperatively: all groups, > 90% reported excellent and good outcomes (nonsignificant).
Study level and comments	Level 2, quasirandomized controlled trial. Conclusion: PRP has enhanced effect on graft maturation evaluated by magnetic resonance imaging intensity at 6 months. PRP + bone plug did not show a synergistic effect.

as no adverse effects related to the application during the procedure.[25,51]

PRP USE IN LIGAMENT INJURIES

The use of PRP to augment the healing of ligamentous injuries remains controversial yet promising. As in the in vitro and preclinical studies performed with tendons, GFs (PDGF, TGF-β1, and bFGF) are actively involved during the early stage of medial collateral ligament and anterior cruciate ligament (ACL) healing.[6,32,52,65] Application of PRP to ligaments in ex vivo culture has also been shown to improve matrix synthesis.[56]

In animal ACL transection models, platelet hydrogels improve healing of central ACL partial-thickness defects, load to failure, and stiffness, when compared with controls.[45,58] Augmentation of ACL autograft reconstruction with PRP has been shown to preserve the mechanical integrity of the graft during the first 12 months postoperatively.[6,11,13,20,47,52] Although these studies seem promising, note that conflicting data do exist showing no effect of PRP on graft healing.[46]

Biological augmentation may play a role in graft integration, potentially allowing for a quicker return to function without prematurely exposing the graft to increased forces. However, in a recent prospective clinical ACL study that analyzed osseous integration of hamstring autograft in the ACL tunnel using magnetic resonance imaging evaluation, graft integration was not accelerated at 3 months.[57]

As with the ACL, animal studies investigating the effects of GFs on medial collateral ligament healing have yielded conflicting results.[60] Increased strength and improved healing time has been reported after application of PDGF.[7,26] Conversely, Spindler et al[59,60] found that the addition of PDGF and TGF-β1 did not change the mechanical properties of healed medial collateral ligaments in rabbits.

PRP IN THE TREATMENT OF MUSCLE STRAIN INJURIES

GFs, in particular IGF-I, hepatocyte GF (HGF), fibroblast GF-2, and TGF-β1 may be key regulators of muscle regeneration and myogenisis.[25,39] In a recent animal study, Hammond et al, found that local delivery of PRP to a multiply loaded, eccentric muscle injury model in animals decreased full recovery time from 21 days to 14 days. To date, the authors are unaware of any human clinical studies investigating PRP for use in the treatment of muscle injuries.

PRP FOR USE IN CARTILAGE INJURIES AND EARLY OSTEOARTHRITIS

Articular cartilage is frequently exposed to multiple macro- or microtraumatic events that may lead to the loss of tissue homeostasis, resulting in the accelerated loss of articular cartilage and progressing to arthritis. The inherently poor regenerative capacity of cartilage continues to make articular cartilage disease a challenging problem for orthopaedic surgeons.[9,10]

GFs play a crucial role in modulating the phenotypic expression of chondrocytes. TGF-β affects cartilage regeneration through increased chondrocyte phenotype expression and matrix synthesis, through chondrogenic differentiation of mesenchymal stem cells, and through suppression of interleukin-1-mediated decrease in proteoglycan synthesis.[22,48] PDGF helps maintain the hyaline-like chondrogenic phenotype; it increases chondrocyte proliferation; and it up-regulates proteoglycan synthesis.[55] IGF-I has been shown to stimulate proteoglycan synthesis and suppress proteoglycan catabolism.[35,55] Other GFs, including bFGF and VEGF, have chondroinductive roles. These GFs are all present in the α-granules of platelets, with the possible

exception of IGF-I,[49] and they may be delivered intra-articularly in high concentrations. In vitro, PRP stimulates chondrocyte proliferation and matrix synthesis,[1] and animal model studies have indicated that injection of PRP prevents progression of osteoarthritis after ACL transection.[51] In a clinical study of 100 patients diagnosed with degenerative cartilage lesions (based on the Kellegren scoring system), PRP injections resulted in improved function and diminished pain.[30]

CONCLUSION

The emergence of PRP as a vehicle for the localized delivery of an abundance of biologically active GFs to the site of injury is supported by its simplicity, safety, availability, and potential cost-effectiveness. Unfortunately, despite the widespread use of PRP in muscle strains, tendinopathy, and ligament injuries, and as surgical adjuncts to rotator cuff repair, ACL reconstruction, and meniscal and labral repairs, research on its clinical efficacy is still in its infancy. Although several animal studies have offered promising results,‖ well-controlled human studies are lacking.

Variables inherent to the generation and application of PRP can impede the design and execution of reliable clinical studies. The ideal concentration of platelets, leukocytes, and GFs has yet to be proven. Furthermore, the favored microenvironment at the lesion and the mechanical stimulus need to be considered as influences of cellular differentiation and tissue repair independent of the presence of stimulatory GFs. Combined, these factors may act synergistically or antagonistically with the biological treatment in the healing process of musculoskeletal tissues. Although there appears to be sufficient data to warrant continued clinical study of PRP as an adjuvant to healing, its clinical role is not yet defined.

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