Platelet-Rich Plasma

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KEYWORDS

• Platelet-rich plasma • Musculoskeletal • Healing • Regenerative • Sports
• Rehabilitation • Injection

KEY POINTS

- PRP is a regenerative therapy that has gained popularity in musculoskeletal medicine for its potential to augment repair of tissues with low healing ability.
- Basic science and preclinical studies have begun to elucidate the therapeutic roles of platelets, leukocytes, and red blood cells, suggesting greater benefit from leukocyte-poor PRP.
- Clinical studies have investigated PRP for tendon, ligament, muscle, and cartilage repair, yielding limited Level I evidence supporting use for lateral epicondylosis and knee osteoarthritis.
- Patient selection and education and postprocedural rehabilitation are essential to maximize the therapeutic effect of PRP.
- Investigations are needed to determine the ideal PRP composition, while large clinical trials with standardized reporting of formulations used are needed to determine PRP efficacy.

INTRODUCTION

The clinical application of platelet-rich plasma (PRP) and other regenerative therapies in sports, spine, and musculoskeletal medicine has soared in the last decade. Over this period, many factors have converged to fuel this development. Advances in scientific understanding of tendinopathy as a degenerative cellular and connective tissue process; lack of long-term efficacy of steroid injection therapies, which has prompted the need for alternative therapies; advances in musculoskeletal ultrasound (US) to facilitate diagnosis and guide interventions; as well as translation of treatment paradigms from colleagues in oral and veterinary surgery have all contributed to the advancement of this regenerative field.

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This article provides the latest clinically relevant information on the basic science of PRP and practical considerations for its use, evidence for PRP use in musculoskeletal medicine, recommendations for PRP preparation and patient selection, as well as suggested postprocedure rehabilitation and return to sport protocols. The authors will identify the limitations in current knowledge of this regenerative therapy and recommend critical areas for future research.

BASIC SCIENCE AND RATIONALE

Definition of Platelet-Rich Plasma

PRP is a preparation of autologous plasma enriched with a platelet concentration above that normally contained in whole blood.[1] In clinical musculoskeletal medicine, PRP is classically prepared by centrifuging autologous, anticoagulated whole blood to separate its components and concentrate platelets above baseline levels. Typical protocols include either 1 or 2 centrifugation steps to separate whole blood into 3 layers: a top plasma layer, middle leukocyte layer, and bottom red blood cell (RBC) layer, to collect a concentrate of platelets in plasma.[2] The rationale for use and therapeutic potential of a high concentration of platelets is based on their capacity to supply and release supraphysiologic amounts of essential growth factors and cytokines from their alpha granules to provide a regenerative stimulus that augments healing and promotes repair in tissues with low healing potential.

Early Use of Platelet-Rich Plasma

PRP therapy has gained popularity in regenerative medicine and other specialties since the earliest reports of its clinical use in the 1980s and 1990s, with applications traced to the fields of cardiac, dental, and maxillofacial surgery. In cardiac surgery, PRP was shown to be an effective autologous source for transfusion to address surgical blood loss and hematologic derangements from cardiopulmonary bypass.[3,4] In dentistry, Anitua[5] demonstrated application of PRP to tooth extraction sites facilitated bone regeneration in these sockets with compact mature bone that had normal morphology. In maxillofacial surgery, Marx and colleagues[6] evaluated the effect of PRP on bone maturation rate and bone density in bone graft reconstructions of mandibular continuity defects, demonstrating that addition of PRP to grafts resulted in increased bone formation.

Today in musculoskeletal and sports medicine, PRP therapy has become highly attractive for its potential benefit and influence on repairing injured tissue, treating a wide range of degenerative disorders, and accelerating return to sport, finding its role as an injectable biologic used to augment healing of tendon, ligament, muscle, and cartilage.[7]

Basics of Wound Healing

The utility of PRP in promoting healing is especially significant for tendons, ligaments, and cartilage, the repair processes of which can be particularly slow and poor due to their limited blood supply and slow cell turnover.[8,9] In general, wound healing can be separated into 3 phases: inflammation, proliferation, and remodeling.[10] The initial inflammation phase is characterized by hemostasis, with platelets establishing clot formation, and the release of growth factors that aid in activating and attracting inflammatory cells like neutrophils and macrophages to the site of injury. The proliferation phase is characterized by the construction of an extracellular matrix associated with granulation, contraction, and epithelialization.[7,10] Finally, the remodeling phase is associated with production of collagen and scar tissue. The physiologic progression

through these phases of wound healing is orchestrated by growth factors and cytokines, many of which are released and modulated by blood components in PRP.

Components of Platelet-Rich Plasma

Platelets

Although platelets play a key role in hemostasis, they are central to mediating the anabolic effects of PRP by virtue of releasing growth factors stored in their alpha granules. During the initial phases of wound repair, activated platelets attract and foster cell migration into the wound by aggregating and forming a fibrin matrix. This matrix then serves as a tissue scaffold for sustained release of platelet growth factors and cytokines, which stimulate cell recruitment, differentiation, and communication.[11] Although both angiogenic and antiangiogenic factors are stored in platelets, they are released differentially.[11,12] Notable growth factors released from platelets that are involved in the healing process include platelet-derived growth factor (PDGF), transforming growth factor (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), and insulin-like growth factor (IGF-1) (**Table 1**).[8]

Leukocytes

Leukocytes are essential mediators of the inflammatory response, host defense against infectious agents, and wound healing.[8] Neutrophils are involved in the inflammation phase of wound healing. Monocytes and macrophages facilitate tissue repair by debriding and phagocytosing damaged tissue and debris. Similar to platelets, macrophages also secrete growth factors that are important in tissue repair and have been shown to contribute to subchondral bone regeneration.[2,13] Although leukocytes play key roles in tissue repair and provide desirable protection against infectious agents, their proinflammatory and immunologic effects can also induce undesirable local

Table 1
Key regenerative growth factors stored in platelet alpha granules and their functions

Growth Factor	Function
PDGF	Stimulates cell proliferation, chemotaxis, and differentiation Stimulates angiogenesis
TGF-β	Stimulates production of collagen type I and type III, angiogenesis, re-epithelialization, and synthesis of protease inhibitors to inhibit collagen breakdown
VEGF	Stimulates angiogenesis by regulating endothelial cell proliferation and migration
EGF	Influences cell proliferation and cytoprotection Accelerates re-epithelialization Increases tensile strength in wounds Facilitates organization of granulation tissue
bFGF	Stimulates angiogenesis Promotes stem cell differentiation and cell proliferation Promotes collagen production and tissue repair
IGF-1	Regulates cell proliferation and differentiation Influences matrix secretion from osteoblasts and production of proteoglycan, collagen, and other noncollagen proteins

Abbreviations: PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; bFGF, basic fibroblast growth factor; IGF-1, insulin-like growth factor.
Data from Refs.[1,2,8,12]

cell and tissue damage that opposes the intended healing effects of PRP therapy. In vitro studies have shown that high concentrations of leukocytes in PRP can produce an inflammatory environment that can be detrimental to the healing response.[14–17] In addition, studies of tendon models by Boswell and colleagues[18] showed that reducing leukocyte concentrations, and thus decreasing the inflammatory response, may be more important than maximizing platelet concentrations to optimize PRP efficacy. A summary of several preclinical studies involving leukocyte concentration in PRP is provided in **Table 2**. Further preclinical studies are needed for each target tissue type to elucidate the optimal concentration of leukocytes that can augment healing without inciting damage.

Red blood cells

RBC content is typically reduced or absent in PRP because of the centrifugation process. Using hemoglobin, RBCs perform their primary function of carrying and delivering oxygen, other metabolic gases, nutrients, and regulatory molecules like nitric oxide. Although nitric oxide is known to stimulate vasodilation, it has also been implicated in mediating insensitivity in diseased cartilage to the anabolic effects of IGF-1.[8] During oxidative stress, iron contained in heme molecules can release cytotoxic oxygen free radicals that induce apoptosis of host cells.[8] This destructive process is thought to occur in human synoviocytes treated with RBC concentrates, leading to significantly greater cell death and cartilage degradation.[15,19–21] Such findings suggest that RBC concentrations should be reduced or eliminated in PRP preparations used for intra-articular applications.

Considerations for Platelet-Rich Plasma Use

Differences among platelet-rich plasma products

To date, there is no general consensus on how best to prepare PRP or the optimal concentrations of blood components to include in the product, with each PRP formulation having its own unique biologic properties and effects, which has contributed to

Table 2
Findings from preclinical studies of leukocyte concentration in platelet-rich plasma

Tissue of Interest	Findings
Human synoviocytes[15]	Treatment with leukocyte-rich PRP and RBC concentrates resulted in significant cell death and proinflammatory mediator production. Consider using leukocyte-poor and RBC-free preparations of PRP for intra-articular therapy
Rabbit patellar tendons[16]	Leukocyte-rich PRP resulted in significantly greater inflammatory response 5 d after intratendinous injection compared with leukocyte-poor PRP. There was no difference in inflammatory response 14 d after injection between leukocyte-rich and leukocyte-poor PRP
Human synoviocytes[14]	Leukocyte-rich PRP is able to maintain long-term upregulation of proinflammatory factors and downregulation of anticatabolic mediators in cartilage compared with leukocyte-poor PRP and platelet-poor plasma
Equine flexor digitorum superficialis tendons[13]	High leukocyte concentrations in PRP can contribute to the expression of inflammatory cytokines in flexor digitorum superficialis tendon explants. Leukocyte-poor PRP may be the preferred preparation to stimulate healing without scar tissue formation

mixed results of PRP's clinical efficacy from human trials. In the literature, investigators have used a variety of PRP preparation protocols, differing by preparation kits, centrifugation systems, number of centrifugation steps, activation methods with or without thrombin and/or calcium, and ultimate concentrations of PRP components (platelets, leukocytes, RBCs).[22,23] The large variability in PRP formulations used creates a challenge to accurately draw conclusions from the literature to guide PRP production and determine indications for use, prompting the development of PRP classification schemes to facilitate reporting of clinical investigations.[24–27]

Activated versus nonactivated platelet-rich plasma

PRP preparations are commonly activated before administration in order to induce release of a highly concentrated bolus of growth factors to the target tissue. Up to 70% of growth factor content from activated PRP can be released over 10 minutes.[6] Roh and colleagues[28] demonstrated that PRP activated with a low-dose mixture of thrombin and calcium significantly increased growth factor release over 7 days compared with nonactivated PRP. Nevertheless, uncertainty exists as to whether rapid, bolus delivery of growth factors is ideal. Studies have shown mixed results supporting PRP activation, with activated preparations resulting in less efficient fibroblast differentiation and wound healing but providing equivalent bony regeneration compared with nonactivated preparations.[11,29] Given limited data, there is no agreement on whether activation is beneficial or deleterious, but it is understood that activation alters the properties of PRP and must be considered when comparing results from clinical studies.

Drug interactions

Application of PRP has generally not been recommended in individuals who take or cannot suspend taking antiplatelet therapy, which may inhibit platelet degranulation and release of growth factors and bioactive molecules, thereby significantly reducing the healing potential of this biologic approach. Such antiplatelet agents come from drug classes with various mechanisms of action that include reversible and irreversible cyclo-oxygenase inhibitors, adenosine diphosphate receptor inhibitors, adenosine reuptake inhibitors, phosphodiesterase inhibitors, and glycoprotein IIB/IIIA inhibitors.[30] Autologous PRP produced from subjects taking nonsteroidal anti-inflammatory drugs (NSAIDs), reversible cyclo-oxygenase inhibitors that are commonly taken for anti-inflammation and pain management, was shown to have significantly impaired platelet aggregation and thus potentially diminished therapeutic effect.[31] Other medications may also inhibit platelet function. Pioglitazone, an anti-hyperglycemic medication, was shown to both directly inhibit platelet release of thromboxane, an inducer of platelet aggregation, and potentiate aspirin inhibition of platelet aggregation and ATP release.[32]

EVIDENCE BASE FOR MUSCULOSKELETAL DISORDERS

PRP therapies are used increasingly for treating musculoskeletal soft tissue injuries, including tendinopathies and tendon tears, and ligament, muscle, and cartilage injuries.[33] Therapies have been used as both principal treatment and augmentative therapy alongside surgical repair. A most recent 2014 *Cochrane Review* of single-center, randomized controlled trials (RCTs) of PRP in the literature reveals that evidence for the primary outcomes of function and pain are of low quality and at high risk of bias. Overall results showed PRP provides no clinically significant improvement in short- and long-term function and only a small reduction in short-term pain compared with control. Adverse effects were associated with concerns about persisting pain. Difficulty in drawing clear conclusions from this collection of studies stems from using

heterogeneous PRP preparation methods, application techniques, and outcome measures; treating disparate musculoskeletal disorders; and conducting underpowered studies. The current evidence also comprises a collection of earlier, smaller studies, many with nonrandomized or uncontrolled methodology, that demonstrate variable results for the effectiveness of PRP to treat musculoskeletal injuries. The review presented here emphasizes findings from the most recent RCTs over earlier case reports, cohort or retrospective studies.

Tendon

Lateral epicondyle tendinopathy

Results for PRP treatment of lateral epicondyle tendinopathy (LET) have been promising.[34–37] RCTs have demonstrated the efficacy of PRP for treating chronic LET, with superior 1-year[38] and 2-year[39] improvements in function and pain compared with steroid injection. However, more recent RCTs have demonstrated variable efficacy of PRP compared with saline, steroid, autologous whole blood, and bupivacaine:[40–43]

- PRP was superior at reducing pain at 6 weeks[41] but inferior at improving function by 6 months compared with autologous blood injection.[40]
- PRP was no different than steroid or saline at reducing pain and improving function at 3 months, was inferior to steroid at improving pain and function at 1 month, and was associated with greater postinjection pain.[42]
- PRP was superior to bupivacaine at improving pain at 6 months.[43]

A further RCT comparing the efficacy of PRP with that of autologous whole blood injection showed both methods are comparably effective in treating LET, with no significant difference between groups in pain reduction and functional improvement in 12 months of follow-up.[44] Although results suggest there may be no need to have platelet concentration greater than in whole blood to obtain therapeutic effects, limitations of this study included a relatively small number of cases and the absence of a placebo control group; thus, whether these treatment approaches are superior to natural recovery remains unverified.

Results are pending from a multicenter RCT comparing autologous PRP, autologous whole blood, dry needle tendon fenestration, and physical therapy (PT) alone on pain and quality of life in patients with LET (IMpact of Platelet Rich Plasma Over Alternative Therapies in Patients with Lateral Epicondylitis: IMPROVE Trial).[45]

Achilles tendinopathy

Results for PRP treatment of Achilles tendinopathy have been mixed. Earlier return to sport by 8 weeks has been observed after local application of platelet-rich fibrin at the time of open repair of complete Achilles tendon tear.[9] However, PRP injection did not improve mechanical properties or functional performance of Achilles tendon up to 1 year after surgical repair of an acute rupture compared with no PRP injection.[46]

For chronic Achilles tendinopathy, case series,[47–53] pilot studies,[54] and retrospective studies[55–57] have reported promising results for the efficacy of PRP injection, with lasting improvements in functional outcomes at 4 years.[58] RCTs, however, demonstrated no significant difference in outcomes of clinical function, tendon healing, or return to sport times at either 6 months[59] or 1 year between PRP and saline control,[60] nor did PRP injection provide a significantly different neovascularization response or ultrasonographically assessed change in tendon structure over 6 months than saline injection did for chronic Achilles tendinopathy.[61]

Meta-analyses comparing various injection therapies for lateral epicondylitis[62,63] and noninsertional Achilles tendinosis[64] revealed no strong evidence for selecting

one injectable over another and indicated large-scale studies are needed before treatment recommendations can be made.

Patellar tendinopathy

Results from case series[49,51,65–67] and retrospective studies[57] have shown promise for PRP injection to improve function in patients with chronic patellar tendinopathy, with lasting effects in functional outcomes at 4 years.[68]

Although a small comparative study did not find the addition of PRP injection to rehabilitation to provide greater pain reduction at 6 months,[69] studies have demonstrated efficacy of PRP for treating patellar tendinopathy, with superior 1-year outcomes compared with extracorporeal shockwave therapy.[70–72]

In an RCT, US-guided PRP injection administered with dry needling accelerated recovery from patellar tendinopathy relative to dry needling alone, but benefits to pain and function dissipated after 3 months, occurring without any significant improvement in quality of life.[73]

Application of PRP to patellar tendon harvest sites for ACL reconstruction was found in RCTs to provide significant reduction in postoperative pain, greater donor patellar tendon healing at 6 months,[74] and greater function at 12 months.[75]

Rotator cuff tendinopathy

Studies of augmentative PRP use alongside rotator cuff repair have been of variable quality and have shown mixed results:

- Following initial safety studies,[76] early, underpowered studies demonstrated no significant benefit to pain or function of PRP augmentation during arthroscopic rotator cuff repair.[77,78]
- Intraoperative local application of autologous PRP to the arthroscopic repair site of complete rotator cuff tears has been associated with significantly less pain within the first postoperative month and greater strength within the first 3 months compared with standard repair alone, with benefit more pronounced for less extensive tears;[79] however, benefits to pain, function, and healing integrity were not found to endure beyond a year for small, moderate,[80] or complete[81–83] rotator cuff tears.
- PRP improved repair integrity for large tears without an associated greater improvement in function[84] and had lower rates of re-tears for small to large tears at 1 year.[79,80,84,85]
- Other studies have demonstrated not only no significant benefit of PRP, but also possible negative effects on rotator cuff healing.[83,86] Platelet-rich fibrin injection during arthroscopic rotator cuff tendon repair was associated with a greater persistence of rotator cuff tendon defect at 3 months.[83] Similarly, PRP injection with arthroscopic acromioplasty in patients with chronic rotator cuff tendinopathy was associated with reduced cellularity and vascularity and increased levels of apoptosis in tendons at 12-week follow-up.[86]

For principal treatment of chronic rotator cuff tendinopathy, PRP injection was no more effective than autologous whole blood by 1 year, but significantly more effective than dry needling by 6 months, in improving pain, disability, and shoulder range of motion.[87,88]

Ligament

Anterior cruciate ligament reconstruction

Several studies of PRP applied during anterior cruciate ligament (ACL) reconstruction demonstrated no benefit to postoperative functional scores. Intraoperative application of PRP during ACL reconstruction using hamstring tendon grafts improved graft

maturation[89,90] and anteroposterior knee stability at 6 months[91] but was ineffective in preventing femoral or tibial bone tunnel enlargement[89,92] and improving postoperative functional scores at 15 months.[93] PRP improved maturation of bone-patellar tendon-bone allografts,[94] but did not improve clinical function or biomechanical properties of these grafts at 24 months.[95] PRP application has been inconsistently shown to accelerate graft-to-bone incorporation, ranging from being ineffective for osteoligamentous integration,[89,96,97] to improving healing,[98] reducing edema, increasing vascularity at the bone-graft interface,[99,100] and reducing time for the graft to achieve a "ligamentous-like" MRI signal by 48%.[101] Significantly less swelling and inflammation have been associated with use of PRP without leukocytes to augment ACL reconstruction.[102]

Medial collateral ligament

Presently, there is no strong evidence to support the efficacy of PRP injections for treating medial collateral ligament (MCL) lesions in humans. A case report described favorable outcomes in managing a high-grade acute MCL lesion using PRP treatment.[103] A small study showed PRP augmentation of arthroscopic meniscal repair did not improve reoperation rates or accelerate return to activity.[104]

Plantar fasciopathy

Early cohort studies have reported the benefit of PRP injection on improving pain,[105] function,[106] and tissue structure[107] for chronic plantar fasciopathy.

RCTs have compared PRP with conventional treatments. A most recent double-blinded RCT showed that PRP was as effective as or more effective than corticosteroid injection when compared with normal saline control to reduce pain over 3 months of follow-up and improve functional scores for chronic plantar fasciopathy.[108]

Multiple prior studies have compared the efficacy of PRP and corticosteroid without a placebo control and showed variable results, ranging from PRP providing greater early pain reduction and functional improvement[109,110] with lasting effects at 1[111] and 2 years of follow-up,[112] to being equally effective at 3 months[113] and at 6 months,[111,114] to being less effective in reducing pain at 3 months.[115]

A single-blinded RCT showed PRP was as effective as prolotherapy at reducing pain and improving function at 6 months for plantar fasciopathy.[116]

Further trials showed PRP was as effective as extracorporeal shockwave therapy at improving pain and functional outcomes beyond conventional therapy for plantar fasciitis.[117]

Ankle sprains

A double-blinded RCT comparing the injection of PRP and saline placebo in addition to standard therapy for severe ankle sprains showed no statistically significant difference in pain and function outcomes between groups over 30 days of follow-up.[118]

A separate study comparing the addition of US-guided PRP injection to rehabilitation to treat anterior inferior tibiofibular ligament tears from high ankle sprains in elite athletes showed PRP accelerated return to sport by nearly 3 weeks, improved joint stability, and reduced residual pain.[119]

Ulnar collateral ligament

A case series described favorable outcomes from PRP treatment of partial ulnar collateral ligament tears of the elbow.[120]

Muscle

Following case reports describing the promise of PRP injection for muscle injuries,[121] a small, randomized, nonblinded study demonstrated US-guided PRP treatment for acute muscle injuries (thigh, shoulder, foot, and ankle) compared with conservative therapy provided greater reduction of early pain, improvement of range of motion, and earlier return to sport.[122]

Hamstring

Acute hamstring injury is one of the most common types of muscle injury affecting athletes, resulting in loss of competition time.[123,124] A single-blinded RCT demonstrated PRP significantly reduced pain intensity over 10 weeks and accelerated return to sport by 16 days for acute hamstring partial tears.[125]

Larger, double-blinded RCTs, however, showed PRP injection provided no significant benefit. A single PRP injection in combination with intensive rehabilitation provided no significantly greater benefit when compared with intensive rehabilitation alone to accelerate return to sport, improve muscle strength, or influence reinjury rates after 2 and 6 months in athletes following an acute hamstring injury.[126]

Similarly, US-guided intramuscular injection of PRP compared with saline, both combined with a rehabilitation program, for acute hamstring injury showed no significant difference between groups in reinjury rate at 2 months or 1 year or return to sport at 6 months[127] or 1 year.[128]

Gastrocnemius and rectus femoris

Injection of autologous PRP in combination with standard conservative care compared with standard care alone for gastrocnemius and rectus femoris muscle tears with hematoma did not significantly improve healing.[129]

Cartilage

Although few studies have been published on use of PRP for management of hip and ankle arthritis, several trials have focused on PRP use for knee arthritis.

Knee

Several trials have suggested the efficacy of PRP to improve functional outcomes for mild knee osteoarthritis (OA).[130–140] Overall findings from RCTs have been unable to consistently demonstrate the superiority of PRP over traditional approaches. Comparative trials have demonstrated that autologous PRP intra-articular injections have greater efficacy than hyaluronic acid injections in reducing pain and recovering articular function,[141–143] especially for younger patients and milder knee OA,[144–146] with one study showing benefit of PRP even for grade 3 knee OA.[147] Others have shown inconsistent superiority of PRP over viscosupplementation.[136] In an RCT with 1-year follow-up, PRP was not superior to viscosupplementation for knee OA, with diminishing benefit beyond 9 months.[148,149]

No difference in outcomes for pain and function came from having a single or a double injection of PRP, but both provided superior outcomes compared with saline control.[150] Another study demonstrated superiority of PRP compared with viscosupplementation only when multiple PRP injections were used.[146]

PRP was shown to be superior to steroid injection for knee OA.[151]

Adverse effects have been minor, with leukocyte-rich PRP associated with increased pain and swelling relative to leukocyte-poor PRP.[23]

Hip

Two case series demonstrated the safety and promise of PRP injection for treating hip OA,[152] but with time-dependent benefit and nonsuperiority over viscosupplementation.[153,154]

Ankle

A small, prospective study comparing the efficacy of PRP injection to viscosupplementation for talar osteochondral lesions proved PRP to be significantly more effective in controlling pain and re-establishing function.[155] PRP injection was shown, similarly, to provide clinical improvement for low-grade ankle OA[156] and as an adjunct to arthroscopic microfracture surgery for treating osteochondral talus lesions.[157]

Meniscus

Few studies have evaluated the use of PRP for meniscal applications. A small retrospective study demonstrated the promise of PRP injection to relieve pain, facilitate return to sport, and halt progression of injury over 6 months for intrasubstance, grade 2, knee meniscal lesions.[158] A clinical trial reported PRP augmentation of open meniscal repair improved outcomes compared with open repair alone.[159]

Future Work

Questions remain as to the proper preparation, dosing, and timing of PRP. There is need for future studies to have better randomization and blinding procedures, larger sample sizes, adequate and consistent descriptions of preparation and injection techniques, radiographic data to provide additional objective data for analysis, standard postinjection rehabilitation protocols, longer-term follow-up of at least 2 years, and standard functional outcome scores. Further studies comparing leukocyte-rich to leukocyte-poor PRP are needed.

PATIENT SELECTION AND PREPROCEDURE COUNSELING

Consultation

During the initial consultation, a thorough history of the current injury should be obtained, including pain onset, duration, and quality. A past medical history and current medication list should also be obtained to identify any contraindications to PRP treatment. It is vital to confirm the clinical diagnosis by physical examination and diagnostic workup. Imaging modalities such as MRI, computed tomography, and/or musculoskeletal US should be performed as needed. If uncertainty remains, a diagnostic injection with a local anesthetic like 1% lidocaine may be performed to determine whether symptoms from a potential pain generator are temporarily alleviated. A response to this diagnostic procedure can suggest a potential positive clinical response to PRP.

Furthermore, it is crucial to review prior treatments to identify standard care options that remain to be explored and offered before, along with, or instead of PRP therapy. Therapeutic options may include activity modification, oral and/or topical analgesics, focused PT, orthoses/bracing, alternative injection-based therapies (eg, corticosteroids, hyaluronic acid), and even surgery in some cases. It is not uncommon to repeat standard therapies tried previously for various reasons. For example, a patient's time constraints, goals, or preferences may warrant a repeat corticosteroid injection or course of PT. In some cases, the severity of the condition may indicate surgical intervention as the best option to pursue.

Selection Criteria

Indications

Different clinics may vary in their preference for and experience in using PRP. In some Sports Medicine practices, PRP therapy may be commonly reserved for second-line treatment of chronic conditions like tendinopathy or refractory OA of large joints that have failed first-line conservative management, which may have included activity modification, PT, analgesics, complementary therapies, and steroid injections. Less frequently, PRP may be administered for acute myotendinous injuries. Indications for consideration of PRP can include the following:[7]

1. Pain duration greater than 3 to 6 months that averages higher than 4 on a 0 to 10 visual analog scale.
2. Physical examination, diagnostic imaging, and diagnostic procedures confirming clinical suspicion of tendinopathy, OA, and/or myotendinous injuries.
3. Symptoms refractory to standard conservative care (activity modification, NSAIDs, PT).
4. Patient goals to prolong or avoid surgical intervention.
5. Anticipated recovery time consistent with patient's timeline to return to activity.
6. Patient is dedicated to commit to a postinjection course of PT of at least 6 weeks.

Contraindications

Medical contraindications that warrant caution or avoidance of PRP therapy may include blood dyscrasias, current infections being treated by antibiotics, use of antiplatelet agents, and use of systemic immunosuppressant medications such as oral glucocorticoids. Non-medical contraindications may include being unable to tolerate injection therapies, commit to a PT program, or afford to undergo a potential series of injections.

Patient Education and Counseling

The patient should be informed that PRP injections for musculoskeletal injuries are currently not covered by the Centers for Medicare and Medicaid Services and most medical insurance companies; therefore, the patient should expect to pay "out of pocket" for PRP therapy. Notification of cost at the initial consultation is important because multiple injections may be needed to obtain a desirable clinical outcome.

Because PRP is not considered the standard of care, it is important to educate the patient on evidence from clinical studies that support its use, the variability of outcomes to expect, as well as the variables that can potentially influence response to PRP treatment, including duration of symptoms, injury severity, medical comorbidities, sports participation, and activity level. Although no significant adverse effects have been reported from PRP, patients should be informed that they may experience temporary local discomfort or pain, lasting up to a week, following an injection.

The procedure of preparing and administering PRP should be thoroughly explained. PRP may not be the most appropriate therapy to pursue for a patient who is "needle phobic" because it involves venous blood draws to collect whole blood and potentially multiple PRP injections.

It is common to recommend courses of PT before and after PRP injection to maximize therapeutic effect; therefore, a patient is considered a better candidate for PRP if they can commit adequate time for PT. Athletes, however, require further counseling on the need for postprocedural activity restrictions and sufficient time off from play to allow for optimal recovery and to avoid reinjury by returning to sport too soon.

Postinjection recommendations entail avoiding the use of NSAIDs for 2 to 6 weeks after the procedure. Although no studies have investigated the effect of taking NSAIDs

following PRP injections, the theoretic concern involves the capacity of NSAIDs to alter the inflammatory phase of the healing process.[160] Over-the-counter acetaminophen is recommended as an alternative to NSAIDs for postprocedural analgesia.

APPLICATION OF PLATELET-RICH PLASMA

Specifics and Logistics

Studies have shown the best time for PRP injections is 3 to 6 months after injury, with repeat administrations ranging between 2- and 8-week intervals. The efficacy of multiple injections is under investigation, with some studies showing no significant difference in outcomes between single and double injections for knee OA,[150] and others demonstrating the superiority of multiple injections for knee OA[146] and patellar tendinopathy.[72] By alleviating pain and increasing activity tolerance, PRP allows for earlier return to sport and activity by 2 to 3 weeks, compared with no PRP injection (**Box 1**).[7]

Preparation

The numerous names and preparation methods used in studies for this biologic treatment, such as PRP, autologous conditioned plasma, and platelet lysate, as well as newer methods of production, such as preparation rich in growth factors,[161]

Box 1
Clinical use of platelet-rich plasma injections

Indications for PRP therapy

Tendinopathy: lateral and medial epicondyle tendons, rotator cuff, hip girdle, peroneal tendon

Chronic pain and OA: knee, ankle, foot, shoulder, hip

Chronic ligamentous injury and pain: ankle, knee, hip, sacroiliac joint, plantar fascia

Muscle tears

Consider PRP therapy if the following conditions are met:

History:
- Duration of pain >3 to 6 months and is on average >4 on a 0 to 10 visual analog scale
- Signs and symptoms consistent with tendinopathy or muscle or ligamentous injury
- Pain persists despite standard conservative treatments

Workup:
- MRI or US evidence of tendinopathy or muscle or ligamentous injury
- A diagnostic bupivacaine injection was successful

Patient factors:
- No contraindications
- Patient is pursuing a nonsurgical solution and has time to be out of play for about 4 weeks

Contraindications to PRP therapy

Immunocompromised state

Active infection

Inability to comprehend or comply with postprocedure instructions for activity modification

Coagulopathy or anticoagulation, international normalized ratio greater than 2.5

Patients with prosthetic joints

Prosthetic hardware infection

Severe cases of advanced OA

platelet-rich fibrin matrix,[162] simplified buffy coat method, and platelet-rich fibrin,[163] reflect the complexity and diversity of this therapy and the challenges in translating findings from clinical trials to clinical practice.[2] Ongoing efforts strive to elucidate the influence of PRP preparation methods and formulation characteristics on growth factor release, biologic effect, and therapeutic outcomes.

Validation studies have shown that PRP cellular composition and biomolecular characteristics vary according to the preparation protocol[164,165] and system used.[162,166–171] Preclinical investigations suggest PRP preparation methods additionally affect growth factor release kinetics and efficacy, with significant differences between classic PRP and second-generation preparations like platelet-rich fibrin.[172–179] Furthermore, PRP biologic activity is known to diminish with storage time.[180]

Regarding platelet content, the clinical literature has commonly suggested using platelet concentrations 4 to 6 times greater than that in whole blood for PRP. Concentrations greater than an optimal amount may provide no additional effect or even inhibit healing.[18] In vitro studies have shown that 1.5×10^6 PLT/μL was optimal to promote human umbilical vein endothelial cell proliferation, motility, and morphology, with greater concentrations causing inhibition.[181] A range of 0.5 to 1.5×10^6 PLT/μL was optimal for normal human dermal fibroblast proliferation, motility, and wound healing.[182] Tenocyte function plateaued by a concentration of 2.0×10^6 PLT/μL, beyond which no greater benefit to function was achieved.[183]

The superiority of leukocyte-poor or leukocyte-rich PRP has been investigated given concern over the proinflammatory effects of leukocytes and their inhibitory effect on tissue healing.[184] Although interaction between mononuclear cells and platelets results in greater anabolic growth factor release and cellular effect,[185,186] high leukocyte concentrations (>21,000/μL),[16] especially of neutrophils, result in greater release of proinflammatory and catabolic substances[187,188] that is independent of the ratio of platelets to leukocytes,[17] produce an acute inflammatory response,[16] and increase synoviocyte cell death,[15,16] suggesting leukocyte-poor (<1000/μL) PRP is a better option. The optimal concentration of leukocytes and ratio of leukocytes to platelets to have in PRP, however, remain unknown.

Most preparation methods minimize the RBC content in PRP, with concentrations of less than 1000/μL reported.[16]

The role of activation further contributes to variations in growth factor release[28] and has been shown to lower the platelet concentration required to reach a plateau in

Table 3
PLRA classification system

PLRA Classification	Criteria	
P: Platelet count	____P Volume Injected	____M Cells/μL
L: Leukocyte content[a]	>1%	+
	<1%	–
R: Red blood cell content	>1%	+
	<1%	–
A: Activation[b]	Yes	+
	No	–

[a] If white blood cells are present (+), the percentage of neutrophils should also be reported.
[b] The method of exogenous activation should be reported.
Adapted from Mautner K, Malanga GA, Smith J, et al. A call for a standard classification system for future biologic research: the rationale for new PRP nomenclature. PM R 2015;7(4 Suppl): S53–9.

Table 4
Post-PRP and BMAC Rehabilitation Protocol – PT Version

Phase	Length of Time Post Injection	Restrictions	Rehabilitation
Phase I GOALS: Protect tissue; allow PRP to absorb	Days 0–7	• Doctor may recommend using crutches or walking boot for lower extremity procedures; braces, slings or splints for upper extremity procedures. • No exercise, with exception of this rehabilitation protocol. • If you had an upper extremity injection, no lifting more than a toothbrush. • Avoid NSAIDS (Ibuprofen, Aleve, Advil, etc.). • You may take Tylenol (up to 2500 mg/day) or prescribed medications (Tramadol, Oxycodone, Percocet or Vicodin) for pain after this procedure. • Avoid ice. • Use heat after injection as needed to help with pain control. • You may take a light shower on the same day after the injection. Avoid a hot tub bath or swimming. • You may have driving restrictions for up to 1 wk after your injection	• Pain is expected after your procedure. • Daily activities as tolerated within your provided device; avoid excess loading or stress to treated area. • Gentle movement of the extremity (active range of motion) out of immobilizing device. • Avoid exercise unless approved by your doctor. *PT protocol:* Gentle AROM. If shoulder was injected, PROM to point of tissue resistance. Gentle submax Isometrics. WB restrictions: Foot/Ankle – boot and WBAT with crutches Knee – immobilizer, WBAT with crutches Hip – WBAT with crutches Shoulder/Elbow – sling Wrist –splint May initiate use of modalities for pain management and symptom control: non-thermal ultrasound, cold laser, E-stim.

Phase II GOALS: Protect tissue; start early movement; wean off immobilizing device PT protocol: Facilitate collagen deposition; avoid disruption of collagen crosslink	Days 8–14	• Progress to full weight bearing without protective device. • Gradually progress active range of motion without feeling stretching sensation. • No overstressing of the tendon through exercise or impact activity. • If you had an upper extremity injection, no lifting more than a coffee cup. • Avoid NSAIDS and ice.	• Continue Phase I Rehabilitation recommendations. • Consult your physical therapist regarding cross-training and return to exercise options (initiating exercise to upper body if you had a lower body injection or exercise to lower body if you had an upper body injection). *PT protocol:* Continue Phase I exercises. Gradually progress AROM to point of initial tissue resistance. No concentric exercises to affected tissue outside ADLs and ambulation. May continue to utilize modalities for symptom control: non-thermal US, cold laser, Russian E-stim. Initiate appropriate cross training exercises.
Phase III GOALS: Protect tissue; continue gentle movement; minimize deconditioning PT protocol: Facilitate collagen deposition; avoid disruption of collagen crosslink	Days 15–21	• Gradually progress active range of motion without feeling stretching sensation. • No overstressing of the tendon through exercise or impact activity. • If you had an upper extremity injection, no lifting more than a dinner plate. • Avoid eccentric exercises (this is the part of exercise when the weight is being lowered). • Avoid NSAIDS and ice.	• Pain with daily activities should be improving. • Consult your physical therapist regarding initiating low resistance exercises. *PT protocol:* Progress AROM to point of initial tissue resistance. Avoid tissue strain with ADLs and exercises. Avoid repetitive use of stairs if lower extremity was injected. Initiate low resistance, high repetition, concentric, open chain exercise (pain should not increase more than 2 points on 11 point VAS). No eccentric exercises to affected tissue. Gentle soft tissue mobilization along the line of the fibers of injected tissue. May continue to utilize modalities for tissue proliferation: non-thermal US, cold laser, Russian E-stim.

(*continued on next page*)

Table 4
(*continued*)

Phase	Length of Time Post Injection	Restrictions	Rehabilitation
Phase IV GOALS*:* Restore normal tissue integrity; improve range of motion PT Protocol: Reparative phase: tissue proliferation; stimulate collagen lay-down in organized fashion	Weeks 3–6	• Progress as tolerated. • Avoid NSAIDs and ice.	• Consult your physical therapist regarding initiation of eccentric exercise, proprioceptive training, preparation for plyometrics and sport-specific exercises. *PT Protocol:* Full AROM. OK to initiate stretching. Initiate and gradually progress eccentric loading exercises. Initiate cross friction soft tissue mobilization to injected tissues. Progress exercises and functional mobility. May continue to utilize modalities for tissue proliferation: non-thermal US, cold laser, Russian E-stim. If patient is not experiencing improvement or making expected progress by the end of this phase, contact referring MD.
Phase V GOALS: Restore normal tissue integrity; prepare for return to prior level of function and sport PT Protocol: Strengthening, Function, and Sport-Specific Training Phase	Weeks 6–12	• With sport-specific training, keep level of intensity: ○ Below 50% effort up to week 8 ○ Below 75% effort up to week 10 ○ Below 90% effort up to week 12 • Do not return to contact sport prior to week 10.	• Prepare for return to sport at 6–12 wk. • Consult your physical therapist regarding progression of eccentric exercise, proprioceptive training, plyometrics and sport-specific exercises. • Sprinting can begin after week 10 at 75% effort. • Patient should be at 100% effort with sport-specific training at the completion of this phase.

If you had a PRP injection to a ligament, the following protocol may be delayed 2-4 weeks due to decreased blood supply in ligaments.

Credits Podesta L, Honbo E. Clinical Applications for Platelet Rich Plasma Therapy. In: Rehabilitation for the Postsurgical Orthopedic Patient. 3rd edition. St Louis (MO): Elsevier Health Sciences; 2013. p. 171–92; Mautner K, Mason RA. Post PRP & Stem Cell Rehabilitation. Emory Sports Medicine Center. Accessed January 20, 2015; University of Wisconsin Health Sports Rehabilitation. Platelet-Rich Plasma Rehabilitation Guidelines. 2014. Available at: http://www.uwhealth.org/sports-medicine/physical-therapy-athletic-training/sports-medicine-rehabilitation-guidelines/20398. Accessed 2014.

tenocyte proliferation from 2.0 × 10^6 PLT/μL to 4.0 × 10^5 PLT/μL.[183] Thrombin and calcium have a dose-response effect on growth factor release from platelets, with higher concentrations leading to immediate and significantly greater anabolic growth factor release, and lower concentrations leading to delayed and reduced release.[189] Compared with thrombin, collagen activation results in a more sustained growth factor release.[190] Although activation can accelerate growth factor release, this may not be ideal to optimize therapeutic effect, as thrombin-activated compared with unactivated PRP has been shown to be less effective for wound healing.[11]

PLRA Classification System

The lack of standardized protocols for PRP preparation and the subsequent interproduct variability among PRP formulations[191] contribute to variability in clinical outcomes. The inconsistent and insufficient quantification of PRP components in clinical studies further contributes to confusion over results. The lack of accepted standards for reporting PRP in research has limited the interpretation of data, comparison of results, translation of findings to clinical practice, and progress of further investigations, prompting classification schemes to be developed to clarify use and communication of PRP therapy. Earlier classification schemes were proposed, including those by Dohan Ehrenfest and colleagues,[192] DeLong and colleagues,[24] and Mishra and colleagues,[27] but none were widely adopted nor do they now adequately capture all of the PRP attributes that may affect efficacy based on current knowledge.

Most recently, in 2015, Mautner and colleagues[26] proposed the PLRA classification, a new standard reporting system for PRP, which accounts for platelet count, leukocyte presence, RBC presence, and activation. Recommendations are to document the following when reporting PRP treatments: (1) concentration of platelets, total number of platelets, and injected volume delivered to a target tissue; (2) concentration of leukocytes, and if present, the percentage of neutrophils; (3) concentration of RBCs; and (4) type of exogenous activation applied, if used (**Table 3**).

Postprocedure Rehabilitation Protocol

PRP administration is recommended to be accompanied by a postprocedure rehabilitation and PT program that gradually incorporates range-of-motion exercises and weight-bearing to avoid reinjury (**Table 4**).[193]

SUMMARY

This is an exciting era for regenerative sports medicine. We are beyond infancy and now toddling as we strive to optimize platelet-based therapies. Research on PRP continues to advance. Presently, moderate-quality evidence supports the use of PRP for lateral epicondylosis and knee OA. Low-quality evidence suggests safety and benefit of PRP for ankle and hip OA; patellar and Achilles tendinopathy; and injuries of the ulnar collateral ligament of the elbow, ankle ligaments, and possibly medial meniscus. For the next phase of advancement, further investigations are needed to optimize platelet dosing, cellular composition, and postprocedure rehabilitation protocols for PRP. Patient physiologic and genetic factors that influence response to treatment should also be considered and investigated. Precise outcome measures as well as follow-up over years, not weeks to months, are required to accurately evaluate efficacy. PRP is a therapy for and investment in long-term connective tissue health and should not be regarded as a short-term pain management strategy. Until research consistently accounts for and measures this scope of therapeutic benefit, results will likely continue to mislead and frustrate.

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