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Narrative Review

Platelet Rich Plasma in Musculoskeletal Pathology: A Necessary Rescue or a Lost Cause?

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Background: Platelet rich plasma (PRP) has been used for decades to facilitate surgical tissue repair; therefore, the current trend of percutaneously injecting PRP to theoretically enhance tissue regeneration and repair is a logical progression. Applications include treatment of osteoarthritis, tendinopathy, chondropathy, acute and chronic soft tissue injuries, muscle or ligament tear, as well as enhancement of healing after bone or tissue reconstruction. However, there is limited evidence to support the use of PRP in the abovementioned conditions. Variations in the preparation of PRP and its application in various conditions influence its effect on various orthopedic conditions.

Objective: To provide a basic overview of the current use of PRP in treating musculoskeletal conditions.

Methods: Studies relevant to PRP were extracted from the PubMed and Medline database within the dates ranging from 1990 through 2015. These studies included in vitro as well as in-vivo animal experiments and careful analysis of the study population, type of intervention, and outcomes was made.

Results: PRP has been noted to be a beneficial solution for tissue healing based on limited current literature. However a variety of factors such as method of preparation, composition, medical condition of the patient, anatomic location of the lesion, and tissue type can alter outcome.

Conclusion: The effectiveness and potential adverse effects of this treatment require high quality studies prior to widespread clinical application.

Key words: Growth factors, platelet rich plasma, regeneration, regenerative healing, tissue repair, stem cells, mesenchymal stem cells, tissue engineering

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An increasing number of physicians believe that localized injection of platelet-rich plasma (PRP) is an effective treatment for various musculoskeletal disorders. Proponents consider PRP as a bridge between conservative modalities and invasive surgical interventions. PRP has been used for decades to facilitate surgical tissue repair; thus, a percutaneous injection of PRP for theoretically enhancing tissue regeneration and repair is a logical progression. PRP is applicable in the treatment of osteoarthritis, tendinopathy, chondropathy, acute and chronic soft tissue injuries, and muscle or ligament tear. It is also used to enhance healing after bone or tissue reconstruction. However, there is limited evidence to

support its use in these conditions.

This article provides an overview of the use of PRP for treating orthopedic conditions, explores the prevalence of level I clinical evidence, and concludes that although PRP is an attractive and promising treatment modality, further studies on its quality, safety, and efficacy are required.

Pathophysiology

The proposition that PRP is an effective treatment modality is based on evidence that PRP enhances and expedites the wound-healing process (1,2). This process can be divided into inflammatory, proliferative (repair), and maturation (remodeling) phases. The typically painful inflammatory phase begins in the first week after injury and is initiated by the lysis of cells that release debris and inflammatory mediators such as kinins and prostaglandins. First, platelets aggregate to form a fibrin matrix that facilitates hemostasis. The aggregated platelets degranulate, releasing cytokines that attract leukocytes. Neutrophils are the first cells to eliminate bacteria and cellular debris. Growth factors released from activated and degranulated platelets attract macrophages and fibroblasts. Vasodilation follows the activation of cyclooxygenase-2.

Typical processes that occur within the 2 weeks of the proliferative phase include phagocytosis by macrophages that further cleanse the wound; however, fibroblasts fill the wound with granulation tissue and promote neovascularization. Three months post injury, the remodeling phase is characterized by healing through the production of collagen and scar tissue. Type I collagen replaces proteoglycan and fibronectin to form a matrix with increased tensile strength. Soft tissue or tendon healing occurs through angiogenesis, cell proliferation, deposition of extracellular matrix (ECM), remodeling, and maturation. Various growth factors stimulate tissue repair and play important roles in cell regulation, differentiation, proliferation, chemotaxis, and matrix synthesis (1,3).

Table 1. *Growth factors involved in wound healing.*

IGF-1	• Early inflammatory phase • Anabolic effects • Protein synthesis, proliferation of myoblasts and fibroblasts • Enhances collagen and matrix synthesis • May modulate swelling
TGF-β	• Proinflammatory • Immunosuppressant during inflammatory phase • Aids cell migration and fibronectin binding • Augments production of tendon sheath fibroblasts, expression of type I and III collagens • Improves tendon mechanics during healing • Controls angiogenesis and fibrosis
PDGF	• Early phase of tendon damage • Facilitates proliferation of other growth factors • Attracts stem cells and white blood cells • Stimulates angiogenesis • Contributes to tissue remodeling
VEGF	• Expression peaks after the inflammatory phase • Promotes angiogenesis–neovascularization
b-FGF	• Appears to stimulate angiogenesis • Mediates cell migration • Stimulates proliferation of capillary endothelial cells • Influences fibroblasts to produce collagenase • Enhances angiogenesis • Contributes to production of granulation tissue

Nguyen RT, Borg-Stein J, McInnis K. Applications of platelet rich plasma in musculoskeletal and sports medicine. An evidence-based approach. *PMR* 2011; 3:226-250 (4).

Roles of Growth Factors

Growth factors released from the α granules of aggregated platelets play critical roles in mediating healing. These growth factors bind to specific high-affinity transmembrane receptors to trigger intracellular signaling pathways. Some of the key growth factors involved in this process are insulin-like growth factor (IGF)-1, transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (b-FGF), hepatocyte growth factor, and epidermal growth factor. Furthermore, various cytokines, chemokines, and metabolites supplement the action of growth factors. The dense granules of platelets also release serotonin, adenosine, dopamine, calcium, histamine, adenosine diphosphate, adenosine triphosphate, and catecholamine.

Growth factors influence chemotaxis and cell migration via chemical mediators as noted in Table 1 (4). Furthermore, they induce mitosis, contribute to the production of extracellular matrix, and mediate angiogenesis that promotes proliferation, maturation, differentiation, and ultimately repair (4,5). During wound healing, activation and migration of various cell types such as mesenchymal stem/stromal cells present in wounds play an integral role along with native tissue (6).

Biological Effects of PRP

PRP has been used since the early twentieth century in veterinary medicine as well as to manage der-

matologic and oromaxillofacial conditions. The interest has grown exponentially pertaining to its use in orthopedic applications such as bone formation, soft tissue injury, and as an adjunct to surgical reconstruction. PRP is the term used when a sample of autologous blood has concentrations of platelets above baseline values. PRP is prepared from anticoagulated whole blood using plasmapheresis, which generates the PRP solution through a 2-phase centrifugation process that separates liquid and solid components. Thus, a platelet will settle proportionally slower and better in a test tube than the larger red blood cells (RBCs) that settle at the bottom or white blood cells (WBCs) that settle between the red blood cells and the platelets. The first phase comprises a "soft" spin that separates plasma and platelets from RBCs and WBCs. The second phase, or "hard" spin, is performed to further concentrate and separate the platelet-rich and platelet-poor plasma components. This step is controversial because it is not implemented in some commercial formulations. Furthermore, the potential beneficial effects of platelet-poor plasma on tissue healing are unknown (3,4).

To create PRP, whole blood is most often collected in the presence of an anticoagulant, which binds calcium and prevents the initiation of the clotting cascade by inhibiting the conversion of prothrombin to thrombin (7). PRP can be produced as well in the absence of an anticoagulant, although the time required between blood draw and PRP injection must be significantly shortened. Although several anticoagulants are available, acid citrate dextrose-A and citrate phosphate dextrose have been shown to maintain the structural and functional integrity of platelets (5). Amaral and colleagues (8) recommend sodium citrate for platelet recovery due to its property of higher platelet recovery after the blood first centrifugation step and a minimal change in mesenchymal stem cells (MSC) gene expression.

PRP contains other cell types that potentially benefit tissue healing. WBCs such as monocytes and polymorphonuclear neutrophils may trigger localized inflammation. Although some investigators believe that this inflammatory effect is critical to the tissue repair process, neutrophils were shown to impede healing as well as contribute to increased post-injection soreness. The inclusion of WBCs in PRP preparation varies depending on the indication.

Proteins such as PDGF, VEGF, endothelial cell growth factor, and b-FGF2 can be detected at high concentrations in PRP; consequently, many investigators postulated that PRP may be beneficial for tissue healing. Moreover, local placement of PRP gel can lead to a systemic inductive effect that induces a transient increase in serum levels of IGF-1, VEGF, and b-FGF2 (9).

Although the plasma levels of these growth factors were evaluated for 96 hours after a single injection of PRP, no correlation has been established between the plasma levels and the intensity and duration of effect (10). Conversely, other proteins present in PRP demonstrate inhibitory effects, including TGF-β1, which may lead to variable clinical results in certain applications. Although growth factors are key components that mediate tissue healing and regeneration, their exact activities in situ are unknown.

Variations in Preparation, Applications, and Effects of PRP

Not all PRP preparations are equivalent. Variations in the volume of whole blood, concentration of platelets in plasma, volume of PRP, the presence or absence of RBCs or WBCs or both, the addition of thrombin or calcium chloride to activate platelets, and differences in pH can affect the potency of PRP preparations. At least 40 commercial systems claim to segregate and concentrate various components of whole blood (11). Because these systems vary in growth factor concentrations, presence or levels of RBCs and WBCs and utilize methods that carry different platelet recovery efficiency, it is difficult to determine their relative efficacy. Moreover, because of this variation in addition to operator variability, the success or failure of a specific PRP or PRP-related product for a specific pathology cannot be universally applied to all PRP products. This limits the interpretation of the available data and its ability to draw a meaningful conclusion.

Unlike prescription drugs, whose quality, efficacy, and consistency are set by the United State Pharmacopeial Convention and are enforceable in the United States by the Food and Drug Administration, PRP-related products are not subject to oversight; therefore, they have no such guarantees. It is incumbent upon anyone using a specific PRP product to understand its precise formulation and consistency as well as the rationale for the technique used in its production and application. The lack of standardization and quality control in addition to the diverse applications of PRP and outcomes, make it difficult to generate convincing data.

According to a web-based search on PRP that yielded 44 articles, 26 unique articles met the inclusion criteria (12). For example, 20 of these 26 articles made

inappropriate statements regarding evidence, treatment, efficacy, or safety of PRP injections. Moreover, 23 articles discussed only perspectives of physicians favoring the treatment. Eight articles discussed alternative treatment options and 22 used individual dramatized patient experiences to demonstrate efficacy. Nineteen articles made unsubstantiated promises regarding health outcomes of PRP injections. Many internet sites accessed represented medical practices or institutions where PRP therapy was used. The conclusions of this study indicate that some web-based references pertaining to PRP therapy are biased and inaccurate and raise concerns of injudicious use of unproven therapies.

As stated earlier, PRP is classically described as a volume of plasma that has a platelet count above that of whole blood. For clinical use, 4 to 10 times platelet concentration has been described in the literature. After centrifugation, the whole blood separates into a clear plasma layer on top, a buffy coat layer consisting of the WBCs and platelets in middle, and RBCs at the bottom. Although this definition suggests a mixture of plasma and platelets, the generic term "platelet-rich plasma" was recently expanded to include diverse final products. PRP can include any combination of concentrated RBCs, WBCs, and any or all activating factors such as thrombin or calcium chloride (13-15). Because their inclusion may affect the potency and efficacy of the final product, the general term "PRP" does not distinguish between different products and should be more specifically referred to as pure PRP, leukocyte rich PRP (L-PRP), pure platelet-rich fibrin, and leukocyte- and platelet-rich fibrin, etc.

Identifying the optimum composition, if one exists, will require well-designed, prospective, randomized, blinded level 1 clinical studies that comprehensively investigate the efficacies of the various PRP preparations used for connective tissue repair. No single PRP is conclusively superior. Once we understand the precise mechanism of the enhancement of tissue healing mediated by PRP in various applications and ensure the uniformity of composition and potency of the final product, PRP may serve as a useful tool in the armamentarium available for the treatment of the musculoskeletal and orthopedic injuries.

The lack of a validated classification system that identifies crucial differences between PRP formulations makes it difficult to compare studies. Two studies describe attempts to standardize different PRP systems by classifying them according to activation mechanism, platelet number, and/or cell content (16,17). These discussions are paving the way toward a more unified and systematic approach among health care practitioners.

Measurements of platelet and growth factor concentrations are widely used to evaluate PRP (11,18) and different individuals may require different platelet concentration ratios to achieve a comparable biological effect (19). For example, a study compared different PRP kits by producing PRP from blood samples from a single individual and emphasized that a comparison of platelet and growth factor concentrations was required (20). A study on single-donor PRP preparations produced using 7 commercially available PRP separation systems demonstrated wide variations in WBC, RBC, and platelet counts as well as the growth factor concentrations (21).

The concentrations of platelets and growth factors do not exhibit a direct proportional relationship. Kobayashi et al (22) recently demonstrated that leukocyte concentrations could have direct effects on both growth factor and catabolic factor concentrations within the PRP solution. Hsu and colleagues (23) noted that final platelet concentration of any PRP product depends on the initial volume of the whole blood, platelet recovery efficiency of the technique, final volume of the plasma, relative concentration of the blood cells, and the concomitant use of thrombin. This further illustrates the need to examine how different components contained within a particular PRP solution may affect healing responses among varying tissue types, as well as optimization techniques for varying applications.

In addition, a higher concentration or absolute number of platelets within PRP may not necessarily lead to an enhanced effect on tissue healing (23). For example, a study proposed that the most efficacious platelet concentration for tissue healing is 1.5 × 106 platelets/μL (24). Moreover, the dose-response curve is not linear, and a saturation effect occurs that is accompanied by the activation of an inhibitory cascade once a sufficiently high concentration of platelets is achieved. Because platelets can exert the greatest influence on healing during or immediately after the inflammatory phase of an injury, some authors postulate that the timing of the administration of PRP has greater influence on healing than the number of platelet (23,25). Others stress the precise location of injections is the prime factor in determining efficacy.

The timing of PRP injections was studied in a rat model of patellar tendon injury (26). PRP injections were administered to wounded tendons on day 3 or 7 after injury. Tendon segments harvested on day 14

show greater gains in mechanical properties including peak loads and maturation of healing tendons when injected with PRP on day 7 compared with those injected on day 3. These findings suggest that the optimal time for injecting acute tendon injuries is immediately after the inflammatory phase terminates to augment the initiation and progression of the proliferative phase.

The exact role of thrombin in PRP is a subject of debate. Thrombin, calcium chloride, or both are necessary to catalyze the conversion of fibrinogen to fibrin, but they induce platelets to secrete growth factors. However, some data suggest that exogenous thrombin activation of PRP may diminish the ability of PRP to induce bone formation compared with nonthrombin-activated PRP.

PRP injections appear relatively benign and are not associated with performance enhancing drugs. In 2010, the World Anti-Doping Agency (WADA) prohibited the administration of intramuscular injections of platelet-derived preparations. In 2011, the WADA removed platelet-derived preparations from the prohibited list "after consideration of the lack of current evidence concerning the use of these methods for purposes of performance enhancement, current studies on platelet-derived preparations do not demonstrate a potential for performance enhancement beyond a potential therapeutic effect." The WADA plans to monitor ongoing research closely, and further research will likely be required. Further larger studies are required to characterize the variability in the numbers of platelets, WBCs, and RBCs as well as growth factor concentrations in PRP and their influence on the efficacy and longevity of outcomes. Further economic studies evaluating potential cost savings are required to advance the use of PRP in the therapy of orthopedic conditions.

Bone

PRP exerts osteogenic effects (27); however, level I studies do not provide conclusive evidence. A level III prospective study investigated nonunion rates after lumbar posterolateral spine fusion with local bone graft in 67 consecutive patients comprising 34 who were treated with additional platelet glue (28). At the 2-year follow-up, there was no statistically significant difference in the nonunion rate determined from flexion-extension radiographs and fine-cut computed tomography. Similarly, in a retrospective cohort study of 76 consecutive patients who underwent posterolateral lumbar fusion, the nonunion rates at clinical follow-up ≥ 24 months did not differ significantly between iliac crest bone graft plus platelet-gel preparation compared with autologous bone graft alone (9). Furthermore, there is a significantly lower fusion rate using autologous growth factors of PRP and an autograft in single-level posterolateral lumbar fusion compared with iliac crest bone graft alone (29).

Limited clinical evidence demonstrates the beneficial effects of PRP in bone formation and healing applications. Thus, PRP is not efficacious alone or as an adjunct to local bone graft healing in contrast to other studies that report opposite results. For example, in vivo implanted cells treated with PRP exhibit increased proliferation and alkaline phosphatase production (30). Further review of these studies reveal that factors such as platelet concentration and activation method, and type of scaffold that are important in predicting osteogenic outcomes were not uniformly applied in these studies, thereby leading to inconclusive data.

Conversely, PRP is promising for treating osteoarthritis. PRP contains factors that are critical for joint repair, including TGF-β1, thrombospondin-1, and IGF-1 (18). Consequently, PRP was proposed to treat patients with symptomatic cartilage defects or osteochondral lesions. A study of 78 patients with bilateral knee osteoarthritis who were randomized to receive a single WBC-filtered PRP injection, 2 PRP injections at 3-week intervals, or a single saline injection shows that outcomes of the PRP groups are significantly better than those of the control groups 6 months after treatment (31). A randomized controlled trial (RCT) of 120 patients found that outcomes were significantly better 24 weeks after a local injection of PRP compared with those after an injection of hyaluronic acid (32). A randomized clinical trial in 160 patients with Kellegren Lawrence grade 1 – 4 knee osteoarthritis demonstrated better the Western Ontario and McMaster Universities arthris index (WOMAC) and pain scores in both groups but better results in the PRP group compared to the hyaluronic acid group (33). In general, PRP, when administered with scaffold or matrix, has shown better results than the injection of PRP alone; this is also supported by the study demonstrating PRP contained in gelatin dramatically attenuates the progression of early osteoarthritis (34). A recent comparative study in 46 patients with full-thickness cartilage defects of the femur treated with scaffold implantation augmented with bone marrow aspirate concentrate (BMAC) or PRP demonstrated improved cartilage maturation with greater fill and mean T2 values closer to that of superficial native hyaline cartilage at 12 months with BMC

compared to PRP (35).

Another recent study compared PRP injections with hyaluronic acid injections for the treatment of knee osteoarthritis. In this study, Montanez-Heredia et al (36) demonstrated that while short-term pain relieving effects were comparative between the 2 treatments, a greater number of participants in the PRP group had more significant improvements in functionality and maintained these improvements in greater numbers at 3 month post-injection follow-up compared to the hyaluronic acid group. Furthermore, a recent study compared a standard conservative treatment for grades 1 and 2 knee osteoarthritis with oral acetaminophen (APAP) 500 mg q 8 hours (TID dosing) against PRP injections. The PRP group was given a single intraarticular injection of LP-PRP (leukocyte poor PRP) every 2 weeks for a total of 3 injections (37). After 6 weeks of treatment only the LP-PRP group demonstrated increases in quality of life scales in addition to significantly better pain relief. By 24 week follow-up, only the LP-PRP group maintained the increases in quality of life, functional knee improvements, and sustained pain relief (37).

Although preliminary evidence exists, high quality studies are required to formulate conclusions about specific techniques and compositions, degree of pathology, and variations in age of the patient that may alter the efficacy of PRP for the management of osteochondral lesions in osteoarthritis. Moreover, no established guidelines are available to address this issue at this time.

Tendons

Tendon healing is typically characterized by an initial inflammatory response that is associated with the influx of factors such as PDGF and TGF-β within 2 days, resulting in angiogenesis in 2 – 3 days and collagen synthesis in 3 – 5 days. Because PRP contains these critical growth factors, administering PRP in the setting of acute soft tissue injuries may provide enhanced healing, and its utility may be greatest when administered early during healing.

As early as 2005, PRP was shown to increase tenocyte number and vascularity, although accurate alignment and strength evaluation after PRP treatment were not known (2). Contrary to that, Carr et al (38) found that PRP significantly alters tissue characteristics in tendons after surgery with reduced cellularity and vascularity and with increased levels of apoptosis.

A comparison of local injections of a PRP formulation or bupivacaine administered to 20 patients with chronic elbow epicondylar tendinosis revealed significant improvements in clinical outcomes in patients treated with PRP with 93% reduction in pain compared with baseline at an average follow-up of 25.6 months (39). Similarly, a level I study of 100 patients with lateral epicondylitis compared the effects of local injections of PRP with those of injections of corticosteroids and found that a significantly greater reduction in VAS scores is achieved using PRP up to 24 months after injection (40). Comparison of outcomes at 1- and 2-year follow-up examinations demonstrated a steady decline in the clinical scores in the corticosteroid group and maintenance of the scores of the PRP group (40,41). These studies suggest that PRP formulations improve patient outcomes compared with injection of local anesthetic or corticosteroids.

The results of treating other tendinopathies with PRP are not as promising. For example, in a RCT comparing local injection of PRP to saline for Achilles tendinopathy in conjunction with eccentric exercises, no differences in the improvement of clinical outcomes at the 24-week follow-up were observed (42). In a follow-up study, 54 patients diagnosed with chronic Achilles tendinopathy were randomized in a blinded manner to receive injections containing PRP or saline as well as a training program (43). Although the clinical outcomes of patients in both groups improved one year after injection, there was no significant difference in benefit (43). For patients previously treated with cortisone, ethoxysclerol, and/or surgery for patellar tendinopathy, PRP does not confer as much improvement in visual analogue scales (VAS) scores as for patients who did not receive a previous intervention (44).

In conclusion, clinical evidence suggests that local injection of PRP may benefit patients with chronic elbow epicondylitis refractory to standard nonsurgical treatment. However, the benefits of PRP treatment for other chronic tendinopathies are not as clear, and higher quality studies of chronic and degenerative tendinopathies are required.

Muscles

Transforming Growth Factor-beta-1 and Prostaglandin E2 strongly synergize to regulate the level of fibrosis during the repair of muscle injuries, which is an important link in the complete restoration of muscle function (45). Philippou and colleagues (46) demonstrated IGF-1 being the key factor in the healing of tendons and muscle injuries. Furthermore, there is no significant difference in constant and tendon scores

graded using magnetic resonance imaging 16 months after primary arthroscopic rotator cuff repair with or without the use of an autologous platelet-rich fibrin matrix. Thus, PRP does not benefit healing of small to medium-size rotator cuff tears (47). Yang and colleagues (48), through their meta-analysis of 8 studies, demonstrated application of PRP with arthroscopic rotator cuff repair can decrease postoperative pain and promote functional recovery. Moreover, the difference in re-tear rate between the groups at the 9-month follow-up was not statistically significant. A systematic review concluded that PRP does not influence re-tear rates or clinical outcomes after arthroscopic repair (49,50).

Conversely, in a double-blind RCT of 53 patients compared with controls, the intraoperative application of PRP with an autologous thrombin component in the patients during arthroscopic rotator cuff repair increased strength in external rotation, which was measured using a dynamometer 3 months after surgery but not at 6, 12, and 24 months. In grade 1 and 2 tears, the use of PRP led to significantly higher postoperative strength in external rotation scores postoperatively at 3, 6, 12, and 24 months and a lower rate of re-rupture (51). Although there is evidence demonstrating potential benefit, further studies are required to conclusively demonstrate the efficacy of PRP in repairing muscle injuries routinely with surgery.

Ligaments

There was a 73% increase in the strength of repaired tibial collateral ligaments in rats compared with controls 12 days after the application of a combination of growth factors (52). Thereafter, several studies were conducted on anterior cruciate ligament (ACL) injuries both in vitro and in vivo. The maturation of the tendon graft is necessary for optimal biomechanical strength and return of function. Graft maturation is accelerated by PDGF, TGF-β1, and IGF-1 (53). Conversely, the ACL's environment is poorly vascularized and produces synovial fluid containing proteases that prevent fibrin clot formation required for initiating wound healing (54). Therefore, it is important to study the ACL to develop techniques to supply sufficient concentrations of growth factors to accelerate healing.

PRP improves the viability and function of cells residing in the ACL in vitro (55). A prospective study of 50 patients treated with an ACL autograft with or without a PRP gel surgery revealed that the autograft treated using the PRP gel matured twice as fast as the untreated autograft (53). A study of the outcomes of 37 patients who underwent second-look arthroscopies after ACL reconstruction using autogenous hamstring grafts with and without injection of a PRP preparation rich in growth factors demonstrated improvements in graft remodeling and the amount of new connective tissue enveloping the graft as well as increased graft thickness and synovial coverage rating for patients treated with PRP (34).

A level I study of 100 patients with ACLs reconstructed using patellar tendon allografts who were treated with or without a platelet-enriched gel that was sutured into the allograft and applied in the tibial tunnel, found no significant differences associated with the PRP gel (56). These findings are consistent with those of another study that found no difference in patient-reported outcomes or number of additional surgeries at end of 2 years with or without the use of PRP gel (57). The variability in clinical outcomes may be attributed to PRP preparation and centrifugation, graft choice, rehabilitation protocols, and application techniques. Therefore, uniform clinical studies are required to better evaluate the role and benefit of PRP for repairing injuries to the ACL and other ligaments.

The studies quoted per each tissue type are summarized in Tables 2 – 5.

Cost Utility

Despite the rapidly expanding body of evidence supporting the use of PRP for orthopedic conditions, insufficient data exist to perform an adequate cost-benefit analysis. PRP therapy is not covered by many insurance plans in the United States, and this policy may persist until appropriate data are available. A single PRP treatment of diabetic ulcer wounds in 2006 was estimated to cost $450 compared with alternative treatments of uncomplicated ulcers costing $3,600 per, indicating that PRP gel is more cost effective than wet-to-dry saline dressings in managing non-healing diabetic foot ulcers; this comparison was analyzed over a 5-year period (58).

Although the short-term costs of PRP are greater than those of standard steroid injections, if the incidence of further intervention is decreased at long-term follow-up or if satisfaction is significantly greater according to patients' demographics, time of treatment, or efficacy of PRP, then overall costs will decrease. PRP may be less expensive than corticosteroids at the 2-year follow-up of the management of lateral epicondylitis (44).

Table 2. *Evidence of platelet rich plasma categorized by tissue types - bone.*

Study (Reference number)	Year	Conclusions
Iqbal et al (27)	2011	The study reviews in vivo and in vitro osteogenic action of PRP and concludes that PRP does not impact bone healing or induce bone formation. There is some evidence that suggests PRP might augment recruitment of osteoblast progenitors to injection site.
Tsai et al (28)	2009	The use of platelet gel/fibrin glue did not increase fusion rates in 34 patients undergoing posterolateral lumbar fusion with artificial bone expander and laminectomy autograft.
Weiner and Walker (29)	2003	The fusion rate of 32 patients undergoing single level intertransverse lumbar fusion using autologous growth factors was inferior 62% compared to the control group 91%.
Huang and Wang (30)	2010	This in vitro study of rats demonstrated that PRP containing osteoinductive growth factors stimulate cell proliferation and osteogenic differentiation of rat-derived MSCs
Patel et al (31)	2013	This clinical study in 78 patients randomized in to 3 groups, first with single PRP injection, second with 2 PRP injections 3 weeks apart, and third with normal saline injection demonstrated that a single dose of WBC filtered PRP in concentrations of 10 times the normal is as effective as 2 injections in early knee OA. The results diminished in 6 months. Both PRP groups did better than control group.
Cerza et al (32)	2012	60 patients received 4 PRP and 60 patients received 4 HA injections, PRP group showed better clinical outcomes with lower WOMAC scores until 24 weeks after injection.
Raeissadat et al (33)	2015	This study with 87 patients receiving 2 PRP injections and 73 patients receiving 3 HA injections showed better WOMAC and SF 36 in the PRP group than in the HA group.
Sánchez et al (34)	2010	37 volunteers who underwent either conventional or PRP rich in Growth factors (PRGF) ACL reconstruction showing more tendon remodeling in the PRP group compared to the conventional group.
Montañez-Heredia et al (36)	2016	55 total participants with grade 1 – 3 knee OA compared leukocyte-poor PRP (LP-PRP) injections with hyaluronic acid injections. At 3 and 6 month follow-up the PRP group had significantly better functional improvements in all grades of knee OA and significantly better pain improvements in lower OA grades (1 & 2). Both groups had equivocal results in pain relief in those with grade 3 or higher OA.
Simental-Mendía et al (37)	2016	65 participants with grade 1 & 2 knee OA compared leukocyte-poor PRP (LP-PRP) injections with oral acetaminophen (APAP). 32 participants took 500 mg of APAP (every 8 hours) over 6 weeks and 33 participants were given a total of 3 LP-PRP intra-articular injections (one injection every 2 weeks for a total of 3 injections). The LP-PRP group demonstrated significant improvements in both pain and functionality and maintained these improvements up to the maximum 24-week follow-up. Additionally, only the LP-PRP group showed improvements in quality of life measures and these improvements were identified as early as the initial 6 week follow up.

Table 3. *Evidence of platelet rich plasma categorized by tissue types - tendons*

Study (Reference number)	Year	Conclusions
Mishra and Pavelko (39)	2006	15 patients received PRP and 5 patients received Bupivacaine for elbow epicondylar pain. 8 weeks post treatment the PRP group reported 60% improvement in VAS compared to 16% improvement in control group. At 6 months, 81% improvement and at 25.6 months, 93% pain reduction compared to pre procedure.
Gosens et al (40)	2011	100 chronic lateral epicondylitis patients, 51 treated with PRP compared to 49 with corticosteroid injection has reduced pain and improved function at 2 years follow-up.
Peerbooms et al (41)	2010	100 chronic lateral epicondylitis patients, 51 treated with PRP compared to 49 with corticosteroid injection had reduced pain and improved function with DASH score or VAS at one year follow-up.
de Vos et al (42)	2010	Among 27 patients each of chronic Achilles tendinopathy treated with eccentric exercises and injected with PRP or placebo did not show any statistically significant improvement in pain and activity at 24 weeks.

Table 3 (cont.). *Evidence of platelet rich plasma categorized by tissue types - tendons*

Study (Reference number)	Year	Conclusions
de Jonge et al (43)	2011	Among 27 patients of chronic Achilles tendinopathy treated with eccentric exercises, injected with PRP or placebo did not show any clinical or ultrasonographic superiority in one year follow-up.
Gosens et al (44)	2012	36 patients with chronic Patellar tendinopathy were treated with PRP injections. The ones without prior treatment with cortisone, ethoxysclerol and/or surgery showed statistically significant improvement in the VAS and VISA-P scales.
Shen et al (45)	2008	Study of macrophages, TGF-beta1, Cox 2 pathway in all phases of muscle healing. They concluded macrophages influenced muscle healing by inducing production of TGF-beta1 and PGE2. Also macrophages, TGF-beta1, Cox 2 regulate each other's levels and influence muscle healing.
Philippou et al (46)	2007	The cellular proliferation and differentiation as well as protein synthesis required for muscle repair or hypertrophic adaptation are regulated by IGF-1 isoforms.
Castricini et al (47)	2011	Arthroscopic rotator cuff repair of 45 without and 43 with autologous platelet rich fibrin matrix (PRFM), there was no statistically significant difference in the MRI tendon score between groups.

Table 4. *Evidence of platelet rich plasma categorized by tissue types - muscles.*

Study (Reference number)	Year	Conclusions
Yang et al (48)	2015	Based on the meta-analysis of 8 studies, applying PRP within arthroscopic repair of rotator cuff can decrease postoperative pain. No better integrity of the rotator cuff could be identified with PRP.
Warth et al (49)	2015	Of 11 studies of rotator cuff repair selected, 8 were used for meta-analysis and showed no statistically significant differences in overall gain in outcome scores or re-tear rates between treatment groups. Gain in Constant scores was significantly increased when PRPs were applied at the tendon-bone interface than over the top of the repaired tendon. Re-tear rates were significantly decreased when PRPs were used for the treatment of tears greater than 3 cm in anterior-posterior length using a double-row technique.
Chahal et al (50)	2012	Quantitative synthesis of 5 studies of arthroscopic repair of thickness rotator cuff tears with or without PRP treatment, did not show any statistically significant rate of re-tear between the groups.
Randelli et al (51)	2011	Of patients undergoing arthroscopic rotator cuff repair for full thickness tear, 26 underwent intraoperative PRP with autologous thrombin and 27 did not. PRP reduced pain in post-operative months and positively affected healing in grade 1 and 2 tears.
Letson and Dahners (52)	1994	Ligaments receiving platelet derived growth factor (PDGF) were 73% stronger than control. Ligaments treated with PDGF and IGF-1 and PDGF and FGF also had increase in rupture force, stiffness and breaking energy over internal controls.
Radice et al (53)	2010	A prospective single blinded study of 50 ACL reconstructions demonstrated time shortening of 48% with PRPG compared to without.
Murray et al (54)	2007	Bilateral wounds were created in MCL or ACL of canine models and one side treated with collagen PRP hydrogel and other side left untreated. The PRP group resulted in increased wound healing of both intra and extra articular ligament wounds with similar profile of growth factor and protein expression in both groups.

Cost analysis must be conducted in a more systematic manner going forward and must be compared with the cumulative costs of conservative measures and surgery. Proper economic evaluation must take into account accurate indications, population demographics, time of treatment, efficacy, and duration of response

Table 5. *Evidence of platelet rich plasma categorized by tissue types - ligaments.*

Study (Reference number)	Year	Conclusions
Sanchez et al (34)	2010	In this case control study of total 37 volunteers who underwent ACL reconstruction, 22 with Platelet rich growth factor (PRGF) and 15 without, it was noted that PRGF resulted in more remodeling of grafts that untreated group. During 6 – 24 months postoperative period, newly formed connective tissue was enveloping most grafts treated with PRGF.
Fallouh et al (55)	2010	Fresh blood and ACL remnants were obtained from patients who underwent ACL surgery and isolated cells were cultured in vitro in a specific fashion. The study demonstrated autologous PRP can enhance ACL cell viability and function in vitro.
Nin et al (56)	2009	In this prospective randomized double-blinded study of 100 patients undergoing Patellar tendon allograft, 50 used Platelet enriched gel and 50 did not. There were no statistically significant differences between the groups for inflammatory parameters, MRI appearance of graft and clinical evaluation scores.
Magnussen et al (57)	2013	In this retrospective comparative study of 50 patients being treated with intraoperative PRP application and 50 without during allograft ACL reconstruction, clinical benefit in PRP group was minimal and short term. No difference in patient reported outcomes or number of additional surgeries at 2 years was noted.

Conclusion

The changing landscape of health care is rapidly transforming medical practice. Minimally invasive outpatient procedures are displacing invasive and expensive surgeries associated with prolonged recovery times. Similarly, the focus of treatment in many orthopedic and sports medicine practices has shifted towards a more natural and holistic approach from traditional medical and surgical treatments.

Although PRP is theoretically beneficial for augmenting tissue healing, evidence-based literature suggests that success varies depending on its preparation method and composition, medical condition of the patient, anatomic location and severity of the lesion, technique of administration, tissue type, and peri-procedural care. In response to a growing interest among patients and surgeons in PRP, recent studies report outcomes for a variety of conditions. Further critical review and rigorous clinical studies are required to formulate a cost effective, efficacious algorithm for the use of PRP in patients with varying musculoskeletal conditions.

Many animal and basic science studies during the past 2 decades assessed the use and effectiveness of PRP, and most included in this review were published during the last 5 years. Many of these studies show the potentially positive effect of PRP in the treatment of musculoskeletal and spine conditions. However, there remains a paucity of randomized controlled clinical trials that provide level I evidence for the efficacy of this intervention. Most studies of humans reported here are case series or retrospective studies without a control group. Generally, the studies are small and lack analytic power. Given the limited data, no clear definition of a standardized PRP treatment protocol is established.

In summary, this article provides a basic overview of the current use of PRP in orthopedic practice and concludes with the authors' perspectives above on the state of PRP as a potentially effective bioregenerative treatment option for musculoskeletal applications. PRP treatment requires high-quality studies before it can be accepted by insurance payers, consumers, and health care providers.

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