The Emerging Use of Platelet-Rich Plasma in Musculoskeletal Medicine

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Platelet-rich plasma (PRP) is one of many new developments within the expanding field of regenerative medicine. Specialists in areas such as orthopedics, physical medicine and rehabilitation, and rheumatology have been exploring the benefits of this novel therapy. Although PRP therapy remains controversial and has minimal clinical trial support, the use of orthobiologics such as PRP continues to advance as patients seek nonsurgical approaches to acute and chronic musculoskeletal injury and disease. However, academic acceptance as well as insurance reimbursement remain reliant on solid and repeatable positive results from large clinical trials. The authors summarize the evolution of PRP therapy and report on its status.

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Chronic musculoskeletal pain accounts for the most commonly reported medical complaint in the United States. This finding has been highlighted in a comprehensive report by the Bone and Joint Decade (2000-2010) initiative,[1] a jointly led global effort by the United Nations and the World Health Organization. The report stated that 1 in 2 adults aged 18 years or older, comprising 107.7 million people in the United States in 2005, reported having a musculoskeletal disorder that lasted 3 months or longer.[2]

The treatment options for patients with these often debilitating conditions range from physical therapy to surgery. However, physical therapy may be ineffective or too painful, and surgery may result in postsurgical complications (eg, decreased mobility) or may not relieve the pain. Platelet-rich plasma (PRP) and stem cell injections are revolutionary approaches to managing musculoskeletal disorders with the potential to change the face of medicine (*Figure*).[3] Researchers and clinicians in the field of regenerative medicine are developing new techniques aimed at repairing as well as replacing pathologic, damaged, and aged tissue.[4] Platelet-rich plasma and mesenchymal stem cell therapies comprise a dimension of this field termed *orthobiologics*.[5] The healing potential of embryonic and adult mesenchymal cells and the manipulation of the cellular response to both damaged and diseased tissue through the use of growth factors is being studied.

The mechanisms of tissue repair continue to be elucidated, with increased understanding of the intricacies of the complex interaction between the immune system and damaged tissue.[6] When surgeons first began to experiment with tendon repair, little was known about the inflammatory response and its role in wound healing. Incisions were made to allow bloodletting, but any resulting clinical improvements did not reveal the mechanism of action behind them.[7] In the 1950s, with greater understanding of the inflammatory response and its role in tissue repair, other modalities, such as prolotherapy, were used by physicians as an alternative to surgery and conventional injections with cortisone.[8] Similar

to prolotherapy, PRP therapy seeks to initiate an inflammatory response at the site of injury.[5]

The use of PRP therapy to accelerate healing of acute tendon damage was publicized during the 2008 Super Bowl. Hines Ward, the Pittsburgh Steelers wide receiver, was able to compete in the Super Bowl despite having sustained a torn medial collateral ligament 2 weeks previously. A series of PRP injections was credited with accelerating the healing process and thus allowing the athlete to compete.[9]

The efficacy of orthobiologics such as PRP to manage musculoskeletal ailments must be demonstrated and reproduced with positive outcomes from large clinical trials. In the current article, we provide a historical background and overview of the basic science of this new therapy and summarize the current state of research.

Historical Perspective

The idea of inducing inflammation to trigger the healing cascade has its roots in antiquity. Aulus Cornelius Celsus, a Roman encyclopedist, attempted to harness the healing properties of inflammation in helping to manage disease.[10] In the first century BCE, physicians treated patients with hydrocele (accumulation of fluid around the testes) by injecting saltpeter (potassium nitrate) in an attempt to induce scarring.[10]

In the 1950s, George Hackett, MD, began to experiment with injections of substances into hernia sacks to rebuild defects in the fascia. The resultant increased strength of the thinning fascia led him to experiment at other sites where connective tissue was weakened, such as tendons and ligaments. Hackett's treatment consisted of injecting an irritating solution into a relaxed ligament and tendon. This irritation would then stimulate the production of new fibrous tissue and bone cells that would in turn strengthen the weld of fibrous tissue and bone to stabilize the articulation of bone and ligament and permanently eliminate the disability.[11] He became convinced that this therapeutic technique could be applied to musculoskeletal defects and chronic pain. He coined the term *prolotherapy* in his book *Ligament and Tendon Relaxation: Treated by Prolotherapy*.[11]

Akin to prolotherapy, PRP therapy seeks to initiate healing through the administration of a local irritating substance.[5] However, unlike prolotherapy, PRP therapy exploits the ability of platelets to directly deliver growth factors to sites of injury.[6] It is this property that allows PRP injections to both incite and augment inflammation and thus enhance tissue repair.

To our knowledge, the first evidence of the therapeutic effects of platelet-rich compounds was provided by the work of oral and plastic surgeons who reported enhanced bone healing after using PRP therapy to reduce blood loss.[12] As the understanding of platelets and their role in healing grew, physicians began to experiment with the role of platelets in wound healing.

Basic Science

Initially thought to be solely the bandages of the circulatory system, the contents of platelets, specifically α granules, have been found to contain a number of growth factors crucial to the reparative process (*Table 1*). Cytokines that act as homing signals to circulating mesenchymal cells, mitogens that stimulate mitosis and proliferation of fibroblasts, and transcription factors that increase the production of collagen fibrils are all abundant within densely packed α granules in the cytoplasm of circulating platelets.[6]

Histopathologic changes associated with chronic painful tendon injuries or tendonopathy exhibit degeneration and disorganization of collagen, hypercellularity, and little inflammation.[13] Gross changes resulting from the degenerative nature of the healing process include thickening, loss of mechanical properties such as resistance to overload stretching, and subjective pain.[14] These changes in tendon characteristics have been found to be, in part, related to the pathologic replacement of the resilient type I collagen by the less stable type III collagen[9] and neovascularization, with concomitant neurogenesis.[14]

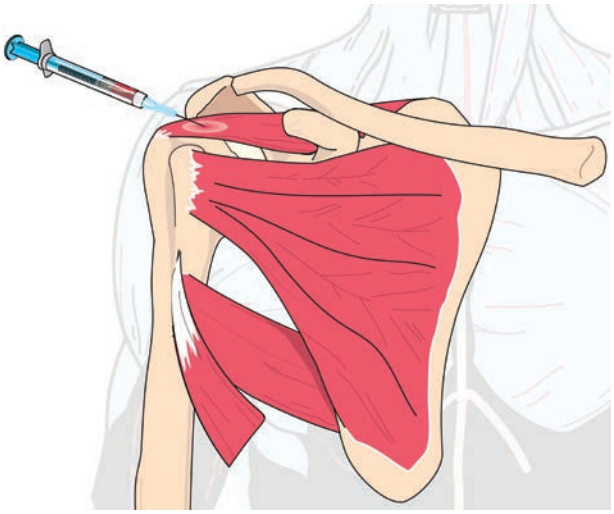

Figure.
Platelet-rich plasma injections can be delivered to injured sites such as rotator cuff tears or labrum tears via ultrasound guidance for minimally invasive delivery of healing growth factors to damaged tissues.

The use of PRP has been theorized to slow the time-dependent decrease in circulation-derived cells, such as macrophages and fibroblasts, to the site of injury. Macrophages have been shown to proliferate at higher rates in the area of injury after local administration of PRP injections and are known to be a tremendous reservoir of growth factors and signaling molecules in damaged tissue. Platelet-derived growth factor concentrations can reach a 5-fold increase in PRP preparations and have been shown to stimulate cell proliferation and mitosis of fibroblasts in injured animal tendons.[15] Transforming growth factor–β concentrations can also reach highly elevated concentrations of nearly 4-fold and have been found to increase the quantity of type I and III collagen synthesized by local fibroblasts.[8] The role of vascular endothelial growth factor in the neogenesis of blood vessels has been known for years. Therapy with PRP results in a nearly 6-fold increase in this potent molecule and is believed to help improve delivery of vital nutrition to the poorly vascularized region of tendons.[16] This combination of increased cell recruitment, increased metabolic activity of recruited cells, increased vessel growth, and improved nutrition provides the foundation of PRP therapy's presumed efficacy.

Clinical Trials

We conducted a search on the US National Library of Medicine's PubMed database for all clinical trials involving PRP application in tendon, ligament, and cartilage disorders on the basis of condition and treatment approach—for example, *tendon*, *clinical trial*, *human*, and *platelet-rich plasma*. Inclusion criteria were human participants, minimally invasive mode of application, and clearly defined outcome measures. Surgical reports were excluded, as our main objective was to review PRP applications in nonsurgical musculoskeletal medicine.

The number of clinical trials investigating the effectiveness of PRP therapy in improving quality of life related to musculoskeletal dysfunction increased between 2009 and 2012. For the present review, we identified 11 studies, most of which were published in 2010 or 2011 (*Table 2*). Herein, we describe some of the studies identified. The first studies were primarily pilot studies that sought to treat patients with chronically injured tendons, and many of these studies showed evidence of improved function. However, it was not until 2010 when the first widely recognized study,[17] consisting of an adequate control group and using randomization, was published in *JAMA*. This randomized controlled study found no evidence of improvement in Achilles tendinopathy in the PRP therapy group vs the control group and was a major setback in gaining wider acceptance of this therapy.[17]

Later in 2010, another randomized controlled trial[18] performed in the Netherlands offered more encouraging evidence. One hundred patients with chronic lateral epicondylitis were randomly assigned to a PRP or corticosteroid group. The 2 groups received an autologous platelet concentrate injection via a peppering needling technique or a corticosteroid injection and were followed

up for 1 year.[18] A 25% reduction in visual analog scale (VAS) score or Disabilities of the Arm, Shoulder and Hand (DASH) score without a reintervention after 1 year defined a successful treatment. Scores on VAS revealed that results in 24 of the 49 patients (49%) in the corticosteroid group and 37 of the 51 patients (73%) in the PRP group were successful ($P<.001$). The DASH scores were similar, with successful treatment in 25 of the 49 patients (51%) in the corticosteroid group and 37 of the 51 patients (73%) in the PRP group ($P=.005$). Initially, the corticosteroid group showed improvement that then declined, whereas the PRP group progressively improved.[18]

A 2-year follow-up study[19] was conducted to analyze further long-term benefits of PRP therapy compared with corticosteroids. When results were compared with the 1-year follow-up, the corticosteroid group showed a decline, whereas the PRP group's benefit continued to be maintained.[19] The primary analysis consisted of VAS pain scores and DASH outcome scores. Baseline VAS and DASH scores were compared between groups. Both groups demonstrated statistically significant improvement across time (intention-to-treat principle). However, the DASH scores of the corticosteroid group returned to baseline, and the PRP group maintained a statistically significant improvement (as-treated principle).[19]

Studies investigating the effectiveness of PRP injections in the management of osteoarthritis began to appear in the literature in 2010. A pilot study[20] of 14 patients with primary and secondary osteoarthritis of the knee, in which 3 PRP injections were administered at 4-week intervals, found statistically significant and near-linear improvements in knee injury and osteoarthritis outcome scores, including both pain and symptom relief. The Brittenberg-Peterson VAS scores showed many improvements, including reduced pain after knee movement and at rest, with the majority of patients expressing a favorable outcome at 12 months after treatment.[20]

Another study[21] showed positive results in patients with osteoarthritis of the knee. Thirty patients were randomly divided into 2 groups, with 1 group receiving a series of 3 intraarticular injections of PRP in the knee at 3-week intervals and the other receiving similar injections of sodium hyaluronate. A 6-month follow-up analysis of the 2 groups' scores on International Knee Documentation Committee, Western Ontario and McMaster Universities Arthritis Index, and Lequesne index demonstrated statistically significant improvements in the PRP group compared with the sodium hyaluronate group.[21]

A prospective comparative study[22] involving 150 patients divided into 3 groups compared the effect of PRP with high- and low-weight hyaluronic acid. All groups had statistically significant improvements at 2- and 6-month follow-up, with patients older than 50 years and those with higher-grade cartilage degeneration faring worse. The PRP and low-weight hyaluronic acid groups both revealed

Table 1.
Growth Factors Present in α Granules of Platelets and Their Immunomodulatory Effects[7]

Growth Factor	Effect
EGF	Chemoattractant for endothelial cells, fibroblasts, and keratinocytes; fibroblast migration and proliferation; collagen synthesis
IGF	Bone maintenance; cell apoptosis modulation
PDGF	Chemoattractant effect on fibroblasts, mesenchymal stem cells, monocytes, neutrophils, osteoblasts; fibroblast migration and proliferation; collagen synthesis; potent mitogen for fibroblasts and smooth muscle cells; involved in all 3 phases of wound healing: angiogenesis, formation of fibrous tissue, and reepitheliazation
TGFβ	Mitogen for fibroblasts, osteoblasts, and smooth muscle cells; promotes angiogenesis and extracellular matrix production
VEGF	Powerful angiogenic growth factor; important in wound healing, improved vascularity, and endochondral ossification

Abbreviations: EGF, endothelial growth factor; IGF, insulinlike growth factor; PDGF, platelet-derived growth factor; TGFβ, transforming growth factor β; VEGF, vascular endothelial growth factor.

Table 2.
Clinical Trials Involving the Application of Platelet-Rich Plasma in Musculoskeletal Disorders

Study	n	Treatment	Study Design	Outcome Measure	Results	Limitations
de Vos et al[17]	54	PRP vs saline injection for Achilles tendinopathy	Double-blind, randomized, controlled trial	Victorian Institute of Sports Assessment Achilles questionnaire	No difference in improvement between PRP and placebo at 24 wk	Lack of quantification of platelets or growth factors in PRP group
Peerbooms et al,[18] Gosens et al[19]	100	PRP vs steroid for lateral epicondylitis	Double-blind, randomized, controlled trial	VAS, disability of the arm, DASH score	PRP reduces pain, increases function, exceeding steroid at 1 y	Previous nonsurgical treatment, including steroid injections, had failed in all patients
Peerbooms et al,[18] Gosens et al[19]	100	PRP vs steroid for lateral epicondylitis	Double-blind, randomized, controlled trial	VAS, disability of the arm, DASH score	PRP reduces pain, increases function, exceeding steroid at 2 y	Placebo group received corticosteroid, owing to Netherlands IRB decision
Sampson et al[20]	14	PRP for primary/secondary knee OA	Prospective, uncontrolled, pilot study	Brittberg-Peterson VAS, activities and expectation score, OA score	Notable improvement in VAS and OA score with PRP	Small sample size, lack of control
Li et al[21]	30	PRP vs hyaluronate in knee OA	Double-blind, randomized, controlled trial	IKDC score, WOMAC score, Lequesne index	Notable improvement in PRP group at 6 mo compared with hyaluronate	Small sample size
Kon et al[22]	150	PRP vs HA for knee cartilage pathology	Prospective, multicenter, comparative study	IKDC score, EQ VAS score, patient satisfaction	Similar results at 2 mo, PRP better at 6 mo and in younger patients and early OA	Lack of randomization of placebo and control groups other than imaging and biologic results, follow-up at different centers, outcome measure used, small sample size
Mei-Dan et al[23]	32	PRP vs hyaluronate in osteochondral lesions of the talus	Prospective, quasirandomized, controlled trial	AOFAS, AHFS VAS for pain, stiffness, function and subjective global function score	PRP significantly better than HA in VAS score and AHFS for 6 mo	Large number of patients who previously underwent surgery, poor documentation of analgesic use by patients

(continued)

statistically significantly higher International Knee Documentation Committee scores, EQVAS scores, and patient satisfaction survey results at 2 months; however, only the PRP group showed further improvements after the 2-month mark.[22]

In a 2012 study[23] on PRP therapy in the management of osteochondral defects of the talus, PRP therapy demonstrated statistically significant improvements compared with hyaluronic acid injections. Thirty-two patients were divided into 2 groups receiving either 3 consecutive in-

Table 2 (continued).
Clinical Trials Involving the Application of Platelet-Rich Plasma in Musculoskeletal Disorders

Study	n	Treatment	Study Design	Outcome Measure	Results	Limitations
Spakova et al[28]	120	PRP vs HA for knee arthritis	Prospective, cohort, controlled trial	WOMAC OA index and 11-point pain intensity scale, numeric rating scale	Statistically significant better results in WOMAC OA index and 11-point pain intensity scale in PRP at 3 and 6 mo	Lack of placebo control, short follow-up period
Thanasas et al[29]	28	PRP vs whole blood for chronic lateral elbow epicondylitis	Prospective, randomized, controlled trial	VAS pain score, Liverpool Elbow score	Improvement in VAS score in PRP group was greater in all follow-ups but only statistically significant at 6 wk	Small number of patients
de Vos et al[30]	54	Effect of PRP on US tendon structure and neovascularization in chronic midportion Achilles tendinopathy	Double-blind, randomized, placebo-controlled trial	Tendon structure evaluation by US tissue characterization and color Doppler US	No statistically significant change in tendon structure or alteration in degree	Neovascularization score used has not been validated, lack of sensitivity of color Doppler US for detecting neovascularization compared with power Doppler US
Filardo et al[31]	31	PRP for refractory jumper's knee	Prospective, nonrandomized, controlled trial	Tegner, EQ VAS, pain level	Statistically significant improvement in all scores with PRP	Nonhomogenous control group, simultaneous exposure to PRP and physiotherapy in the study group

Abbreviations: AHFS, Ankle-Hindfoot scale; AOFAS, American Orthopedic Foot and Ankle Society; DASH, Disabilities of the Arm, Shoulder and Hand; EQ, EuroQol-5D; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; IRB, institutional review board; OA, osteoarthritis; PRP, platelet-rich plasma; US, ultrasonography; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

traarticular therapeutic injections of hyaluronic acid (at 1-week intervals) or PRP (at 2-week intervals) and followed up for 28 weeks. Mean Ankle-Hindfoot scale VAS scores and subjective global function scores improved in both groups, but the PRP group demonstrated a statistically significant better outcome.[23]

Current Issues

The lack of standardization of PRP preparations, the various matrices used to localize the injections at sites of injury, and the differing techniques of activation (ie, inducing the release of growth factors from the concentrated platelets) of the matrix, either before or after

injection, remain a barrier to further acceptance and critical evaluations. Thrombin as an activator has been shown to release transforming growth factor β1 and platelet-derived growth factor β1 immediately on induction and to promote gelation (clotting), thus preventing diffusion away from the target lesion. In contrast, soluble collagen-activated PRP clots, which promote gelation, tend to release more steady concentrations over a longer time, resulting in a net 80% greater cumulative release over 7 days.[28] Centrifugation methods have also shown varying levels of platelet-aggregating capacities.[29]

Procedural heterogeneity complicates evaluation of clinical efficacy. A recent literature review and meta-analysis of PRP therapy in the management of painful tendinopathy found that, owing to the lack of standardization of procedural protocols (eg, number of injections and paratendinous vs intratendinous injection techniques), insufficient evidence exists to guide clinical treatments. This conclusion was drawn despite statistically significant pain improvement at 36-month follow-ups in the clinical trials reviewed.[30]

Further research should be directed at optimizing PRP preparation kinetics and overall effectiveness, as well as procedural design. Standardization of the PRP preparation technique as well as procedural protocols will allow for a higher level of critical evaluation and analysis of clinical results.

Conclusion

Greater understanding of the complex interplay between the immune system and signaling from wound tissue has led to increased use of PRP therapy in musculoskeletal injuries. The use of autologous blood as the source of hyperconcentrated platelets in PRP therapy circumnavigates any potential cross-reaction from infusions. Although PRP therapy is available throughout the United States and other countries, given questionable insurance reimbursements, lack of standardization of preparation and procedural protocols, and the high cost of preparing PRP samples, it is important that the efficacy and safety of PRP treatments be further evaluated.

Author Contributions

All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; and Dr Bashir drafted the article or revised it critically for important intellectual content; and Dr Bashir gave final approval of the version of the article to be published.

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