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BIOLOGICAL ADJUVANTS IN ORTHOPEDIC SURGERY (J DINES AND D GRANDE, SECTION EDITORS)

# Platelet-rich plasma and other cellular strategies in orthopedic surgery

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**Abstract** The use of biologics in the treatment of musculoskeletal disease has become increasingly more common as research studies continue to provide further elucidation of their mechanisms in healing. Platelet-rich plasma, patches, growth factors, and stem cells are among the many biologics under active investigation and have varying levels of success in augmenting surgical or nonoperative interventions. However, the limitations of these treatments exist, and clear guidelines for their indications and application have yet to be established. Well-designed clinical trials will help determine the appropriate future use of biologics to ensure consistent outcomes.

**Keywords** Platelet-rich plasma · Patches · Cytokines · Stem cells · Biologics

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## Introduction

Historically, the biologic milieu of healing tissue has been notoriously difficult to control and improve. However, emerging research is offering new insights and strategies to provide multimodal therapy in combating injury to tendons, cartilage, ligaments, muscles, and bones. Although much work is still in preclinical stages, these biologics could potentially have an enormous impact on the field.

The term biologics refers to natural products that are harvested to augment the biology of healing. The three main categories of therapy provided by these products are growth factor (e.g., platelet-rich plasma), cell (e.g., stem cells), and tissue (e.g., patches) [1]. Innovations in surgical instrumentation and repair constructs have helped to decrease the rate of mechanical failure at the healing site. Yet, surgery still has shortcomings in many conditions. It is the hope that these biologics can either augment operative interventions or provide successful nonoperative treatment. Despite the rapid evolution of biologic therapies, the lack of well-designed clinical trials limits their human use at this time.

## Platelet-rich plasma (PRP)

PRP is a sample of autologous plasma twice centrifuged to contain a platelet count above baseline. PRP is beneficial in bone and soft tissue healing for its high concentration of growth factors and cytokines that stimulate cell proliferation and extracellular matrix protein production [1]. Cytokines such as platelet-derived growth factor (PDGF)-β, transforming growth factor (TGF)-β, bone morphogenetic proteins (BMPs), IGF-1, vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF) play documented roles in the healing process and may increase the body's ability to heal a tendon repair via the normal tendon enthesis, as opposed to scar tissue.

Concentrating platelets harnesses the abovementioned cytokines and growth factors critical to the healing tissue. However, the concentration of cytokines and growth factors released fluctuates and depends upon the platelet recovery method, amount of whole blood used, platelet activation, final volume of platelets, and other variables. In an effort to standardize PRP formulations, classification systems have been proposed by DeLong et al. [2] and Mishra et al. [3] in which grades are based on platelet count, activation method, and WBC count. In a study evaluating respective compositions of PRP solutions prepared by three commercially available separation systems (the Cascade, GPS III, and Magellan systems), Castillo et al. [4•] found that the PRP solutions prepared by the GPS III and Magellan systems were leukocyte rich, including high concentrations of WBC, PDGF-αβ, PDGF-ββ, and VEGF by comparison with the leukocyte-poor PRP preparations from the cascade system.

Giusti et al. [5] have proposed $1.5 \times 10^6$ platelets per microliter as the optimal platelet concentration for tissue healing and reported a saturation effect, involving an inhibitory cascade once a high concentration is reached [6]. Such work, along with a growing bank of clinical research, marks important steps toward a better understanding of the therapeutic use of PRP in orthopedics.

## Rotator cuff

The tears of the rotator cuff are common among athletes and non-athletes alike, and degenerative tears are becoming more common in the USA as the population ages. If surgery is indicated, recovery time is largely dependent on the ability of the tendon to heal the bone. The use of biologic therapy to speed and improve this process is an attractive prospect.

Multiple investigators have evaluated the effect of rotator cuff augmentation with PRP, but results have not been universally positive. In a randomized study of 88 patients with and without a PRP matrix globule, Castricini et al. [7] found no difference in constant scores at a mean follow-up of 20 months. Similarly, Jo et al. [8] randomly assigned 48 rotator cuff tear patients with large to massive rotator cuff tears to PRP-augmented arthroscopic repair or conventional arthroscopic repair. They found that PRP application significantly improved retear rate (20.0 versus 55.6 %) and change in cross sectional area of the supraspinatus compared to those without PRP. However, with the exception of overall shoulder function, clinical outcomes did not differ between the two groups. In contrast, results from a cohort study by Bergeson et al. [9] showed that patients who underwent arthroscopic rotator cuff repair with PRP matrix had a significantly higher retear rate (56 %) compared with controls (38 %). Moreover, postoperative functional scores were not significantly improved compared with controls. Also, in a randomized controlled trial by Rodeo et al. [10•] in which 40 patients received PRP-augmented repair and 39 patients received conventional repair, there were no differences in healing between groups, outcome scores, strength, and vascularity. Interestingly, PRP use was a significant predictor of tendon defect at 12 weeks. These inconsistent results underscore the need to standardize the indications and use of PRP in rotator cuff repair through well-designed studies. The possible areas of investigation include identifying the optimal type of PRP, the timing and number of injections, and the effect of cytokines or other plasma proteins on PRP.

## Ulnar collateral ligament

Injuries to the ulnar collateral ligament (UCL) are common, particularly in overhead athletes. While surgery has provided reliably good outcomes, recuperative time can easily last 12 months. Furthermore, some partial tears may not require reconstruction. To that end, if biologics could be used to enhance the healing of the native ligament, thereby obviating surgery and its associated recovery time, many athletes would benefit.

Podesta et al. [11] studied the use of PRP injection as an alternative to surgical reconstruction in treating a cohort of 34 athletes with partial tears of the UCL. At an average follow-up of 70 weeks, 30 of the 34 athletes had returned to play, averaging a 12-week (range of 10–15 weeks) period before return. Statistically significant improvements were noted in functional outcome measures as well. Similarly, in an unpublished report of high-level throwers with UCL injuries by Dines et al., 73 % of players who had failed a course of conservative therapy had good to excellent outcomes following PRP injection at an average follow-up of 11 months.

## Lateral elbow tendinosis

Lateral elbow tendinosis, or tennis elbow, is a common overuse injury. While treatments such as corticosteroids are often administered to relieve pain, long-term relief and functional improvement remain difficult to achieve. Surgery is often recommended for patients suffering for as long as a year. The treatment of lateral elbow tendinosis with biologics may eventually be a promising nonoperative alternative.

Peerbooms et al. [12] completed a double-blind randomized controlled trial in which autologous PRP was shown to be more effective than corticosteroid injections in reducing pain and increasing function in patients with chronic epicondylitis. Patients were examined periodically throughout the first year following the procedure, and 73 % of patients treated with PRP had improvement in visual analog scale (VAS) and disabilities of the arm, shoulder, and hand (DASH) scores. By contrast, 49 and 51 % of the corticosteroid group had improvements in VAS and DASH scores, respectively. Whereas, the corticosteroid group recovered more rapidly

within the first 8 to 12 weeks before declining, the group treated with PRP continued to improve throughout the year.

These results were consistent with those of Mishra and Pavelko [13], whose 2006 study reported the relative success of PRP treatment versus that with a local anesthetic. In a longer follow-up study, Gosens et al. [14] observed that the baseline VAS and DASH scores of both the PRP and steroid groups significantly improved over time. While the pain and disability of the corticosteroid group returned to baseline levels within the 2-year period, those of the PRP group continued to improve.

### Hamstring

Hamstring injuries are especially common in athletes reliant on their lower extremities for running, jumping, and kicking, thus leaving them with significant impairment and risk of reinjury. Conventional treatments, whether surgical or physical therapy and intramuscular corticosteroid injections, can lead to protracted recovery time, high reinjury rates, and incomplete recovery [15]. Biologic therapies would represent new possibilities for a more rapid and complete recovery from hamstring injury.

Unfortunately, evidence for proximal hamstring treatment with PRP is severely lacking. In a small retrospective series of patients who had failed a course of nonoperative treatment for proximal hamstring tendinopathy, strain, or partial tear, Wetzel et al. [16] found that patients injected with PRP experienced symptom relief and return to sports an average of 4.5 months posttreatment. However, all athletes in the non-PRP injection also returned to sports, and pain scores posttreatment were not statistically different between groups.

In another study, Mejia and Bradley [17] treated NFL players with PRP injection within 24–48 h of hamstring injury. They showed an earlier return to play of 3 days for grade 1 injuries and 5 days for grade 2 injuries, with an overall one-game difference in return to play. Despite this success in a level IV study, more rigorous investigation is needed to clarify PRP's role in hamstring injuries.

### Achilles tendon

Chronic Achilles tendinopathy is typically ascribed to the overuse and the failure of a healing response. Nonoperative treatment can often fail and leave patients with significant functional limitations in their daily activities. Therefore, a successful biologic therapy could have enormous impact on these patients' outcomes.

de Vos et al. [18] performed the first randomized control trial of PRP injections in chronic Achilles tendinopathy. Fifty-four patients were randomized to either an ultrasound-guided injection of PRP plus eccentric exercises or a placebo injection plus eccentric exercises and followed for 6 months. After adjusting for duration of symptoms, there was no significant difference in outcome measures (patient satisfaction, return to sports, etc.) between groups at any time point. The same group reanalyzed results at 1 year and also used ultrasound to evaluate evidence of tendon structural reorganization. Results showed that PRP injection with eccentric exercises did not result in clinical improvement and/or improved structural reorganization at 1 year [19].

### Osteoarthritis

The preclinical use of PRP injections at the site of osteoarthritis has shown significant improvement in joint healing, by targeting both cartilage and meniscal tissues [20].

The clinical applications of PRP in the site of knee osteoarthritis (OA) have resulted in pain reduction and improved clinical scores at up to 12-month follow-ups, though it has not been proven to be more effective than viscosupplementation in every case [1, 21–24]. Studies comparing pain reduction and clinical scores for OA following the use of PRP with that of hyaluronan have shown the clear benefit of PRP to young patients with less degeneration. In middle-aged patients with more substantial degeneration, the improvement was similar between the use of hyaluronan and PRP [1, 21, 23].

## Patches

The mechanical augmentation of tendons has been an area of great interest. Research has led to the development of natural and synthetic scaffolds derived from mammalian extracellular matrix (ECM), synthetic polymers, or a combination thereof. These materials are hypothesized to share the load of forces across the tendon repair site, thus decreasing the likelihood of tendon retear [25]. ECM-derived scaffolds are postulated to provide a conducive chemical and structural environment for repair healing and remodeling [26–28]. In contrast, synthetic scaffolds lack biological factors for repair healing; yet, their mechanical strength may stabilize the repair construct until host tissue healing can occur [29].

Since the source species and tissue of ECM scaffolds may vary widely, there is concern about the in vivo host response. In a rodent abdominal wall model, it was shown that all ECM scaffolds elicited an early, intense cellular response [30]. Removing cells and cellular remnants from the ECM is thought to be crucial for a favorable host response. Overall, the host response is most likely dependent on the species of origin, tissue of origin, processing methods, methods of terminal sterilization, and mechanical loading environment [31].

The clinical use of scaffolds in humans have raised concern in some instances [32–36]. The American Academy of Orthopedic Surgeons currently does not recommend the use of the non-cross-linked porcine small intestinal submucosa Restore™ for the treatment of rotator cuff tears in humans

because of a severe, sterile postoperative inflammatory reaction documented in 20 to 30 % of patients [37, 38]. Better and safer clinical outcomes, however, have been reported in other studies using other synthetic scaffolds such as GraftJacket [39].

### Achilles tendon

In a sheep model, Sarrafian and colleagues [40] evaluated a cross-linked acellular porcine dermal patch and a platelet-rich plasma fibrin matrix in the acute repair of Achilles tendons. Surgically transected tendons were reapproximated with sutures in groups 1 and 2, whereas a gap was left in group 3. The patch was used to augment the repair in group 2, and the PRP matrix was used to fill the gap in group 3, and the gap was also reinforced with a patch. At 24 weeks, all surgically treated tendons appeared healed without apparent fibrosis under light microscopy. However, in group 1 (suture repair only), healing occurred by increasing tendon thickness and disorganized tendon fibers. The other two patch-augmented groups did not exhibit this degree of tendon thickness or disorganization. Additionally, the insertion of PRP fibrin matrix within the gap in group 3 appeared to have aided in the complete bridging of the gap in all specimens.

Achilles repair augmentation appears to create a biomechanically strong construct, according to an analysis by Magnussen et al. [41]. In this study, tendons from fresh-frozen human cadavers were sharply tenotomized and repaired with suture plus ECM xenograft or with suture alone. The tendons were then subjected to 1000 loading cycles to 86 N and repair site gapping recorded, followed by distraction to failure. Results showed significantly less gapping in the augmented tendon group as well as higher load to failure. Despite the success of patches in animal studies, further investigation is warranted to determine the indications and outcomes in humans.

## Cytokines

Research has shown that growth factors and cytokines can be manipulated to enhance the healing process. PDGF-β has been found to promote fibroblast chemotaxis and proliferative activity, macrophage activation, extracellular matrix production, angiogenesis, and collagen synthesis [42]. It has also been demonstrated that PDGF-β enhances the proliferation of bone cells, which can improve the biochemical, mechanical, and structural properties of the healing site [43].

TGF-β can enhance the proliferative activity of fibroblasts and stimulate the synthesis of type I collagen and fibronectin. TGF-β is found not only during normal fetal tendon development but also in the differentiation of scar tissue during tendon-to-bone healing. The type of healing that occurs depends on the ratio of different isoforms expressed, with TGF-β1 associated with scar-mediated healing and TGF-β3 associated with tissue regeneration and "scarless" healing [44].

Bone morphogenetic proteins (BMPs) are cytokines normally expressed during embryonic development, which participate in fibrocartilage tendon formation via a series of physiologically orchestrated signals. Recombinant human BMP (rhBMP)-12, rhBMP-13, and rhBMP-14 are expressed at the tendon interface during embryonic development and are primarily involved in the formation of fibrocartilage and tendon.

Lastly, FGF, expressed by fibroblasts and inflammatory cells, is involved in the promotion of cellular migration and angiogenesis to aid in proliferation and remodeling at the site of tendon repair [45].

### Rotator cuff

Preclinical work on the use of growth factors to enhance rotator cuff tendon healing has promising results. Rodeo et al. [10•] used a mixture of osteoinductive growth factors (BMP-2 to BMP-7, FGF, TGF-β) in a sheep rotator cuff repair model. Biomechanical testing showed a stronger repair and increased bone and soft tissue formation at the repair site. Seeherman et al. [46] delivered rhBMP-12 via a type I/III collagen sponge to sheep rotator cuff repair. Results showed a significantly greater load to failure and stiffness compared to controls. In a rat model of rotator cuff repair augmented with FGF-2, Ide et al. [47] showed improved biomechanical and histologic outcomes at 2 weeks. However, there were no differences between experimental and control groups at 4 or 6 weeks. Uggen et al. [48] transduced rat tendon fibroblasts with PDGF and found increased DNA and collagen synthesis in transduced fibroblasts. A sheep rotator cuff repair model with PDGF-BB + type I collagen matrix by Hee et al. [49] revealed an increase in ultimate load to failure in two middle dosages of PDGF. However, the highest dose group of PDGF had inferior results indicating a potential negative feedback loop and the need to elucidate an ideal concentration.

### Achilles tendon

A study by Cummings et al. [50] coated Vicryl sutures with varying concentrations of human platelet-derived growth factor-BB to evaluate its augmentation effect on suture repair of Achilles tendon ruptures. Four weeks following repair, they found a significant increase in the tensile strength of the two highest dose groups. There was also a trend toward improved collagen organization in the treated group compared to controls.

In a rat Achilles tendinopathy model, Solchaga and colleagues [51] compared the effect of intra-tendon delivery of recombinant human platelet-derived growth factor-BB (rhPDGF-BB), PRP, and corticosteroids versus saline. Two

different amounts of rhPDGF-BB were administered (3 and 10 μg), and outcomes were assessed at 7 and 21 days after treatment. Relative to saline, cell proliferation increased 65 % in the 10 μg rhPDGF-BB. At 7 days, maximum load to failure was increased in the 3 μg group relative to saline, PRP, and steroids. At 21 days, maximum load to rupture was increased in the 10 μg compared to saline, PRP, and steroids and in the 3 μg group compared to saline and steroids. Lastly, stiffness was increased in the 10 μg relative to the other non-rhPDGF-BB groups.

## Stem cell therapy

Stem cells are undifferentiated, unspecialized cells that have the potential to be expanded and differentiated into various cell types in the body. Once implanted, stem cells may function by direct participation in the repair process, a paracrine effect by stimulating other local (or distant) host cells, or an anti-inflammatory/immunomodulatory role. Studies have indicated potential for stem cell-based approaches to improve tendon healing, tendon-to-bone healing, tendon-to-tendon healing, and muscle regeneration and possibly reversal of fatty infiltration and muscle atrophy. Ni et al. [52] created a rat patellar tendon window defect model and delivered tendon-derived stem cells in a fibrin glue carrier. The tendon-derived stem cells significantly enhanced tendon healing as evidenced by increased collagen fiber alignment and a significantly higher ultimate stress and Young's modulus. Nixon et al. [53] isolated stem cells from adipose tissue and induced tendonitis in eight horses. Forty-two days after injection of the stem cells, there was a reduced inflammatory cell infiltrate, significant improvement in tendon fiber architecture and organization.

Based on animal studies, isolated stem cells may not be sufficient for healing. In a rat rotator cuff model in which animals received bone marrow-derived mesenchymal stem cells in a fibrin carrier, Gulotta et al. [54] showed there was no difference in fibrocartilage formation, collagen fiber organization, and biomechanical strength of the repairs, peak stress to failure, or stiffness. They concluded that the repair site may lack the cellular and/or molecular signals necessary to induce appropriate differentiation of transplanted cells. In another study, this group modified mesenchymal stem cells with Membrane type 1 matrix metalloproteinase, a gene upregulated during embryogenesis in areas that develop into tendon-bone insertion sites. At 4 weeks, the modified stem cells had significantly more fibrocartilage, higher ultimate load to failure, higher ultimate stress to failure, and higher stiffness values compared with the unmodified stem cells [55]. A subsequent study by Gulotta et al. transduced stem cells with scleraxis, a transcription factor that is thought to direct tendon development during embryogenesis. Results at 4 weeks were similar to the previous study, and the authors concluded mesenchymal stem cells genetically modified with scleraxis can augment rotator cuff healing at early time points [56].

Scaffolds may also provide additional enhancement of cell-based approaches. In a rabbit model, Yokoya et al. [57] reconstructed a surgically created defect in the infraspinatus tendon with a polyglycolic acid (PGA) sheet seeded with mesenchymal stem cells (MSCs) or PGA alone. Their findings showed that the MSC group had more consistent restoration of fibrocartilage and Sharpey's fibers, improved type I to type III collagen ratio, and better tensile strength than PGA alone or control groups. Unlike stem cells, the addition of PRP to patches does not appear to confer significant additive healing effect according to a recent study. In their rabbit model, Chung et al. [58] demonstrated that the local administration of PRP on repaired supraspinatus tendon enhanced biological tendon-to-bone healing and increased the load to failure of the repaired rotator cuff; however, porcine dermal collagen graft augmentation did not improve the biological and mechanical properties.

Research has also focused on developing other methods of manipulating cells to create successful new therapies. Cell culture modification and slow cytometry sorting can both improve these approaches. Determining the optimal timing, concentration, and combination of different growth factors with stem cells would produce useful clinical information [59–61].

Stem cell therapy in osteoarthritis has been investigated by numerous groups. A meta-analysis by Wolfstadt et al. noted that using intra-articular injections of MSCs have proven to improve pain and function scores in knee OA but that there is yet little evidence showing any disease-modifying effect [62]. Furthermore, while intra-articular injection is common, several other methods of delivery and formulation—including scaffold media, encapsulations, combination with factors, and injecting bone marrow concentrate—are untested and may be more effective.

## Summary

Biologics have been shown to be beneficial adjuvants in the treatment of tendon, ligament, and cartilage injury. New insights into the healing process have uncovered an important role for novel therapeutic strategies that use these natural products. However, before biologics become routine tools in the surgeon's armamentarium, further research is necessary to overcome the current limitations.

The work of Castillo et al. [4•] demonstrates that commercially available PRP separation systems produce differing types of platelet-rich concentrates and WBC concentration, and these differences have unknown clinical implications. Therefore, caution is warranted when comparing studies utilizing various commercial systems. Additionally, clinicians may choose PRP compositions that are either leukocyte rich or leukocyte poor, but no studies directly investigating the

ideal composition currently exist. It is becoming more evident that leukocyte concentration may significantly affect the healing process. In an animal study, McCarrel et al. [63] found that a high absolute WBC concentration in PRP contributes to the expression of inflammatory cytokines. Their results suggest that leukocyte-reduced PRP formulations may possess the best potential to stimulate superior healing without scar tissue formation. Conversely, other investigators have demonstrated detrimental effects of leukocyte-rich PRP. In a study by Braun et al. [64], synovial cells treated with leukocyte-rich PRP resulted in significant cell death and proinflammatory mediator production.

## Conclusion

Despite its increasing clinical use, the indications for and expected outcomes of PRP and other biologics need more clarification. Ideally, well-designed high-quality randomized controlled clinical trials would produce adequate data to give physicians accurate guidelines in treating appropriately selected patients. Yet, until consensus is reached on the optimal preparation, concentration, and cytology of PRP, conclusions from studies will continue to lack full merit and generalizability. With proper guidelines and formulations, biologics may have the potential to revolutionize the approach to treating many orthopedic ailments. The community eagerly awaits evidence of their safety and efficacy to improve patient outcomes.

### Compliance with Ethics Guidelines

**Conflict of Interest** Phillip N. Williams, James P. Bradley, George Moran, and Neal El Attrache declare that they have no conflict of interest. Joshua S. Dines reports personal fees from Arthrex and from Conmed Linvatec, outside the submitted work.

**Human and Animal Rights and Informed Consent** No human or animal studies performed by the authors: this article does not contain any studies with human or animal subjects performed by any of the authors.

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