Since the 1970s, platelet rich plasma has been studied as one of the autologous products thought to have influence on biological healing.1 Platelet rich plasma (PRP) is a concentrate of platelets and the associated growth factors (GF) which is obtained through a patient’s own blood by withdrawal and centrifugation.2 It wasn’t until the 1990s that PRP started to gain popularity.3 It was first introduced for maxillofacial and plastic surgery.3 Since then, it has gained popularity and diversified its areas of indication. PRP is now established in fields of dentistry, dermatology, plastic and maxillofacial surgery, acute trauma, cosmetic surgery, and veterinary medicine.4 More recently, platelet rich plasma has been introduced in the orthopedic setting. In 2009, PRP was raised to a new level of public awareness when *The New York Times* detailed the use of PRP to treat an injured Pittsburgh Steelers player before the Superbowl.5 This is only one example of mainstream media that is making PRP more popular among professional and recreational athletes. In 2009 the PRP market was valued at $45 million and is expected to be more than $120 million by 2016.6

Platelet rich plasma is a simple, efficient, and minimally invasive method of obtaining a natural concentration of autologous growth factors.4 It has demonstrated the potential to modify the natural healing pathway in several ways. In the most simple of terms it is suggested that the healing potential is created by the ability of PRP to recruit, proliferate, and differentiate cells.2 The increased concentration of GFs and bioactive proteins released by activated platelets seems to be able to increase regeneration of tissue and restore biomechanical properties that are similar to normal tissue. It also amplifies the surge of chemical mediators to the injured area that mimics the initial stage of inflammatory response.2 In the normal healing process, platelets are responsible for clotting the blood and for homeostasis. Once a mediator activates them, the platelets degranulate and release bioactive proteins or growth factors that also have a role in healing. These growth factors include transforming growth factor-beta, platelet-derived growth factor, insulin-like growth factors I and II, fibroblast growth factor, epidermal growth factor, vascular endothelial growth factor, and endothelial cell growth factor.6 See Table 1 (as seen in Cole et al.) in Appendix A for a better understanding of these growth factors function. Some evidence suggests that PRP may have an inhibitory effect on certain proinflammatory cytokines that could be detrimental in early healing stages.2 The enhancement to reparative action and the minimizing power of tissue breakdown may allow local PRP application to speed up tissue healing process. This could lead to a wide range of potential applications and advantages for improved outcomes and faster recovery.2

 The literature focused on PRP is becoming more popular, however many of the studies focused on orthopedic injuries share controversial results in terms of the clinical efficacy. Many uncontrolled studies have shown benefit for a variety of indications, but recent controlled studies demonstrate less favorable results.6 In orthopedic surgery and sports medicine, the use of PRP has not been well standardized in the literature. The studies have not established standard techniques and the majorities are based on small case studies that are often underpowered.1 This paper will focus on the preparation and application of PRP, the orthopedic applications and the respective clinical outcomes. Finally, we will look at PRP in professional sport and the regulations that are associated.

The general protocol of preparing platelet rich plasma is to separate the blood components through one or two centrifugation steps. First differentiating the red and white blood cells from plasma and platelets and then again to produce an increase of concentration of platelets and GFs.2 The second centrifugation process separates the platelet poor plasma from the platelet rich plasma. Some studies implement the platelet poor plasma as one of their testing groups. PRP can only be made from anticoagulated blood. If the blood has already begun to clot, the technique will not work since platelets are a major component of the clot itself.1 The addition of a citrate marks the beginning of PRP preparation. By adding citrate to whole blood, the ionized calcium becomes bonded which inhibits the clotting cascade.1 Depending on the technique chosen, either an exogenous or endogenous platelet activation occurs by using either bovine thrombin or CaCl2.2 The clotting is required for platelet activation and thereby the release of growth factors. There are some studies that choose to use both techniques and other studies that do not report which, if any, activation agents are used.2

When bovine thrombin is used as the clotting activation system, 70% of the stored GFs are released in the first 10 minutes and nearly 100% released within an hour.1 Bovine thrombin is an intense platelet activator. However when CaCl2 is used, the goal is to create a platelet rich fibrin matrix. This dense fibrin matrix traps platelets. This system results in only a small amount of thrombin and therefore a smaller amount of platelet activation. This allows the growth factors to be released over a 7-day period. Studies also suggest that this fibrin matrix may act as a scaffold for cell migration and new matrix formation.1

With the non-standardized procedures, there are conflicting results regarding the correlation between GF content and platelet counts in PRP. This may likely be due to the various methods of processing, handling, and storing of samples, in addition to the type of assay performed.4 Little consistency is also noted on the time between retrieval and application. Due to the coagulate properties of PRP and platelets, this timing may directly influence its activity and reparative potential.2 Some studies choose to solidify the components into a gel-like substance. While this may keep preparation localized, it eliminates its injectability. In turn keeping this form limited to use in open surgeries only.2 These differences in PRP products must be taken into account when interpreting and comparing results and methods of the current literature.4

As one explores the research focused on platelet rich proteins, it is noticed that the level of research available is lacking and the potential for growth elaborate. In a meta-analysis that focused on a wide range of orthopedic indications (ACL reconstruction, spinal fusion, total knee arthroplasty, humeral epicondylitis, and Achilles tendinopathy) found that out of twenty-three RCTs, only six found significant functional benefits with the addition of PRP.6 Also of the ten prospective cohort studies, only three found PRP to have significant functional benefit.6 In another article that is a systematic review, they found 13 articles to meet their criteria and only three were prospective, randomized, double-blind studies (level 1).2 As researchers expand on the potential of this product, we can see animal studies being published to encourage the progression of literature. Many animal models that show significant effects on accelerated healing processes. However other studies have shown no biomechanical benefit. Despite lack of hard evidence through randomized clinical trials, the use of PRP in humans has increased significantly.2 Although, the amount of variability is extensive across the outcomes in the literature in terms of follow-up. Due to this lack of consistent study time lines, it makes it very difficult to compare findings across studies.6 Even with the gaps in the literature, there are some noticeable trends. PRP is being focused on extensively in areas such as tendons, ligaments, cartilage, and muscle strains.

Commonly in tendinopathy, the microscopic tears that occur in the hypovascular tissue heal by scar formation rather than normal vascular and inflammatory driven tendon healing pathways. However, theory states that PRP may be able to modulate the bioactive factors and increase potential for tendon healing.4 At this time, elbow tendinosis has the most evidence for use of PRP than any other anatomical area.2 Peerbooms et al. performed a study that found when comparing PRP to corticosteroid injections in people with lateral epicondylitis, they found significant effects on pain and function in the PRP group.7 Animal studies support positive effects of PRP on tendon repair—particularly with abundant tendon callus, increased force to failure, and enhancement of circulated derived cells that contribute to healing in the early phases.8

 Other preliminary studies were found to have increased interest in the effects of PRP on jumper’s knee, rotator cuff injury, and Achilles tendon repair, but higher level research is not yet documented.2 Rotator cuff repair shows some promising effects but the study format is not optimal.4 There have been reports showing benefit in range of motion and reduction in pain, but with no control group. Others have showed improvements in function and pain as a prospective trial but as a prospective case series, one also must hold reservation with the low level research that is being presented. At this time, more RCTs are needed to confirm the promises that the research has shown thus far with rotator cuff repair.4 Achilles tendinopathy seems to be one of the most controversial indicators of PRP. While some have found no significant differences between PRP groups and the control, others report earlier return to training in PRP groups. Since some of these preliminary studies show promise, but RCTs are needed to further confirm these proposed benefits.2 ACL reconstruction studies have found that there is no significant effect on accelerating the bone-tendon integration or prevention of tunnel widening, however PRP seems to have positive effects on accelerating the maturation process of the graft.2

Articular cartilage frequently undergoes macro or microtraumatic events that can lead to a loss of tissue homeostasis.4 This lack of equilibrium can result in accelerated loss of articular cartilage and in turn progress to arthritis. Cartilage has an inherent poor regenerative capacity, which makes these injuries particularly challenging for orthopedists. Biologists are confident that growth factors play a critical role in the phenotypic expression of chondrocytes. Many in vitro studies have found that PRP has the potential to proliferate chondrocytes and matrix synthesis. There is also documentation of animal models that have indicated PRP prevents progression of osteoarthritis after ACL transection. In some of the more recent human studies, they report that patients who are diagnosed with degenerative cartilage lesions can benefit in terms of function and pain with the application of a PRP injection.4 Filardo et al investigated 40 patients with osteoarthritis of the knee and were treated with three separate intra-articular PRP injections.9 Clinical outcomes revealed significant improvements in visual analog pain scale, International Knee Documentation Committee scores, and subjective evaluations at 6 months. More specifically, patients who were under the age of 60 demonstrated 85% satisfaction as compared to those older than 60, who reported only 33% satisfaction.9

In a systematic review published this year, they discuss two recent papers that have reported on PRP for plantar fasciitis.10 Aksahin et al compared the efficacy of PRP versus corticosteroids for plantar fasciitis in a cohort of 60 patients.11 Divided into two groups, participants either received an intra-lesional injection of PRP or corticosteroid injection and were observed at 6-month follow-up. Both groups reported significant improvement in functional status and pain with no inter-group differences.11 In the second paper, 25 patients were treated with a single injection of PRP via a peppering technique.12 This technique included one skin portal and 4-5 penetrations in to the fascia. They found that approximately 90% of patients reported full satisfaction and complete recovery. Patients reported being able to return to daily activities only two weeks after treatment. Follow up was done at approximately 10 months and with ultrasound evaluation, the researchers noted that the plantar fascia thickness was significantly reduced.12 While PRP did not prove to be superior to corticosteroid in Aksain’s report, we do know that by choosing this option, patients could avoid the well-known potential risks of corticosteroids.11

The literature is much more sparse when researching PRP and muscle injury application. In an animal study, they found that local delivery of PRP to multiply loaded, eccentric muscle injury models decreased full recovery time from 21 days to 14 days.13 Another animal study done on mice with a gastrocnemius contusion found that if the autologous conditioned serum was injected at 2, 24, and 47 hours, there were accelerated satellite cell activation and an increased diameter of regenerating myofibrils.14 However, there is some concern with introduction of PRP to muscular injuries. This is based on the increase of TGF-β and its potential to cause fibrotic changes. This chance of fibrotic healing is associated with increased incidence of reinjury.1 Foster mentions a case series presentation of 14 professional athletes with acute muscle injuries. Autologous PRP was injected directly into the tear under direct ultrasonic guidance and they found the return to play interval was diminished. A greater than 50% reductions in return to play was reported. However, this was a retrospective design and no control group was used.1 Some researchers hold very high caution with implementing PRP directly into the muscle due to its potential for fibrotic scarring.1

The reports mentioned above do lead us to believe there is some promise to PRP in clinical application. PRP has several theoretical advantages such as faster recovery and improved functional outcomes in tendon and ligament injuries.2 This could allow for earlier return to training and competition, improved immediate post injury performance and possible a reduction in injury relapse.2 In 2002, $15.8 billion in total health care expenditures was estimated for the medical management of sports related injuries.2

While the frequency of injury is high in sport, it is important, as healthcare professionals, to stay up to date on information regarding professional sports and their organizational regulations.

In 2009 the WADA rules prohibited the use of PRP and decided that platelet deprived preparations would be prohibited when administered intramuscularly.4 However, as of 2011, PRP is no longer prohibited for intramuscular use.2 Based on a recent search of the World Anti-Doping Program, they state, “Despite the presence of some growth factors, platelet-derived preparations were removed from the List as current studies on PRP do not demonstrate any potential for performance enhancement beyond a potential therapeutic effect.” 15 It is important to note though that he World Antidoping Agency does prohibit the use of individual concentrated GFs and the use of autologous blood intravenously (blood doping).4 Healthcare providers who may find themselves working with this population need to understand the implications of the rules and whom they apply to. For example, Olympic-affiliated and international antidoping governing bodies do not have jurisdiction over United States professional sports leagues.1 Professional baseball, football, soccer, hockey, and basketball are not specifically governed by WADA rules and are instead under the agreements made by the provisions of the league and unions. While these organizations do have a list of banned substances, PRP is not one of them.1 This is due to the thought that its effects are limited to the healing capabilities.

While platelet rich plasma has minimal adverse effects, there are still some serious concerns that have not been fully addressed in the literature. There are questions about the local or systemic carcinogenic effects related to high levels of growth factors. The theory exists based on the possibility of promotion of division and proliferation of the mutated cells.2 Even with these speculations, to date there have been no adverse events or deleterious effects on recovery or functional outcome have been documented.2 As mentioned previously, the use of PRP in soft tissue application is weakly supported and there is some concern on carry over. The positive effects being found in the in vitro studies may not directly represent PRPs in vivo function. The interrelation amount the numerous growth factors may be such that they require presence of other growth factors to properly modulate their effects.4 Current literature demonstrates positive effects on healing of PRP in animal and in vitro studies, however we are unsure if this can apply to non-healthy, degenerative tissues.

As platelet rich plasma continues to be researched, there are many changes that will need to be made before coming to any hard-and-fast conclusion. Establishing PRP as safe, reliable, and efficient will require completion of high-quality clinical trials with long term follow up. There is notable controversy on the optimal dosage, number, and interval of platelet rich plasma injections. In the meta-analysis published in 2012, the criteria included that articles had to be published no earlier than 2006. They claim that the dramatic surge in clinical trials on this topic reflects the enormous interest and growing use of autologous blood concentrates in orthopedics. Sheth gives multiple suggestions on how to improve this domain of literature. He suggests that if researchers intend to identify the minimally important differences in patient outcomes such as pain and function, their study will require sample sizes that are up to four times greater than the current average sample size seen in the literature. Basic science and clinical studies need to clarify optimal preparation and dosage of autologous blood concentrates. Sheth also comments on the fact that researchers should use validated, disease-specific, and patient-important outcome measures that can be consistently applied. Along with research design, we should be concerned on the comparison of platelet separation systems. An experimental model would be beneficial to further standardized the preparation of PRP. With time and these changes, PRP may become better understood and more effectively implemented.

PRP’s goal is to help us maintain a natural ratio of growth factors to allow maintenance of the body’s homeostatic environment and in turn hopefully provide a plethora of healing factors without disruption to the body’s complex system. PRP will continue to be appealing and validate further research due to its simplicity, low cost, availability, and absence of significant adverse consequences.

Appendix A

Table 1. Growth factors present in platelet-rich plasma.4

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

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