



# The Use of Platelet-Rich Plasma Preparations in the Treatment of Musculoskeletal Injuries in Orthopaedic Sports Medicine <sup>☆</sup>

Simone Cerciello, MD,<sup>\*</sup> Knut Beitzel, MA, MD,<sup>†</sup> Nathan Howlett, MS,<sup>‡</sup> Ryan P. Russell, MA,<sup>§</sup> John Apostolakos, BS,<sup>§</sup> Mary Beth McCarthy, BS,<sup>§</sup> Mark P. Cote, DPT, MSCTR,<sup>§</sup> and Augustus D. Mazzocca, MS, MD<sup>§</sup>

The use of platelet rich plasma (PRP) has been has become extremely popular in orthopaedic practice. The goal of PRP treatment is to concentrate growth factors present in the platelets and reintroduce them at the site of injury augmenting the natural healing process. The most common application of PRP is the treatment of tendon injuries. Other current applications include muscle strains and cartilage repair. Most reports over the use of PRP in in-vitro models have been particularly promising. However clinical applications are more controversial. This is the consequence of the lack of well-performed randomized controlled trials (RCT) and general confusion concerning the manufacturing process of PRP. Up to date there is still no consensus regarding the optimal platelet concentration, the platelet separation technique, the volume of concentrate, number of applications, and inclusion of leukocytes. Since these aspects are fundamental to achieve optimal PRP action, further research is needed to adopt standardized protocols and to prove the real efficacy of PRP.

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## Introduction

Autologous blood concentrates, such as platelet-rich plasma (PRP), have gained increasing attention in orthopaedic sports medicine. This increase is in part due to the growing attention these products have received in the media. As a result of this increased attention, it has been estimated that the market for PRP will grow from \$45 million in 2009 to more than \$120 million by 2016.<sup>1</sup> This exponential growth and

attention has necessitated the role of research to explore the capability of PRP to have a therapeutic effect on common musculoskeletal injuries in orthopaedic sports medicine.

Platelets are a crucial component of the body's natural response to injury and play a critical role in hemostasis. When activated, platelets release growth factors that enhance the healing process.<sup>2,3</sup> Marx reported that active secretion of these growth factors begins within 10 minutes of clotting with more than 95% of presynthesized growth factors being secreted within 1 hour.<sup>4</sup> The growth factors found in platelets include transforming growth factor-beta, fibroblast growth factor-2, platelet-derived growth factors, insulinlike growth factor-1, epidermal growth factor, hepatocyte growth factor, and vascular endothelial growth factor. Previous in vitro studies also suggest an additional role of PRP that includes over-expression of supplementary endogenous growth factors beyond what is contained within the platelet concentrate.<sup>5,6</sup> The ultimate goal of PRP treatment is to concentrate these growth factors and reintroduce them at the site of injury augmenting the natural healing process.<sup>7</sup>

The increasing popularity of PRP may in part be due to the preliminary results of in vitro and in vivo studies in animal

<sup>\*</sup>Orthopaedic Department, Science of Health, Molise University, Campobasso, Italy.

<sup>†</sup>Department of Trauma and Orthopedic Surgery, Trauma Center Murnau, Germany.

<sup>‡</sup>University of New England College of Osteopathic Medicine, Biddeford, ME, USA.

<sup>§</sup>Department of Orthopaedic Surgery, University of Connecticut Health Center, Farmington, CT.

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Address reprint requests to Augustus D. Mazzocca, MS, MD, Department of Orthopaedic Surgery, University of Connecticut Health Center, Farmington, CT 06032. E-mail: mazzocca@uconn.edu

models, which have reported positive effects of PRP on healing.<sup>5,8,9</sup> These studies, however, included healthy tendons or acute traumatic lesions, which are different pathologic entities than degenerative conditions commonly encountered in orthopaedic practice. Owing to the positive results of these earlier studies, the use of PRP has been advocated in the management of bone, muscle, tendon, and cartilage injury.<sup>7,10,11</sup> Initial results in uncontrolled studies were promising and reported benefits such as decrease in pain levels, improvement in healing, and improvement in function for several conditions.<sup>12-14</sup> However, further studies have reported less favorable results.<sup>15,16</sup> A recent meta-analysis concluded that the use of PRP provided no significant benefit up to 24 months.<sup>17</sup> The wide discrepancy in the efficacy of PRP is likely the consequence of poor standardization. Variability in plasma preparations as a result of differences in patients, as well as methods of procurement; the broad range of diseases, disorders, and conditions included; and varying methods of outcome measures, has resulted in substantial heterogeneity among current clinical research regarding PRP.

## Platelets Concentration

A sample of blood will normally contain 93% red blood cells, 6% platelets, and 1% white blood cells with an average platelet concentration of 200,000 per  $\mu\text{L}$  (normal range 150,000-350,000 per  $\mu\text{L}$ ).<sup>18,19</sup> In PRP, the ratio of red blood cells to platelets is reversed, thereby increasing factors that would be more useful in healing. The exact ratio of red and white blood cells to platelets in PRP is variable depending on the way in which the PRP is prepared. From a quantitative perspective, PRP is broadly defined as a sample of autologous plasma with platelet concentrations above baseline blood values.<sup>7,18</sup> In an attempt to make preparations more specific, some authors have adopted a more objective definition of 5 times the platelet concentration of whole blood,<sup>20</sup> that is, 1,000,000 per  $\mu\text{L}$  platelet count.<sup>21,22</sup>

Mazzucco reported that a concentration greater than  $200 \times 10^3/\mu\text{L}$  was sufficient for a therapeutic effect<sup>23</sup>; platelet concentrations of approximately 2.5 times greater than native blood ( $142.7 \pm 57.9 \times 10^3/\mu\text{L}$ ) have positive effects on osteoblasts and fibroblasts in vitro.<sup>23</sup> Conversely, adverse events have been observed at higher dosages ( $> 3.5$  times platelet concentration of native blood).<sup>24</sup> According to these results, different concentrations of PRP may produce varying effects.

## Separation and Activation

PRP may be prepared in the laboratory, operating room, outpatient sports medicine clinic, or radiology setting using a centrifuge. The first step is to add an anticoagulant, such as citrate, to the autologous whole blood. The centrifuge separates whole blood into 3 layers based on sedimentation rates: red blood cells (RBCs) (specific gravity = 1.09) in the bottom layer, platelet-poor plasma (PPP) (specific gravity = 1.03) in the top layer, and platelet concentrate that contains white

blood cells (PRP) (specific gravity = 1.06) in the middle layer.<sup>25</sup>

There are several types of centrifuge methods for the preparation of PRP: the gravitational platelet sequestration technique that requires only a tabletop centrifuge system and takes less than 30 minutes, the cell separator technique that generally requires a full unit of whole blood, and smaller compact office systems.<sup>7,26,27</sup> Centrifuge systems differ in their ability to separate RBCs from platelets, their ability to separate leukocytes from platelets, and the fact that some may shear platelets during the centrifugation process leading to premature platelet activation and degranulation.<sup>26</sup> Once the PRP has been prepared, platelets must be activated to release growth factors. This can be achieved in several ways. One option is to add bovine thrombin to the PRP, which releases 70% of stored growth factors within 10 minutes and nearly 100% within 1 hour.<sup>27</sup> A second option is to use calcium chloride to convert autologous thrombin to prothrombin resulting in platelets being trapped in a fibrin matrix. As a small amount of thrombin is formed, growth factors are gradually released over 7 days. An additional option is to use type-I collagen to activate PRP. In common practice, bleeding during local infusion of PRP provides sufficient clotting factor, thrombin, to activate platelets.

Furthermore, there are several different methods of PRP application: direct application, single or multiple injections, and delivery in a gel or collagen sponge. A recent study compared the efficacy of different PRP separation methods available on the market, and evaluated the concentrations of platelets, red blood cells, white blood cells, and growth factors.<sup>28</sup> This study measured 3 repetitive blood draws for PRP components. Their results showed that the content and concentration of platelets, white blood cells, and growth factors within the 3 methods of separation differed significantly, however, all techniques resulted in a significant increase in platelet concentration compared with native blood. An additional finding showed that intraindividual results demonstrated wide variations in platelet and cell concentrations as well as levels of growth factors regardless of separation method.<sup>28</sup> The 3 groups of PRP separation methods were then evaluated on different cells cultures: osteoblasts, tenocytes, and myocytes.<sup>29</sup> Interestingly, the differing characteristics of the 3 PRP samples had specific effects on different cells, suggesting that the application of unique PRP separations may result in variable effects on the clinically relevant target cells in vitro. This is relevant to clinical application as 4 different types of platelet concentrate may be obtained: leukocyte-poor or pure PRP, leukocyte-rich PRP, pure platelet-rich fibrin clot, and leukocyte platelet-rich fibrin clot.<sup>26</sup>

The variable amounts of white blood cells in PRP preparations have been discussed in the past and some authors recommend avoiding tissue exposure to white blood cells as they promote an inflammatory reaction leading to inhibitory effects on tissue healing.<sup>11,26,30,31</sup> Other investigators have reported the beneficial effects of increased antibacterial and immunologic resistance,<sup>26,32</sup> as well as an increase in growth factor release.<sup>33</sup>

Platelet concentration levels and composition are influenced by manufacturing and production factors, which include

centrifugation force and duration. Different production methods in regard to achieving a desired concentration and mix of PRP components can assert varying biological effects, and therefore several potential applications. In a recent study, the anti-inflammatory role of PRP has been compared with that of ketorolac and methylprednisolone.<sup>34</sup> PRP and ketorolac reduced cellular inflammation markers (E-selectin, vascular cell adhesion molecule, and human leukocyte antigen DR) compared with controls; however, the most relevant effect was achieved with methylprednisolone.

## PRP and Cartilage

The incidence of cartilage pathology is rising as a consequence of wide participation in sports activities among the young and middle-aged populations.<sup>35,36</sup> The treatment of this wide spectrum of cartilage pathologies is a great challenge for researchers and clinicians as hyaline cartilage has a limited healing potential. This is mainly because of poor blood supply and its inability to regenerate its native microscopic and histologic structure following injury. Several studies have demonstrated the efficacy of PRP on cartilage defects and osteoarthritis. Sun, using a rabbit model of osteochondral defects, found improved healing as assessed by macroscopic examination, microcomputed tomography, and histologic evaluation at 4 and 12 weeks.<sup>37</sup> Saito et al<sup>38</sup> reported similar data in a rabbit model of osteoarthritis. Kwon et al<sup>39</sup> in a similar rabbit model found that PRP effect was independent from the severity of collagenase-induced knee osteoarthritis. Milano et al<sup>40</sup> compared the effects of microfracture with PRP gel to PRP injection in an ovine model. They found the PRP gel to be more effective than a PRP injection. Kon et al<sup>41</sup> in an ovine model compared PRP and scaffold-alone in the treatment of osteochondral defects. They concluded that PRP had a negative effect on repair when compared with scaffold-alone.

Concerning the clinical application of PRP in the treatment of cartilage defects or osteoarthritis, Sampson et al<sup>42</sup> performed a prospective study on 14 patients with primary and secondary knee osteoarthritis. All patients received 3 PRP injections in the affected knee at 4-week intervals. A significant improvement in knee injury and osteoarthritis outcome scores, including pain and symptom relief was achieved. In a similar study, Kon et al<sup>43</sup> evaluated 100 patients (115 knees) treated with PRP. The study demonstrated that PRP treatment is safe, reduces pain, and improves knee function, especially in younger patients. However, at the 24-month follow-up, outcomes worsened from 67% to 59% of normal or nearly normal knees between the 12- and 24-month evaluations. Further evidence of PRP's clinical effect was shown by Wang-Saegusa et al<sup>44</sup> who performed a prospective study on 261 patients with unilateral or bilateral knee osteoarthritis (OA), symptomatic for more than 3 months. All patients received 3 injections 2 weeks apart. At 6 months, statistical analysis revealed significant improvement in all the scores used in the study. Napolitano et al<sup>45</sup> also evaluated the treatment of 27 patients, either affected by simple chondropathy or initial OA, with 3 injections of 5 ml PRP performed 1 week apart from

each other. At 6 months follow-up, significant improvement was observed in subjective scores. Of equal importance, no adverse events were observed.

Other studies have compared the results of PRP injections with those of hyaluronic acid (HA). Spakova et al<sup>46</sup> compared the efficacy of PRP vs viscosupplementation on 120 patients. At 3 and 6 months follow-up, Western Ontario and McMaster Universities Osteoarthritis Index scores and a pain numeric rating scale revealed an increase in both groups. However, statistically superior results were observed in the PRP group. Filardo et al<sup>47</sup> also evaluated PRP vs viscosupplementation in 109 patients (55 treated with HA and 54 with PRP) at 12 months of follow-up. They found that for middle-aged patients with moderate signs of OA, PRP did not offer better results compared with HA. Nonetheless, more promising results were shown in less severe stages of OA. In conclusion, PRP represents a promising option for clinically treating patients with cartilage pathology. However standardized preparation and usage protocols are required for future studies to obtain statistically significant outcomes.

## PRP and Tendon Healing

Common musculoskeletal injuries account for nearly 100 million office visits annually in primary care and orthopaedic clinic settings in the United States.<sup>19</sup> Soft tissue injuries that include damage to ligaments or tendons represent up to 45% of all musculoskeletal injuries.<sup>48,49</sup>

Chronic and degenerative musculotendinous pathologies can be challenging to treat and can have a protracted course compromising an otherwise active lifestyle. Many of these patients with sports or overuse-related injuries might require surgical intervention and extended rehabilitation, yet have unclear outcomes. Tendons and ligaments heal more slowly than most tissues due to their poor vascular supply. This results in new tendon tissue that does not always have the same structural and functional properties as the original tendon or ligament.<sup>50</sup> One possible explanation is that the poor blood supply results in a lack of adequate growth factors being delivered to the site of injury.<sup>51</sup> PRP injections may represent a quick and effective alternative to historical treatment approaches. Anitua et al<sup>52</sup> suggested that platelet-rich clots might be beneficial in the treatment of tendon injuries by inducing cell proliferation and promoting the synthesis of angiogenic factors during the healing process, therefore promoting better quality scar tissue when examined histologically.<sup>53</sup> This hypothesis has been confirmed by *in vitro* studies. de Mos et al<sup>5</sup> demonstrated that both platelet-rich clot releasate and platelet-poor clot releasate stimulated cell proliferation and total collagen production in human tenocyte cultures. Despite that clinical reports and studies on animal models are much more controversial, there have been some promising results of PRP therapy on tendon repair. In a rabbit patellar tendon defect model, a single application of PRP was found to improve tendon defect healing related to over-expression of insulinlike growth factor-I.<sup>5</sup>

In a recent case-control study comparing open suture repair with and without an application of a preparation rich in growth

factors for Achilles tendon tear in athletes, athletes receiving preparation rich in growth factors recovered their range of motion earlier, showed no wound complication, and took less time to resume gentle running and training activities.<sup>54</sup> Similarly, Lyras et al<sup>55</sup> found a significant improvement in the mechanical properties of the regenerated tendon in the PRP-treated group at 14 days, returning to baseline at 28 days, concluding that PRP has a strong effect in the early phases of tendon healing. On the contrary, a randomized controlled trial of 30 patients with surgical repair of the Achilles tendon reported no additional benefit of PRP over standard treatment.<sup>56</sup> In another randomized controlled trial of patients with chronic Achilles tendinopathy, a PRP injection was no better in improving pain and activity compared with saline injection.<sup>57</sup> de Vos et al<sup>15</sup> reported similar results. They showed that PRP had no statistically significant benefit in clinical scoring outcome or ultrasound findings in chronic Achilles tendinopathy at 24-weeks and 1-year follow-up.<sup>58</sup> However one should consider that saline injection might not be the best placebo because it likely has an active role in tendinopathy recovery. Injecting saline into the tendon alters the pressure-volume relationship in a given space, thereby disrupting pathologic vascular and neural ingrowth.<sup>59</sup> Additionally, injection-related needle trauma produces local bleeding, which is a known irritant and recruiter of platelets in both groups.

## Lateral Epicondylitis

Lateral epicondylitis is commonly referred to patients and physicians as "tennis elbow." It is the most common cause of elbow pain in adult athletes, occurring in more than 50% of tennis players.<sup>60</sup> It is characterized by repetitive microtraumas that cause mucoid degeneration of the common extensor tendon where it attaches to the lateral epicondyle of the humerus. This results in pain, weakness, and activity limitation, and therefore treatment of lateral epicondylitis is of great interest to clinicians and patients alike. Mishra and Pavelko<sup>61</sup> in a small group of patients affected by chronic elbow tendinosis, showed that subjects receiving PRP in a single injection session had an 81% improvement in pain scores at 6 months and up to 93% at 25 months compared with their baseline status; however, the large loss of subjects in a control group limited the strength of study conclusions.

Similarly, a recent large trial on 100 subjects compared PRP with corticosteroid injections. A statistically and clinically significant difference in disease-specific quality of life measured through pain scores emerged in favor of the PRP group.<sup>62</sup> Interestingly, the PRP group progressively improved at 1 year compared with the steroid group, which declined after an initial short-term improvement, suggesting that progressive healing may be responsible for clinical improvement in the PRP subjects. Gosens et al<sup>63</sup> reported similar results, which showed by 2 years FU, PRP injection improved healing as compared with corticosteroids injection. Moreover, another interesting study demonstrated that a single PRP injection improved pain and function scores in 29 patients who failed to improve with 6 months of corticosteroid treatment.<sup>64</sup>

## Ligament Injuries

PRP has also been explored in anterior cruciate ligament (ACL) reconstruction. The ability of PRP to enhance graft healing into the bone tunnels and the possibility of reducing donor site morbidity have each been tested. Two randomized controlled trials showed no statistically significant difference in bone filling of the tunnels made for ACL reconstructions as visualized on magnetic resonance imaging, though one of these found an improvement in the clinical score.<sup>16,65</sup> Another randomized controlled trial of 108 patients showed that PRP had an enhancing effect on the maturation of the graft as visualized by magnetic resonance imaging at 6 months.<sup>66</sup>

Similarly, another study demonstrated that locally applied platelet gel enhanced early revascularization of the graft at the interface after ACL reconstruction,<sup>67</sup> leading to better anteroposterior knee stability at 6 months.<sup>68</sup>

## Muscle Injuries

Acute muscle injuries (sprains) are common, especially among elite athletes. The most common localization is the thigh, which accounted for 16% of all muscle injuries as reported by the survey of the International Association of Athletics Federation.<sup>69</sup>

The major concern after muscle sprains is the risk of reinjury. This is an especially common occurrence after hamstring injuries, where there is a 30% reinjury rate within 1 year of initial damage.<sup>70</sup> Thus, recognizing the severity of the lesion according to its size and location is essential to improve healing and decrease the risk of reinjury. Muscle healing is an intricate and dynamic process aimed at restoration of anatomical continuity and function of the injured muscle.<sup>71</sup> Local delivery of PRP has been found to shorten the recovery time after a muscle strain injury in a small animal model.<sup>72</sup>

Similar data were found after creating a tibialis anterior muscle defect in rats. PRP injections led to a quicker time to recovery than in platelet-poor plasma or sham-treated animals.<sup>7</sup>

Similarly, PRP treatment results in athletes are encouraging. Cugat et al<sup>73</sup> conducted a cohort study of 14 professional athletes with acute muscle injuries who were treated with ultrasound-guided injections of PRP. The patients showed a quick return to play and enhanced healing in tears assessed with ultrasound analysis. Similarly, Sanchez et al<sup>74</sup> reported a recovery time that was twice as fast as expected in 20 athletes. However, some researchers have suggested that PRP may actually lead to unwanted fibrotic healing in muscle.<sup>75</sup>

## Conclusion

PRP injections have emerged in recent years as an increasingly common treatment in orthopaedic practice albeit through growing media attention. They are now used in the treatment of several pathologies varying from chronic tendinopathies, including lateral epicondylitis (tennis elbow), plantar fasciitis,

Achilles tendinopathy, and patellar tendinopathy, to acute injuries including ligament and muscle strains.

Current literature demonstrates that use of PRP in animal and in vitro studies has a positive effect on healing.<sup>5,9</sup> However, some concerns still exist about its reliability and efficacy in clinical practice. A recent meta-analysis stressed the uncertainty about the evidence regarding a clinical benefit of the use of autologous blood concentrates, such as PRP, for a variety of disorders in orthopaedics.<sup>17</sup> Fifteen randomized controlled trials and 5 prospective cohort studies were analyzed; they all showed no clinical benefit with PRP. Similar results were reported in 2 other meta-analyses.<sup>76,77</sup> These results might be the consequence of several issues. Human in vitro and animal studies are generally performed on healthy tendon and acute traumatic lesions, whereas most clinical studies generally refer to degenerative tissue diseases that have different histologic properties. Additionally, there is a lack of consensus regarding the optimal platelet concentration, the platelet separation technique (including the use of activating agents), the volume of concentrate, number of applications, and inclusion of leukocytes. This is particularly important considering most commercial preparations of PRP vary in terms of growth factors, activation, and platelet concentration. Nevertheless, the PRP is generally a safe, easily obtained, and relatively simple treatment. The short processing time, availability of multiple growth factors at a relatively inexpensive cost, as compared with obtaining individual growth factors or even stem cells, make PRP an appealing alternative to traditional treatment methods. Further research is needed to distinguish whether clinical efficacy truly exists for PRP treatments.

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