

# Is Platelet-Rich Plasma a Future Therapy in Pain Management?



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## KEYWORDS

• Platelet-rich plasma • Pain management • Future therapy • Chronic pain

## KEY POINTS

- Platelet-rich plasma (PRP) has the potential to regenerate tissues through the effects of bioactive molecules and growth factors in the alpha granules of circulated platelets.
- Several PRP preparation systems exist on the market, but there is no universal protocol or standard dosing for PRP or its related growth factors.
- Although limited evidence in the form of prospective, randomized controlled trials exists, the popularity in PRP therapy has still increased in recent years.

## INTRODUCTION

The practice of medicine relies on evidence-based clinical research, which prompts clinical researchers to search for alternative therapeutic modalities that are more efficacious and/or more tolerable than existing treatments. Platelet-rich plasma (PRP) has been around for decades, dating back to the 1950s through its use in dermatology and oral maxillofacial surgery, but interest in a role as an effective alternative treatment in many other clinical applications has increased greatly over the past several years.<sup>1</sup>

Platelets contain more than 1100 proteins, some of which include enzymes, enzyme inhibitors, growth factors, immune system messengers, and other bioactive compounds that play a role in tissue repair and wound healing.<sup>2–5</sup> These bioactive

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molecules and growth factors that stimulate the tissue healing process are actually found in the alpha granules of circulating platelets.<sup>2–4</sup> Basic science data suggest that platelet-related growth factors should have a beneficial role in enhancing connective tissue healing, but there have not been enough prospective, randomized, double-blinded, controlled studies documenting the positive effect of PRP growth factors on tissue healing.<sup>6–8</sup> Nonetheless, PRP has already been used extensively in various medical specialties, including dentistry, orthopedics, neurosurgery, ophthalmology, maxillofacial surgery, and cosmetic surgery for more than 3 decades.<sup>5,9,10</sup>

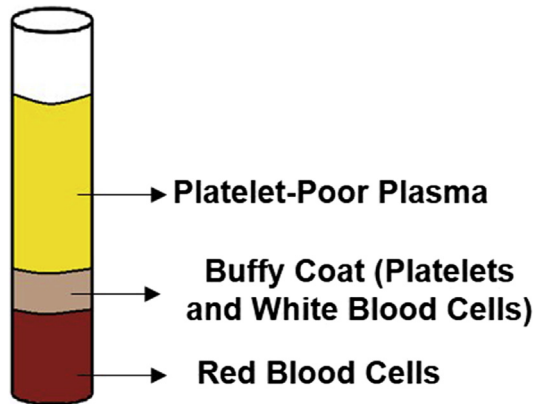
This review article clarifies what PRP consists of, how PRP is prepared, how the various PRP-related growth factors play a role in tissue healing and repair, and how the different PRP components affect wound healing. The use of PRP injections as an alternative treatment in pain management is highlighted through evidence-based research reporting the efficacy of PRP therapy in treating different pain conditions, including lateral epicondylitis, osteoarthritis, and surgical rotator cuff repair, as well as eliminating neuropathic pain and intervertebral disc degeneration (IDD).

## WHAT IS PLATELET-RICH PLASMA AND HOW IS IT CREATED?

Classically, PRP is defined as a sample of plasma with a platelet concentration that is, 3 to 5 times greater than the physiologic platelet concentration found in healthy whole blood.<sup>11</sup> The normal range for platelet concentration in whole blood is between 150,000 and 450,000 platelets per microliter. However, owing to the large variety of PRP products that exist today, the term PRP has become more generic to account for these different end products. The typical process of obtaining PRP can take place in a clinic, or even an operating room, but it begins with collecting whole blood from a subject or patient through venipuncture.<sup>11,12</sup> There is usually a calcium-binding anticoagulant present when collecting the whole blood such that the conversion of prothrombin to thrombin is blocked, thereby inhibiting the initiation of the clotting cascade.<sup>11</sup> Although the use of an anticoagulant is not mandatory for obtaining PRP, the absence of a calcium-binding anticoagulant leads to rapid activation of the clotting cascade within 30 seconds to minutes.<sup>13</sup> Citrate dextrose-A and citrate phosphate dextrose are the only 2 anticoagulants that have been reported to safely separate platelets, while also supporting the metabolic needs of the platelets.<sup>11</sup>

Once whole blood is collected with or without the anticoagulant present, the most common technique to obtain PRP involves 1 or 2 rounds of centrifugation using a table-top centrifuge system.<sup>5</sup> Centrifugation is a process by which blood is separated into 3 layers (**Fig. 1**): with platelet-poor plasma as the top layer (specific gravity of 1.03), platelet concentrate with white blood cells (WBCs) as the middle layer (specific gravity of 1.06), and red blood cells as the bottom layer (specific gravity of 1.09).<sup>14</sup> The completion of the first centrifugation, often termed a “soft” spin (1200–1500 RPM with a low gravitational force), will result in separation of plasma and platelets from red blood cells and WBCs.<sup>15</sup> This plasma and platelet concentrate may still contain some WBCs that did not completely separate. A second centrifugation, often termed a “hard” spin (4000–7000 RPM), acts to further concentrate the platelets and plasma into PRP and platelet-poor plasma fractions.<sup>14,15</sup> The role of platelet-poor plasma in tissue healing is unclear currently.<sup>15</sup> Once PRP is collected via centrifugation, it is maintained in a sterile environment and used as needed for a particular procedure.<sup>16</sup> PRP remains stable in an anticoagulated state for 8 hours or longer, which is beneficial when performing lengthy procedures.<sup>17</sup>

The final concentration of platelets in the end PRP product is related directly to the amount of whole blood taken to create PRP, the volume of plasma that is used to suspend



**Fig. 1.** Example of platelet-rich plasma (PRP) preparation. The buffy coat is the PRP, PRP-related growth factors.

these platelets, and the platelet recovery efficiency of the specific technique used to obtain PRP.<sup>11</sup> It is estimated that the final PRP volume is anywhere between approximately 10% and 16% the volume of whole blood originally obtained from a patient.<sup>12,18</sup>

As stated, the PRP growth factors (**Table 1**) that enhance wound healing are located in the alpha granules of circulating platelets. There have been multiple in vitro studies that have shown a dose-response relationship between the stimulation provided by PRP related growth factors and connective tissue cells.<sup>4,11,19–21</sup> However, most of these PRP growth factors do not have a linear dose-response relationship with connective tissue cells, and some can display an inhibitory effect on cellular function once a certain threshold concentration is reached.<sup>19–21</sup> The exact platelet concentration and the dose of associated growth factors required to optimize the numerous cell types involved in connective tissue healing in vivo remains unclear.<sup>5</sup> Moreover, through in vivo and in vitro research studies, it has been found that PRP actually induces the overexpression of endogenous growth factors in addition to the PRP-related growth factors found in the alpha granules of platelets.<sup>22,23</sup> It also remains unclear if the overexpression of endogenous growth factors offers an additional benefit in tissue healing.

#### ***Variety of Platelet-Rich Plasma End Products***

Because there are numerous techniques available that create PRP, there is no universal PRP end product. The use of various existing techniques has resulted in a wide variety of PRP products. Currently, there are more than 40 commercial systems that create platelet-rich substance from autologous whole blood.<sup>1</sup> Individual patient factors such as age, circulation, and comorbidities can lead to a difference in PRP-related growth factors and overall content.<sup>24</sup> This PRP can vary in several ways, including the volume of whole blood that was harvested, the inclusion or exclusion of WBCs, the exogenous activation of platelets by thrombin, or the formation of a platelet-rich fibrin matrix.<sup>14</sup> Interestingly, even when specific PRP protocols are used implementing the same kits and centrifuges, the final platelet concentration can still vary greatly within a given technique.<sup>24–27</sup> There is no universal classification system for PRP, but there are 4 categories of PRP that are recognized including leukocyte poor or pure PRP, leukocyte PRP, pure platelet-rich fibrin clot, and leukocyte platelet-rich fibrin clot.<sup>14</sup>

Table 1 Growth factors identified within platelet-rich plasma and their biological functions		
Name	Abbreviation	Function
Platelet-derived growth factor	PDGF	Stimulation of fibroblast production, chemotaxis, TGF- $\beta$ 1, collagen production; upregulation of proteoglycan synthesis of fibroblasts, smooth muscle cells, chondrocytes, osteoblasts and mesenchymal stem cells
Insulin-like growth factor-1	IGF-1	Promotion of cell growth, differentiation, recruitment in bone, blood vessel, skin, other tissues; upregulation of collagen synthesis with PDGF of fibroblasts
Transforming growth factor-beta 1	TGF- $\beta$ 1	Promotion of fibroblast proliferation, extracellular matrix formation, cell viability, production of collagen from fibroblasts; suppressed interleukin 1-mediated effects on proteoglycan synthesis in cartilage
Vascular endothelial growth factor	VEGF	Promotion of cell growth, migration, new blood vessel growth and antiapoptosis (anti-cell death) of blood vessel cells
Basic fibroblastic growth factor	bFGF	Stimulation of collagen production, angiogenesis and myoblast proliferation
Epidermal growth factor	EGF	Promotion of cell recruitment, proliferation, differentiation, angiogenesis, cytokine secretion by mesenchymal and epithelial cells
Connective tissue growth factor	CTGF	Promotion of angiogenesis, cartilage regeneration, fibrosis, platelet adhesion

From Wang SZ, Rui YF, Tan Q, et al. Enhancing intervertebral disc repair and regeneration through biology: platelet-rich plasma as an alternative strategy. *Arthritis Res Ther* 2013;15(5):220; with permission.

**Platelet-Rich Plasma Containing White Blood Cells**

Some of the techniques used to create PRP results in the inclusion of WBCs with the final PRP product. Currently, it remains unclear if PRP products containing WBCs are beneficial or harmful in tissue healing. PRP containing WBCs has been shown to not only increase healing in soft tissue injuries complicated by infection, but to also inhibit the growth of some bacteria causing infection.<sup>12,28,29</sup> Some studies have reported a positive correlation between increased WBC concentration in PRP and increased levels of the inflammatory cytokines interleukin-1 $\beta$ , tumor necrosis factor- $\alpha$ , interleukin-6, and interleukin-8, which leads to the current concept that WBCs in PRP could potentially inhibit healing in certain tissues or in certain phases of recovery.<sup>2,30-37</sup>

However, it can be stated that positive or negative effects cannot be generalized to all tissues or all clinical conditions and that PRP preparations with WBCs may be beneficial in some conditions.<sup>27,30,31</sup> Additionally, the presence of WBCs in PRP products could also be attributed to the fact that processing techniques are unable to separate these cells completely from the platelets and plasma concentrate.<sup>5,14,26</sup> Prospective clinical studies are therefore needed to prove whether PRP containing leukocytes is advantageous or deleterious.

**Platelet-Rich Plasma Activated by Exogenous Thrombin**

The half-life of circulating platelets is 7 days.<sup>3</sup> When these circulating platelets become activated by the forces of fluid flow, contact with fibrillar collagen, contact with

thrombin, or contact with the basement membrane of cells, the cytokine contents and bioactive molecules present in the alpha granules of the platelets are released and subsequently secreted.<sup>3,38</sup> There are some PRP preparation techniques that implement exogenous bovine or autologous thrombin activation of platelets before injection of PRP because of the assumption that this makes the bioactive molecules in the alpha granules of platelets readily available to target cells.<sup>38</sup> However, it has yet to be proven clinically that the exogenous activation of platelets with thrombin improves connective tissue healing or that it is a recommended step in tissue repair. In fact, when PRP is injected into connective tissues, the platelets become activated by coming into contact with the collagen and tissue thromboplastin present in these tissues.<sup>38</sup> About 70% of the PRP growth factors are secreted within 10 minutes of platelet activation, and within 1 hour approximately 100% of the growth factors are secreted.<sup>11</sup> Thus, activating platelets with exogenous thrombin before injecting PRP leads to a rapid secretion of the platelet growth factors and therefore may shorten the time that target tissues are exposed to these growth factors.<sup>11</sup> Overall, the clinical impact of exogenous thrombin activation of platelets on tissue healing remains unclear because there is limited research at present.<sup>39</sup>

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### ***Platelet-Rich Fibrin Matrices***

Fibrin serves a very important role in the initial stage of the healing process by acting as a scaffold to provide a surface for cell attachment, adhesion, and migration.<sup>40</sup> These fibrin scaffolds can be created via initiation of the clotting cascade during PRP preparations by adding calcium chloride and/or thrombin after the first centrifugation of whole blood.<sup>24,41–43</sup> The resultant platelet-rich fibrin matrices have the potential for acting as a conductive matrix for migration of cells involved in wound repair and as a reservoir for growth factors, thus serving to prolong growth factor activity, delivery, and availability.<sup>44</sup> Even though there has been a recent study demonstrating the ability of platelet-rich fibrin constructs to initiate healing in lower extremity ulcers, more prospective, randomized, blinded clinical trials are needed to study the role of such constructs in treating other tissues and areas.<sup>45</sup>

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### ***Current Clinical Applications of Platelet-Rich Plasma***

There is not substantial scientific evidence available in the form of randomized, double-blind clinical studies that document the reliability and effectiveness of PRP therapy in various injuries, because PRP has become increasingly popular over time and its use has increased in similar degrees by orthopedists, primary care physicians, sports medicine physicians, dentists, and other medical specialists.<sup>46,47</sup> Some small, nonrandomized studies and anecdotal case reports have reported that PRP can reduce surgery-related swelling and pain, decrease wound infection rate, promote bone healing in a shorter period of time, increase bone strength, and decrease recovery time.<sup>12,14</sup> PRP has been documented to be used in heart bypass surgery, plastic surgery, maxillofacial surgery, dermatology, and orthopedic surgery.<sup>16</sup> Currently, PRP is used commonly to treat lateral epicondylitis, plantar fasciopathy, Achilles and patellar tendinopathies, acute muscle tears, medial collateral ligament tears, anterior cruciate ligament tears, and ankle sprains.<sup>16</sup>

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### ***Platelet-Rich Plasma Injection in Lateral Epicondylitis (Tennis Elbow)***

PRP use in tennis elbow has been rather extensively studied. In fact, a recent large double-blinded randomized controlled trial ( $n = 100$ )<sup>48</sup> that compared PRP injections with corticosteroid injections concluded that there was a statistically and clinically significant difference in tennis elbow-specific quality of life in pain scores favoring the PRP

group.<sup>48</sup> Criteria to participate in the study included having lateral epicondylitis for longer than 6 months with a pain score of at least 50 on a visual analog score (0–100), and excluded patients age younger than 18 years and a history of cervical radiculopathy or carpal tunnel syndrome.<sup>48</sup> As part of the double-blind approach, 27 mL of whole blood was collected from both the PRP group and the corticosteroid (control) group into a 30-mL syringe containing 3 mL sodium citrate.<sup>48</sup> After 3 mL of PRP was obtained from this blood, all the tubes were masked with opaque tape, then 3 mL of PRP was injected in each patient in the PRP group and 3 mL of corticosteroid was injected in each patient in the control group.<sup>48</sup> The study suggested that progressive healing could be playing a significant role in the clinical improvement of the PRP group based on the finding that the PRP group progressively improved at the 1- and 2-year follow-up visits in comparison with the corticosteroid group, which only showed short-term clinical improvement followed by a decline.<sup>48,49</sup> Mishra and Pavelko<sup>50</sup> did a controlled trial with 20 patients comparing PRP injections containing WBCs with bupivacaine local injections for treating chronic elbow epicondylar tendinosis. They found that the PRP group had a 93% reduction in pain at an average follow-up of 25.6 months ( $P < .0001$ ). Additionally, after 8 weeks of treatment with PRP, there was a significant clinical improvement in the visual analog scale and Mayo elbow scores ( $P = .001$  and  $P = .008$ , respectively). Based on the results of these studies, it is suggested that PRP injections provide better clinical outcomes than local anesthetic and corticosteroid injections in treating pain related to tennis elbow.

### ***Osteoarthritis and Articular Cartilage Healing***

Overall, through the results of several studies, it seems that PRP may offer therapeutic benefits for repairing cartilage in patients with joint disease secondary to arthritic changes. A particular prospective, double-blind, randomized trial that randomized 78 patients with bilateral knee osteoarthritis to receive either a single saline injection, a single WBC-filtered PRP injection, or 2 PRP injections 3 weeks apart, concluded that both of the PRP groups had significantly better clinical outcomes than the control group 6 months status post treatment.<sup>51</sup> Cerza and colleagues<sup>52</sup> performed a prospective, double-blind, randomized controlled trial that showed better outcomes 24 weeks after treatment in a group receiving a single PRP injection when compared with a group receiving a single injection of hyaluronic acid ( $P < .001$ ). In another prospective, double-blind, randomized controlled trial that involved 109 patients, Filardo and colleagues<sup>53</sup> reported that the group receiving intraarticular PRP injections had significant clinical improvement 1 year after treatment, but their improvement was not better than the group receiving a single hyaluronic acid injection. Although the benefits of PRP injections in treating osteoarthritis is highlighted by these 3 studies, a group of authors of a Clinical Practice Guideline sponsored by the American Academy of Orthopedic Surgeons were “unable to recommend for or against growth factor injections and/or PRP for patients with symptomatic osteoarthritis of the knee.”<sup>54</sup>

Mei-Dan and colleagues<sup>55</sup> performed a prospective, nonrandomized controlled trial comparing the effects of PRP and hyaluronic intraarticular injections in 32 patients with symptomatic osteochondral lesions of the talus. The results of the study at 28 week follow-up showed that the PRP group had significantly greater clinical improvements in pain, stiffness, and function scores when compared with the hyaluronic acid group ( $P < .0001$ ). Overall, 87% of the patients in the PRP group obtained good results. These findings led the authors of the study to state that PRP should be a first-line treatment for symptomatic osteochondral lesions of the talus.<sup>55</sup>

Even though these studies reveal that PRP offers clinical benefits in the treatment of osteoarthritis, further research still needs to be done to determine just how effective PRP is in treating damaged articular cartilage related to arthritic changes.

### ***Platelet-Rich Plasma as an Adjunct Therapy to Surgical Rotator Cuff Repair***

Based on the results of 5 level I and II controlled studies, there seems to be some potential benefit of using PRP therapy as an adjunct to the surgical repair of rotator cuffs; however, further evidence is still needed before PRP therapy can actually be recommended as a routine treatment with rotator cuff repairs.

Three of these studies did not show a significant benefit from using PRP therapy. Castricini and colleagues<sup>56</sup> reported that PRP does not have a significant benefit for small to medium sized rotator cuff tears. Likewise, in a different study consisting of 79 patients, Rodeo and colleagues<sup>57</sup> found that the group with platelet-rich fibrin matrix sutured in the tendon–bone interface did not show any difference in clinical scores at a 1-year follow-up when compared with the control group.<sup>57</sup> Furthermore, there was also a prospective cohort study with 42 patients done by Jo and colleagues<sup>58</sup> that studied the effects of PRP gel applied to arthroscopic rotator cuff repairs. The authors of this study concluded that the PRP group did not have accelerated recovery with respect to pain, motion, strength, or overall patient satisfaction at any time point beginning with 16 months status post surgery.

On the other hand, the remaining 2 clinical trials did document a potential benefit of using PRP in rotator cuff repair surgeries. The first of these studies, done by Randelli and colleagues,<sup>59</sup> consisted of a double-blind randomized controlled trial of 53 patients in which the experimental group had PRP with autologous thrombin applied during arthroscopic rotator cuff repair. The findings of this study demonstrated that using PRP in grade 1 and 2 rotator cuff tears led to significantly higher strength in external rotation scores at 3, 6, 12, and 24 months postoperatively ( $P < .05$ ) and a lower rate of rerupture ( $P = .08$ ). Randelli and colleagues<sup>59</sup> used a different commercial preparation of PRP than Castricini and colleagues<sup>56</sup> and Rodeo and colleagues<sup>57</sup>. Moreover, another randomized trial consisting of 40 patients with subacromial decompression also concluded that the PRP group had significantly decreased pain scores and improved shoulder range of motion after surgery when compared with the control group ( $P < .001$ ).<sup>11</sup>

### **HOW PLATELET-RICH PLASMA CAN HELP TO RELIEVE NEUROPATHIC PAIN**

PRP was found to promote axon regeneration in studies involving animal models.<sup>60–65</sup> In this regard, Cho and colleagues<sup>64</sup> conducted a prospective, controlled study investigating the effects of PRP and neural-induced human mesenchymal stem cells (MSC) on axonal regeneration from a facial nerve axotomy injury in 24 albino guinea pigs. The guinea pigs were anesthetized with pentobarbital sodium by intraperitoneal injection and surgery was performed under an operating microscope.<sup>64</sup> The guinea pigs were randomly divided into 4 groups: group I received microsuture only, group II received microsuture with 5  $\mu$ L PRP, group III received microsuture with  $1 \times 10^5$  cells in 5  $\mu$ L of neural-induced human MSCs, and group IV received microsuture with 5  $\mu$ L PRP and  $1 \times 10^5$  cells in 5  $\mu$ L of neural-induced human MSCs.<sup>64</sup> This 6-week study concluded that the combined use of PRP and neural-induced MSCs promoted facial nerve regeneration and was of greater benefit for facial nerve regeneration than using either treatment alone.<sup>64</sup>

Studying tissue cultures, PRP was also seen to promote axon growth by spinal cord tissue and PRP related factors insulin-like growth factor (IGF)-1 and vascular endothelial growth factor.<sup>60,66</sup> Although, there exists 1 study that did not find axonal



regeneration in the presence of PRP, this result may have been attributed to the methods in which PRP was prepared.<sup>67</sup> A specific component in PRP that might play a pivotal role in axonal regeneration is multipotent MSCs.<sup>68–70</sup> Axonal regeneration occurred in 1 series of experiments after MSCs were applied to the end of transected peripheral nerves.<sup>71</sup> The means by which this axonal regeneration occurs in the presence of MSCs may be related to the promotion of angiogenesis and secretion of nerve growth factor and brain-derived neurotrophic factor by MSCs.<sup>72–76</sup> The importance of MSCs remains unclear, because in another study involving a series of experiments, axonal regeneration was not enhanced in the presence of MSCs.<sup>64</sup> However, in this same study, axonal regeneration increased when MSCs were combined with PRP compared with the impact of PRP alone on axonal regeneration.<sup>64</sup>

### ***Clinical Evidence That Platelet-Rich Plasma Has the Potential for Relieving Neuropathic Pain***

A recent small clinical study was performed by Kuffler<sup>77</sup> using PRP therapy in patients suffering from mild to severe neuropathic pain secondary to a damaged nonregenerated nerve. The purpose of this study was to determine whether the neuropathic pain in these patients would decrease or resolve as a result of PRP's promotion of axonal regeneration and target reinnervation. The surgical procedure used in this study involved refreshing the central and distal nerve stumps of damaged nerves, followed by inserting these stumps into a collagen tube, and then filling each tube with autologous PRP. The results of this procedure actually caused resected axons to regenerate across long gaps, up to 16 cm in length. Further, neuropathic pain in 94% of the patients, including 1 patient with severe neuropathic pain, was eliminated. Additionally, the neuropathic pain of another patient who had severe pain decreased to a tolerable level. The neuropathic pain of the patients in this study remained eliminated or reduced for a minimum of 6 years after the operative procedure. In fact, every single patient noticed their pain start to decrease within 3 weeks of the surgery, which was weeks before target reinnervation could even begin. Owing to this fact, a correlation cannot be made between the number of axons that reinnervated their targets and the extent to which neuropathic pain decreased. The data from this study suggest that a single PRP injection can lead to a long-term decrease in or elimination of neuropathic pain. It remains unclear whether the actual application of autologous PRP, the reestablishment of axon contact with Schwann cells, or the reinnervation of target tissues was the key factor leading to the reduction of neuropathic pain.<sup>77</sup>

More prospective clinical studies are warranted to confirm the results of this study, determine its reliability, and determine the various nerve conditions under which it is effective. If future clinical studies can demonstrate that autologous PRP therapy is in fact effective at decreasing or eliminating neuropathic pain, then this could pave the way for PRP therapy as a superior treatment approach for neuropathic pain when compared with other treatments and drugs currently available.

### **INTERVERTEBRAL DISC DEGENERATION AND THE ROLE OF PLATELET-RICH PLASMA AS A THERAPEUTIC OPTION**

IDD is a leading cause of lower back pain. This degeneration may be owing to aging, biomechanical loading, genetics, or an individual's daily activity and overall condition. PRP therapy has the potential for reversing IDD and relieving the lower back pain attributed to IDD. PRP may slow or reverse IDD by upregulating the synthesis of aggrecan and collagen and by directly stimulating MSC to differentiate into mature intervertebral disc cells.<sup>78</sup> In an in vitro study, it was proven that PRP increased human



MSC proliferation and MSC chondrogenic differentiation.<sup>79</sup> Aggrecan and collagen are 2 main components of the extracellular matrix of intervertebral discs so an increase in their production through the synergistic effects of PRP growth factors may help to maintain the function of these discs.<sup>78</sup> Aggrecan, as the major proteoglycan, leads to an increase in water absorption and hydration of the disc.<sup>80–82</sup> Collagen anchors tissue to bone and acts to provide tensile strength.<sup>80</sup> The various growth factors secreted by activated platelets all play significant roles in the proliferation of tissues. These growth factors include platelet-derived growth factor, IGF-1, transforming growth factor (TGF)- $\beta$ , vascular endothelial growth factor, basic fibroblastic growth factor, epidermal growth factor, and connective tissue growth factor.<sup>83,84</sup> Platelets may also be able to absorb, store, and transfer molecules that regulate tissue regeneration.<sup>4</sup> In comparison with other bioactive peptides and growth factors involved in tissue healing, autologous PRP seems to be a superior choice. Because autologous PRP is obtained via centrifugation of an individual's own whole blood, disease transmission and immunologic reactions are avoided.<sup>85</sup> However, because of the nature in which PRP is obtained, it is only suitable for patients without hematologic diseases.

In general, PRP injection into intervertebral discs is less invasive than other therapeutic procedures, such as surgery. However, caution is still required when using PRP injection. It is most beneficial to use smaller needles and fewer injections because needle puncture into the intervertebral disc could induce cell death and disc degeneration.<sup>86–88</sup> A few studies using animal models have actually shown that a single PRP injection into the degenerated intervertebral disc has been effective in healing the disc via regeneration. For example, Obata and colleagues<sup>87,88</sup> used a rabbit IDD model to conclude that a single intradiscal injection of PRP had the ability to restore disc height and lead to cell proliferation. Gullung and colleagues<sup>86</sup> concluded that 1 PRP injection in the intervertebral discs of Sprague-Dawley rats was enough to maintain fluid content on MRI. The evidence of the benefits of single PRP injections with small needles in these animal studies may be enough to pave way for clinical application of autologous PRP injections in humans with low back pain attributed to IDD.

### ***The Efficacy of Platelet-Rich Plasma Therapy in Intervertebral Disc Degeneration Seen Through In Vivo and In Vitro Studies***

There have been several in vivo and in vitro studies demonstrating the efficacy of PRP therapy in treating IDD. Through culturing intervertebral disc cells, specifically human nucleus pulposus cells isolated from volunteers of different ages, with TGF- $\beta$ 1 in PRP for 6 weeks, Chen and colleagues<sup>89</sup> concluded that PRP significantly increased disc height index, increased levels of messenger RNAs involved in matrix accumulation and chondrogenesis, and promoted nucleus pulposus regeneration. They determined that the most effective dose for human nucleus pulposus proliferation was 1 ng/mL of TGF- $\beta$ 1 in PRP.<sup>89</sup> A study from Akeda and colleagues<sup>90</sup> concluded that locally administering PRP mildly stimulates intervertebral disc repair by increasing the accumulation of glycosaminoglycan, type II collagen, and aggrecan. Interestingly enough, Akeda and colleagues suggested that directly injecting the intervertebral disc could lead to uncontrolled release of growth factors at variable rates. Nagae and colleagues<sup>91</sup> focused on this unstable release of growth factors and slowed down the release of growth factors through a study using a rabbit IDD model that implemented PRP implanted within gelatin hydrogel microspheres. They concluded that this combination therapy led to a sustained release of the PRP growth factors, resulting in a significant suppression of the degeneration of intervertebral discs over an 8-week period. Furthermore, Sawamura and colleagues<sup>92</sup> strengthened the effectiveness of the same combination therapy through noting results of increased messenger RNA

expression of proteoglycan and type II collagen and maintenance of disc height and signal intensity on MRI.

A study from Gullung and colleagues<sup>86</sup> used PRP injection on Sprague-Dawley rats to compare early intervention and late intervention in IDD. They found that while injecting PRP early in disease and late in disease both resulted in greater intervertebral disc fluid content on MRI, there was a superior effect in the early PRP injection group. Similarly, in a degenerative murine caudal disc compression model, Walsh and colleagues<sup>93</sup> concluded that early intervention during disc degeneration could potentially slow down degeneration. This early intervention makes sense because many viable cells remain and few phenotypic changes are seen during the early stages of disc degeneration.

There have been several studies demonstrating the positive effects of PRP growth factors on intervertebral discs (Table 2). The cytokines and growth factors of PRP help

Table 2 The effects of platelet-rich plasma growth factors on intervertebral discs			
Author(s), Year	Growth Factor	Cell Type	Results
Liu et al, <sup>117</sup> 2010	CTGF	Rhesus monkey lumbar intervertebral disc nucleus pulposus cells	Enhanced synthesis of proteoglycan and collagen II
Thompson et al, <sup>118</sup> 1991	EGF	Mature canine intervertebral disc cells	Enhanced proliferation
Thompson et al, <sup>118</sup> 1991	bFGF	Mature canine intervertebral disc cells	Increased matrix synthesis and cell proliferation
Pratsinis & Kletsas, <sup>119</sup> 2007	bFGF	Bovine coccygeal nucleus pulposus and annulus fibrosus cells	Enhanced proliferation
Fujita et al, <sup>120</sup> 2008	VEGF	Mouse nucleus pulposus cells	Promotion of nucleus pulposus survival
Walsh et al, <sup>93</sup> 2004	IGF-1	Mouse caudal disc compression model	Upward trend of cell density, but not statistically significant (single injection); trend of increased disc height, but not statistically significant (multiple injections)
Walsh et al, <sup>93</sup> 2004	TGF-β1	Mouse caudal disc compression model	Greater percentage of proliferating cells, but not statistically significant (single injection); increased population of annular fibrochondrocytes (multiple injections)

**Abbreviations:** bFGF, basic fibroblastic growth factor; CTGF, connective tissue growth factor; EGF, epidermal growth factor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

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to maintain intervertebral disc homeostasis through shifting from catabolism to anabolism.<sup>94</sup> TGF- $\beta$ 1, IGF-1, and platelet-derived growth factor are 3 important growth factors that have been reported to play a role in this shift to anabolism. For example, Gruber and colleagues<sup>95</sup> reported that TGF- $\beta$ 1 stimulates the proliferation of human annulus fibrosus cells after 4 days of exposure. Lee and colleagues<sup>96</sup> also saw the proliferative effect of TGF- $\beta$ 1 on annulus fibrosus cells through culturing rabbit annulus fibrosus cells with TGF- $\beta$ 1. Additionally, Hayes and Ralphs<sup>97</sup> concluded that TGF- $\beta$ 1 and IGF-1 in combination or alone stimulate annulus cells to synthesize type I collagen, type II collagen, and sulfated glycosaminoglycan. IGF-1 and platelet-derived growth factor have been shown to actually reduce the percentage of apoptotic annulus fibrosus cells.<sup>98</sup> These studies all suggest that the PRP growth factors contribute greatly to the regeneration of intervertebral discs.

### INFORMATION FOR PHYSICIANS USING PLATELET-RICH PLASMA THERAPY

It is suggested that sterile technique should be used when administering PRP injections.<sup>16</sup> Currently, it remains unclear as to what effect, if any at all, local anesthetic has on PRP.<sup>16</sup> Therefore, the use of local anesthetic in the region of PRP injection is typically avoided.<sup>16</sup> The method by which PRP is commonly injected consists of using either a 20-G or 22-G needle under ultrasound guidance.<sup>16</sup> Imaging such as ultrasonography or fluoroscopy can be useful to not only guide PRP injections to the proper location of target tissues, but to also observe tissue healing over time.<sup>16</sup> Additionally, diagnostic imaging before applying PRP injections may be valuable in establishing a diagnosis and a baseline clinical condition. Having a baseline clinical condition of target tissues helps to evaluate tissue healing after PRP injection.

#### ***Patient Disclosure, Potential Side Effects, and Costs of Treatment***

Just like any other procedure, an informed consent is required of any patient receiving PRP injections. The informed consent includes the risks related to PRP injections, which are infection, bleeding, and soft tissue injury.<sup>16</sup> Because PRP causes local inflammation, it is normal for there to be pain at the injection site for 24 to 48 hours after the procedure. However, nonsteroidal anti-inflammatory drugs should be avoided 2 weeks before and at least 2 weeks after the procedure so that they do not inhibit the healing process or the PRP growth factors that play a role in the tissue healing.<sup>16</sup> Currently, no postprocedure guidelines exist that may lead to optimization of PRP therapy.<sup>16</sup>

Because PRP treatment is still considered experimental, it is not usually covered by insurance companies. It is important to disclose this information to patients and make them aware that they will most likely be paying the costs of treatment out of pocket. This information should also be discussed in the informed consent process before administering PRP injections.<sup>16</sup> A physician is restricted from billing for imaging guidance, harvesting, and preparation of PRP separately, because these 3 are grouped under the 0232T billing code, which is a category III temporary code for emerging technologies, services, and procedures.<sup>99</sup> Even though the market for PRP is expected to grow to \$126 million by 2016, there is not enough clinical evidence to do a cost-benefit analysis for the use of PRP in orthopedic conditions.<sup>100</sup> However, if PRP therapy eventually leads to a decreased need for further intervention with regard to pain control or has a greater patient satisfaction during follow-up visits in comparison with other treatment modalities used to achieve pain relief, such as corticosteroid injections, it will likely lead to lower total costs for the patients seeking treatment.

Gosens and colleagues<sup>49</sup> actually suggested that in the long run PRP therapy may be less expensive than corticosteroid therapy based on a double-blind randomized

controlled trial comparing the positive effects of PRP injection with corticosteroid injection in lateral epicondylitis with 2-year follow-up visits. The recurrence rate of pain from lateral epicondylitis and the need for repeated injection was greater in the corticosteroid group than in the PRP group.<sup>49</sup> On a short-term basis, PRP is not cost effective compared with corticosteroid injections, but if the costs of patients failing on corticosteroid therapy who proceed to surgery are taken into account, the differences in cost effectiveness may level out.<sup>49</sup>

## FUTURE CONSIDERATION/SUMMARY

PRP, through the action of its related growth factors, has the potential to stimulate tissue healing and repair.<sup>39</sup> However, no standard procedure for PRP production exists, which leads to varying concentration of platelets produced, varying number of growth factors within the PRP, and thus varying clinical results from PRP therapy.<sup>78</sup> It remains unclear whether PRP containing WBCs or the activation of PRP by exogenous thrombin has a beneficial effect on tissue healing.<sup>39</sup> Platelet-rich fibrin matrices have the ability to increase the migration of cells involved in tissue repair and can lead to the prolongation of PRP growth factor activity, availability, and delivery by serving as a reservoir for these growth factors.<sup>44</sup>

Regardless of the limited clinical-based evidence that currently exists, PRP injections have already been applied clinically to initiate healing and decrease pain associated with lateral epicondylitis, osteoarthritis, rotator cuff tears, and ligament and tendon injuries.<sup>55,101–111</sup> Based on the most recent randomized controlled clinical trial data, PRP therapy seems to be beneficial for treating chronic tendinopathy.<sup>48,50,112</sup>

It is also determined that PRP leads directly to the elimination of neuropathic pain through a full cascade of wound healing, beginning with the induction of enhanced inflammation and its complete resolution, followed by tissue remodeling and wound repair, and concluding with axon regeneration and target tissue reinnervation.<sup>77</sup> This complex cascade of events allows axons to take up target-released factors that will eliminate nociceptive neuron hyperexcitability.<sup>77</sup>

Furthermore, PRP shows promise for reversing disc degeneration via its promotion of wound healing and tissue repair.<sup>113–115</sup> Moreover, steroid injections continue to be a common clinical therapy for pain relief from back pain and other injuries, but studies have demonstrated that the pain relief from these steroids is only temporary and that there is no impact on the actual underlying pathophysiology causing the pain.<sup>116</sup> Corticosteroid therapy tends to have side effects, especially with repeat injections. Based on current research studies, there have been no reported complications associated with PRP injections.<sup>12,48,112</sup>

PRP likely will not be a primary or mainstream therapy until further prospective, randomized controlled clinical trials in human patients are completed documenting its benefits and positive influence on tissue healing. Further research and clinical trials are also needed to study the undesirable effects induced by PRP, to determine optimal dosing of growth factors in PRP for tissue healing, and to determine possible interactions between these growth factors.<sup>78</sup> According to evidence-based literature, the success of PRP therapy will depend on the method of preparation and composition of PRP, the patient's medical condition, anatomic location of the injection, and the type of tissue that is injected.

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