CHAPTER 6

Platelet Rich Plasma Applications in Podiatric Medicine and Surgery

Kevin Alexander, DPM

INTRODUCTION

Platelet rich plasma (PRP) is a preparation of autologous product that concentrates a large number of platelets in a small volume of human plasma. It is defined as a platelet concentration of at least 1 million platelets per microliter in 5 ml of plasma (1). The normal human platelet count is between 150,000-300,000. It is theorized that improvements in bone and soft tissue healing may be seen with platelet counts of up to 1,000,000. There is a large variation in the protocol of preparing PRP and the characteristics for preparation all depend on the commercial system available (Table 1).

PRP is essentially formed from anticoagulated blood. Whole blood is collected and mixed with an anticoagulant factor prior to centrifugation, the process that separates the red blood cells from platelet poor plasma and the buffy coat, which contains concentrated platelets and leukocytes (2). The buffy coat layer maintains the maximum amount of platelets. It is known that PRP has the potential to deliver high concentrations of growth factors, which are concentrated in the alpha granules and dense granules, to target tissues (3). These growth factors and cytokines when released to an injury site are believed to augment the healing process. PRP has an increase of growth factors that are about 3- to 5-times above the baseline of normal platelet concentrations that are found in plasma (1). The various growth factors and chemicals found in alpha granules and dense granules can be seen in Tables 2 and 3, which also show their respective abilities in the healing process.

There have been increasing amounts of clinical studies on the effects of PRP due to its theorized ability to promote healing and enhance osteogenesis. Healing is noted to progress in a series from an acute inflammatory phase that develops into a cell proliferative phase and a final remodeling phase. The growth factors in PRP are involved in the signal pathways that occur during those same healing phases. It is believed that PRP is able to accelerate regeneration of endothelial, epithelial, and epidermal cells, as well as stimulate angiogenesis, enhance collagen synthesis, promote soft tissue healing, and reverse the inhibition of wound healing (4). Currently there are investigations that study the effect of PRP on musculoskeletal and soft tissue disorders in the clinical and surgical setting, bone healing augmentation, and wound healing.

Table 1. Commercially available platlet rich plasma (RPR) systems and their PRP preparations (2)*

System	Company	Blood volume required (ml)	Concentrated volume produced (ml)	Processing time (min)	PPP produced?	Increase in [platelets] (times baseline) (% yield)	Platelet capture efficiency
Leukocyte-rich PRP							
Angel	Arthrex	52	1–20*	17	+	10*	56–75
GenesisCS	EmCyte	54	6	10	+	4–7	61 ± 12
GPS III	Biomet	54	6	15	+	3–10	70 ± 30
Magellan	Isto Biologics/ Arteriocyte	52	3.5–7	17	+	3–15	86 ± 41
SmartPReP 2	Harvest	54	7	14	+	5–9	94 ± 12
Leukocyte-poor PRP							
Autologous conditioned plasma (ACP)	Arthrex	11	4	5	–	1.3	48 ± 7
Cascade	MTF	18	7.5	6	–	1.6	68 ± 4
Clear PRP	Harvest	54*	6.5*	18*	+	3–6*	62 ± 5*
Pure PRP	EmCyte	50*	6.5*	8.5*	+	4–7*	76 ± 4*

* Data obtained from manufacturers' promotional literature or internal studies.

Table 2. Molecules associated with alpha granules (1)

General Activity Categories	Specific Molecules	Biological Activities
Growth Factors	TGF-II	Promotes matrix synthesis
	PDGF	Chemoattraction, cell proliferation
	IGF-I, IGF-II	Cell proliferation, maturation, bonematrix synthesis
	FGF	Angiosynthesis, fibroblast proliferation
	EGF	Cell proliferation
	VEGF	Angiosynthesis
	ECGF	Endothelial cell proliferation, angiosynthesis
Adhesive proteins	Fibrinogen	Blood clotting cascade (fibrin clot formation)
	Fibronectin	Binds to cell surface integrins affecting cell adhesion, cell growth, migration, and differentiation
	Vitronectin	Cell adhesion, chemotaxis
	Thrombospondin-1	Inhibition of angiogenesis
Clotting factors	Factor V, factor XI, protein 5 antithrombin	All play a role in thrombin activation and eventual fibrin clot formation
Fibrinolytic factors	Plasminogen	Plasmin production leads to (fibrinolysis)
	Plasminogen activator inhibitor	Regulation of plasmin production
	Alpha2-antiplasmin	Inactivation of plasmin
Proteases and antiproteases	TIMP-4	Regulation of matrix degradation
	Metalloprotease-4	Matrix degradation
	Alpha1-antitrypsin	Inhibits a wide variety of proteases and enzymes
Basic proteins	Platelet factor 4	Inhibition of angiogenesis
	β-Thromboglobulin	Platelet activation, inhibition of angiogenesis
	Endostatins	Inhibitors of endothelial cell migration and angiogenesis
Membrane glycoproteins	CD40 ligand	Inflammation, synthesis of interleukins. and integrin production; PECAM-1 on leukocytes
	P-selection	Vascular cell adhesion molecule, aids in binding and recruitment of leukocytes to inflamed tissue

Table 3. Bioactive components within platelets (1)

Molecules	Biologic Activities
Serotonin	Vasoconstriction, increased capillary permeability, macrophage attraction
Histamine	Increased capillary permeability, attract and activate macrophages
Dopamine	Regulation of heart rate and blood pressure, neurotransmitter
ADP	Promotes platelet aggregation
ATP	Participates in platelet response to collagen
Ca++	Cofactor for platelet aggregation and fibrin formation
Catecholamines	Sympathomimetic hormones released by the adrenal glands in response to stress

MUSCULOSKELETAL/ SOFT TISSUE HEALING

Musculoskeletal injuries create a problem in the sports medicine realm because they account for most of these acute sports-medicine related accidents and are a common cause of long-term pain and disability. In the setting of chronic injuries, it is believed that PRP can stimulate the tissue to restart the inflammatory process and convert a chronic injury into an acute injury (5).

Achilles Tendinopathy

Achilles tendon injuries are a prominent issue in sports medicine. A study by Finoff et al reported on 24 patients, 12 of whom had Achilles tendinopathies. Ultrasound evaluation revealed significant improvement in structure and reduction in neovascularity and tendon thickness (1). A study by Gaweda et al reported on 14 patients with non-insertional Achilles tendinopathy who were injected with PRP. A significant increase was noted in clinical scores, and post-PRP injection ultrasound revealed reduction of tendon thickening and normalization of the peritendineum (1). In a study by Monto et al, 30 patients with chronic Achilles tendinopathy received a single ultrasound guided PRP injection. Clinical results were noted to be positive with significant improvement as compared to the initial evaluation (1). Magnetic resonance image/ultrasound scans revealed tendon healing in 27 patients (1). A study by Zou et al looked at 36 patients who underwent Achilles tendon repair, with one group receiving PRP and the other acting as a control group. Patients in the PRP group were noted to have better isokinetic muscle at the 3-month span. Routine use of PRP in Achilles tendinopathy is not supported by the current literature (2).

Plantar Fasciitis

Plantar fasciitis is one of the most commonly encountered podiatric clinic conditions and makes up a large number of issues in sports medicine. A study by Barrett et al looked at 9 patients with plantar fasciitis. Ultrasound of the plantar fascia was taken before and after PRP injections. It was noted that 6 out of 9 patients had resolution of symptoms after 2 months and ultrasound measurements of the plantar fascia demonstrated reduced thickness (1). In a study by Aksahin et al, 60 patients with plantar fasciitis were investigated with one group receiving PRP and one group receiving corticosteroids. Both groups had experienced improvement in terms of pain and functional status (1). PRP appears to provide good clinical results with plantar fasciitis and could be applied as a possible first-line injection approach (1).

Ankle Sprains

Another common injury seen in sports medicine is an ankle sprain, especially in the elite athletic population. A study by Rowden et al looked at patients with acute ankle sprains in the emergency department who were either given an ultrasound guided injection of PRP or an injection of local anesthetic and saline (the control group). It was noted that there was no statistical difference in pain or function score between the groups (2). In a study by Laver et al that looked at elite athletes with ankle sprains, patients were either randomized to a treatment group of PRP injections and rehabilitation or a control group of rehabilitation alone. It was demonstrated in their study that the PRP group had significantly less pain compared to the control group and had a shorter time to return to play (2). Overall, PRP does not appear to be clinically efficacious in the setting of acute ankle sprains; however it may provide benefit in an athletic population. (2)

BONE HEALING AUGMENTATION

PRP has also been routinely investigated for its use in bone healing augmentation, whether it be surgical or in the setting of a delayed union. The growth factors in PRP are thought to stimulate osteoblastic cells and differentiation. In a study by Bibbo et al, 62 high-risk patients undergoing 123 procedures (with risk factors that varied from diabetes mellitus to smoking) were investigated. The study looked at adjuvant use of PRP in elective foot and ankle surgery. The results showed that the mean time to union was approximately 41 days. Ankle procedures had a mean time to union of 40 days with a 95% union rate, whereas forefoot procedures had a mean time to union of 38 days with a 100% union rate (6). Another study by Coetzee et al studied the application of PRP on total ankle replacements. The study compared the syndesmotic fusion rate of PRP augmented bone graft in 66 patients with non-PRP augmented bone graft in 114 patients. There was a 97% fusion rate in 6 months in the PRP group compared to an 85% fusion rate in 6 months with the control group. A statistically significant improvement in time to union and overall union rate was noted, as well as a statistically significant reduction in delayed union and non-union rate. In the subset of the smoking population, an 80% union was noted in the PRP group compared to a 50% union rate in the control group at 6 months (7).

PRP has also been studied in the setting of delayed union and fracture management. In a study by Gandhi et al, PRP was used in 9 patients with non-unions, all with a minimum duration of delayed healing for 4 months. With the use of bone graft and PRP, resolution was achieved in

a mean time of 60 days. It is thought that the addition of PRP can provide critical growth factors to a non-union site as it is noted there is a significant reduction in the growth factors at a non-union site as compared to a fresh fracture site (7). However at this time, there is no clinical consensus to support bone healing, because most of the studies are in combination with other orthobiologics.

WOUND HEALING

Chronic wounds continue to be a problem in the clinical setting because they can be a source of constant frustration for the clinician and the patient. PRP is thought to stimulate the ceased inflammatory process in chronic wounds in order to convert them into more acute wounds to augment the healing process. Most of the PRP preparations used in the wound care setting are PRP gel. In a randomized controlled study of 72 patients with diabetic foot ulcers, it was noted that the group who had received PRP gel had a healing rate of 81.3% compared to the control gel group, which had a healing rate of 42.1% (8). A systemic review was also performed by Hirase et al, investigating the use of topical PRP gel to improve wound healing in diabetic foot ulcers. 11 articles were analyzed in the study with a total of 322 PRP subjects and 126 control subjects. The study determined that the topical application of PRP for diabetic foot ulcers resulted in a statistically superior healing rate compared to subjects receiving wound care, with lower complication rates (9). Frykberg et al studied 65 chronic non-healing wounds with various etiologies using PRP gel. They concluded that for most etiologies, 97% of the wounds in their study improved (5). A study by Bielecki et al even theorized that PRP gel inhibited the growth of organisms such as *Staphylococcus aureus* and *Escherichia coli.* This may be due to a high leukocyte-rich preparation (5). The use of the PRP in the setting of wound care can possibly reverse the non-healing state of chronic wounds, with an improved quality of life.

In conclusion, PRP has brought some interesting attention in regards to augmenting healing in the clinical and surgical setting. Although it is not a proven first-line treatment for a variety of conditions, there are potential benefits in its use for certain pathologies. The increased concentrations of growth factors to the site of injury appear to make PRP a viable choice when it comes to healing. It appears that PRP may have a benefit when most conservative treatment options have failed and surgical intervention is a last resort. Patient selection will be important when it comes to healing potential with PRP. There are many clinical applications of PRP in podiatric medicine and surgery, with some conditions showing increased benefits with PRP as compared to others. Further clinical studies, specifically randomized controlled trials, will be necessary in the future to give more compelling evidence of the benefits of PRP, as well as to warrant its use in certain conditions.

REFERENCES

1. Grambart ST. Sports medicine and platelet-rich plasma. Clin Pod Med Surg 2015;32:99-107.
2. Le ADK. Current clinical recommendations for use of platelet-rich plasma. Curr Reviews Musculoskteletal Med 2018;11:624-34.
3. Alser OH, Goutos I. The evidence behind the use of platelet-rich plasma (PRP) in scar management: a literature review. Scars Burn Heal 2018;4:205951311880877.
4. Soomekh DJ. Current concepts for the use of platelet-rich plasma in the foot and ankle. Clin Pod Med Surg 2011;28:155-70.
5. Bibbo C, Hatfield PS. Platelet-rich plasma concentrate to augment bone fusion. Foot Ankle Clin 2010;15:641-9.
6. Gandhi A, Bibbo C, Pinzur M, Lin SS. The role of platelet-rich plasma in foot and ankle surgery. Foot Ankle Clin 2005;10:621-37.
7. Richmond NA, Vivas AC, Irsner RS. Topical and biologic therapies for diabetic foot ulcers. Med Clin North Am 2013;97:883-98.
8. Hirase T, Topical application of platelet-rich plasma for diabetic foot ulcers: a systematic review. World J Diabetes 2018;10:172-9.
9. Smith RG. Platelet-rich plasma: properties and clinical applications. J Lancaster General Hospital 2007;2:73-8.