The use of orthobiologics in the treatment of foot and ankle injuries, both in the clinical and surgical venues, is significantly increasing. The clinician and the surgeon continue to seek better ways to accelerate and mediate healing of bone and soft tissue, while incorporating less invasive techniques. The use of autologous platelet-rich plasma (PRP) by foot and ankle specialists over the last few years has emerged in the forefront of biologic tools in this endeavor. Its use has been investigated in the treatment of tendon injuries, chronic wounds, ligamentous injuries, cartilage injuries, muscle injuries, and bone augmentation (intraoperative fusions and fracture repair). PRP has been studied and used over the last 4 decades. Its use had been based on the theory that increased concentrations of autologous platelets, that then yield high concentrations of growth factors and other proteins, will lead to enhanced healing of bone and soft tissue on a cellular level.

PRP is the concentration of platelets derived from the plasma portion of centrifuged or filtered autologous blood. This platelet-rich solution can then be used as an adjunct to healing (as when used in a fresh surgical fusion) or to reinstate healing (as when used in chronic tendon injuries). PRP and related products have different labels throughout the literature, including platelet-rich concentrate, platelet gel, preparation rich in growth factors (PRGF), platelet releasate, and platelet-leukocyte-rich gel (PLRG). When the PRP is acquired, it may or may not be activated by another product. PRP without activation is usually reserved for the treatment of tendon, muscle, and other soft tissue. PRP activated into a gel or fibrin sealant is used clinically and intra-operatively for wound healing and bone augmentation. There have been several
studies investigating the efficacy of PRP and its applications. It has been widely used in the areas of spine surgery, wound healing, plastic surgery, oral and maxillofacial surgery, orthopedic surgery, and podiatric surgery.1

There have been several basic science reviews and studies as well as clinical studies on PRP. Many are both in vitro and in vivo studies. The few controlled clinical studies are based on small numbers of subjects and have many shortcomings. Major factors in the limitation of the studies to date is to the lack of standardization in technique, concentration of platelets, applications of clinical use, volume injected, separation from whole blood, and postinjection care. This article is meant to review the background of PRP and its use for the foot and ankle clinician and surgeon.

BASICS

Platelets are a major player in the clotting cascade. They are colorless, nonnucleated fragments of cells that are derived from megakaryocytes within the bone marrow. They contain cytokines and granules (α, δ, λ) of which α is the most important, containing more than 30 proteins that play a pivotal role in soft-tissue healing and hemostasis.2 There are several proteins that are generated and secreted by the α granules within minutes of the aggregation of the platelets. Platelet-derived growth factor, insulin-like growth factor, vascular endothelial growth factor, epidermal growth factor, epithelial cell growth factor, osteocalcin, fibrinogen, and fibronectin are some of the secretions from the α granules. These growth factors directly affect their target cells by initiating their growth, morphogenesis, and differentiation. Examples of these target cells are osteoblasts, fibroblasts, endothelial cells, epidermal cells, and mesenchymal stem cells (MSC).2–4

The normal 3 phases of wound healing are inflammation, proliferation, and remodeling. At the moment of tissue injury with the inflammatory phase, the platelets are activated. They begin to secrete their proteins (cytokines and growth factors) through the granules. They also produce bioactive factors, such as serotonin, histamine, dopamine, calcium, and adenosine. The serotonin and histamine will act to increase permeability of the capillaries leading to more of these products being delivered to the wound site. Platelets normally do not aggregate together unless there is a stimulant present. Once there is tissue injury, a cellular mix of proteins allows the platelets to initiate clotting and the thrombus process.5 The platelets are activated by fibronectin, laminins, collagen, von Willebrand factor, and other proteins. Even the platelet’s own secretions, such as serotonin and adenosine diphosphate, will trigger platelet aggregation and activation. Once activated, the platelets will begin to form the fibrin clot.3,6

The determination of the appropriate concentration of PRP for clinical use is difficult. The normal concentration of platelets in blood ranges from 150,000/μL to 350,000/μL. A level of at least 1,000,000/μL is needed to promote an increase in healing.7 Most PRP contains a 3- to 5-fold level more than the baseline. However, there have been other studies that have suggested efficacy at 2.0- to 8.5-fold levels.4

Current Theory Behind PRP

Essentially PRP is used to increase the concentration of platelets to an injured site. In an acute injury, platelets are normally activated during the inflammatory phase to begin healing. The addition of PRP in the acute injury increases the concentration of platelets at the local tissue over the baseline. Chronic injuries that have failed conservative therapies presumably have ceased the inflammatory phase, and have a paucity of platelets and a decrease in healing potential. PRP in these situations would provide 2 beneficial results. First, the simple act of the application of PRP when used through
injection for tendon, ligament, or muscle injuries will stimulate the tissue and restart the inflammatory process, thereby making the chronic injury into a new acute injury; and second, the addition of autologous concentrations of platelets theoretically augments the healing process. This new injury now has a known starting point and can be placed in a controlled postinjection environment (eg, immobilization, bracing, or nonweight bearing). During this time, the use of antiinflammatory medications and therapies are restricted so as not to reverse the desired effect.

**Acquiring PRP**

To acquire autologous PRP, blood is collected from the cubital vein (Fig. 1). The amount of blood acquired is determined by the clinical application (treatment area) and desired concentration. The platelets are then separated from the plasma by means of centrifugation or filtration. Many different systems are available on the market today to obtain the PRP. When using a simple centrifugation process, the blood collected is spun down between 5 and 20 minutes depending on the speed of the centrifuge and the concentration desired. There will be 3 relative layers of product in the tube: plasma layer (platelets), buffy coat layer (white blood cells), and remaining blood products (red blood cells). The platelets are at the top of the tube. There has been debate on the true concentrations obtained through simple centrifugation and the true output of platelet-rich versus platelet-poor product. The platelet-rich plasma is then collected from the tube using a syringe and an 18-gauge needle, being careful not to collect any platelet-poor or red cells.

A similar method of collection uses an automated centrifugation process that separates the platelets from the whole blood and then automatically sends the product to a separate syringe using an infrared microprocessing sensor to differentiate between red blood cells and platelet-rich plasma. This type of system seems to lead to more accuracy and allows for more reproducible concentrations. There is presumably less error with less manual manipulation of the blood product through automated separation. One such devise is the Magellan Autologous Platelet Separator System (Arteriocyte Medical Systems Inc, Cleveland, OH, USA) (Fig. 2). With either method, the tube that initially collected the blood must have an anticoagulant. The kits that come with the products usually have tubes already with anticoagulant or come with separate anticoagulant.

The literature seems to be mixed on the idea of activating the platelets before use. Some studies will not mention either way if the PRP was activated; whereas, others

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*Fig. 1. Acquiring whole blood from the cubital vein.*
specifically delineate the product used to activate the PRP. A study was presented by de Vos and colleagues on the effects of PRP on Achilles tendinopathy without mentioning activation. In their review article, Foster and colleagues suggest activation with bovine thrombin. Thoms and colleagues mention use of a combination of calcium and thrombin (bovine, human, or recombinant). Fufa and colleagues used type I collagen to activate PRP to create a collagen-PRP gel. The brochure for the Magellan system calls for the activation of PRP by using adenosine diphosphate. The proper way to activate the platelets is determined by the intended use of the PRP.

PRP can be activated into a platelet gel using thrombin and calcium, which creates a product that can both distribute growth factors to stimulate wound healing while constricting blood vessels to reduce bleeding. In addition, the activation will increase the function of the platelets. The gel can improve tissue adhesion as a scaffold and protect from infection with its concentration of leukocytes. It has also been shown to reduce pain postoperatively. The platelet gel material is used mostly for intraoperative situations to promote bone healing and as a wound sealant.

With the Magellan system concentrations can easily be determined. A volume of blood is taken and the machine allows the operator to select the volume of PRP desired. For example, if 30 mL of whole blood is collected and the clinician wants to inject 3 mL of PRP, the concentration will be approximately 6-fold more than the baseline; whereas, the same 30 mL will provide a 3-fold concentration more than the baseline if 10 mL of PRP is needed. If 60 mL of whole blood is collected and 3 mL of PRP is required, there will be a 13-fold concentration more than the baseline; whereas, if 10 mL of PRP is needed, only a 5-fold concentration more than the baseline is acquired. This means that as the volume of whole blood collected increases, a higher volume of PRP at a higher concentration is available. Or, when a greater amount of PRP is needed, a lower relative concentration is acquired. In this system, the majority of platelets are recovered in the initial 3 mL of PRP delivered to the 10-mL collected syringe, which means that after the first 3 mL of PRP, the concentrations of PRP are lower because of dilution. Using a smaller volume for applications that only require 10 mL of PRP will allow for an appropriate concentration more than the baseline as discussed earlier in this article. Thus, an area that only needs 10 mL of PRP injected, whether it comes from an initial 60 mL or 30 mL of whole blood collected, will then assure the highest concentrations of PRP.

Fig. 2. Preparing PRP with the Magellan Autologous Platelet Separator System (Arteriocyte Medical Systems Inc, Cleveland, OH).
Clinical Uses

The benefits and safety of PRP have been examined in many animal and human studies. Many of these studies have adequately shown the safety and efficacy of PRP in the clinical and surgical setting. It is difficult to compare studies because of differing concentrations of PRP and postprocedure protocol. There seem to be as many studies that confirm the benefits of PRP as there are studies that are inconclusive. An important distinction that must be made as the use of PRP increases is whether the use of PRP is as beneficial in the acute phases of tissue healing as it may be in chronic pathology.

Foot and ankle applications for PRP can be placed into several categories. These categories include acute and chronic ligamentous injuries, chronic tendinopathy (tendinosis), bone pathology, chronic wounds, and cartilage injury.

Plantar Fasciitis

The use of PRP for plantar fasciitis was investigated in a small study by Barrett and Erredge. They used ultrasound of the fascia before and after treatment and patient pain scale as determination for efficacy. The subjects were weight bearing in a walking boot for 2 days and then in regular shoe gear with limited activity. They were restricted from using antiinflammatories or other modalities. They found that 6 of 9 subjects achieved complete resolution of symptoms after 2 months. One subject had resolution after a second injection. After 1 year, 77.9% of the subjects had no symptoms. They showed that ultrasound measurements of the thickness of the plantar fascia were reduced between preinjection and postinjection. It is unclear how long the patients had their symptoms before treatment.

The author has found promising results using PRP for those patients with chronic, recalcitrant plantar fasciitis. Patients that have failed conservative treatments after 3 to 6 months, including rest, ice, compression, and evaluation (RICE); functional foot orthotics; physical therapy; and cortisone injections, may be candidates for PRP. Diagnosis is confirmed using ultrasound or MRI. A skin marker is used to identify the site of most pain on palpation. An initial anesthetic block is performed at the site. 60 mL of whole blood is drawn using the collection tube supplied with the Magellan system kit. Calcium chloride is used to activate the PRP. Thrombin is not used, to keep the PRP in liquid form for injection. Once the PRP is prepared using the Magellan Autologous Platelet Separator System, using a 10-mL syringe and a 25-gauge needle, patients are injected with 5 mL to 8 mL of PRP from the 60 mL of whole blood collection, yielding a concentration that is a 10 to 6 times more than the baseline, respectively. The author has found that as the concentration increases, the patient’s postinjection pain increases. The injection is performed under ultrasound guidance (Fig. 3). Several 0.25-mL pulsed injections, while peppering the needle, are placed in the medial plantar fascial band starting at the point of maximum tenderness. In many of the patients, during the injection the fibrosis of the ligament can be appreciated by a crepitus that can be felt and heard as the needle passes in and out of the fascial tissue. After completing the injection, continued peppering of the fascia using the 25-gauge needle is performed to further aggravate the tissue. Patients are restricted from using any antiinflammatories or modalities for up to 3 months using acetaminophen or narcotics for pain as needed. The author has found better results with a postinjection protocol of a walking boot and crutches with no weight bearing for 3 to 5 days, and then walking in the boot for 2 to 3 weeks. Activity begins gradually around the third or fourth week in an athletic shoe and functional foot orthotic,
increasing over a 4-week period. Some patients have benefited from a second injection when the first yielded only some relief in symptoms given about 6 weeks afterwards. Those patients that have no change in their symptoms after the first injection rarely benefit from a follow-up injection.

**Achilles Tendinopathy and Rupture Repair**

Recent studies have shown that PRP can positively affect gene expression and matrix synthesis in tendon and tendon cells. It is important, however, to distinguish acute tendon injury from chronic cases when discussing and studying PRP and its use for tendon pathology. The use of PRP specifically for the treatment of Achilles pathology has been investigated. Tendon injury leads to a cascade of degenerating events leading to eventual rupture. These events include hypovascularity, repetitive microtrauma, and the addition of fibrous tissue that can then lead to degeneration and weakness of the tendon. PRP is thought to reverse the effects of tendinopathy by stimulating revascularization and improving healing at the microscopic level. Alfredson and Lorentzon categorize Achilles tendon pathology into paratendinitis, paratendinitis with tendinosis, and pure tendinosis. In paratendinitis, there are adhesions formed between the paratenon and the tendon. Paratendinitis with tendinosis involves degenerative changes within the substance of the tendon as well as inflammation in the paratenon. In cases of pure tendinosis there is a palpable nodule that often presents. It is hypothesized that the introduction of PRP into the pathologic tendon will aid in the repair and remodeling of the tendon by tenocytes.

Lyras and colleagues studied the effect of PRP on angiogenesis during tendon healing. The study was performed on the Achilles tendon of rats against a control group injected with saline. They found a significant increase in angiogenesis in the PRP group compared with the control group during the first 2 weeks of the healing process (ie, the inflammatory and proliferative phases), and the number of the newly formed vessels in the PRP group was significantly reduced at 4 weeks compared with the controls, suggesting the healing process was shortened. They observed that the orientation of collagen fibers in the PRP group was better organized. They concluded that PRP seems to enhance neovascularization, which may accelerate the healing process and promote scar tissue of better histologic quality.

Gaweda and colleagues performed a prospective study on 15 subjects with Achilles tendonitis. Subjects were followed for 18 months. They found improvement in pain scores and ultrasound imaging.
Society scores improved from a median of 55 points to 96 points, and the achilles tendon score improved from 24 points to 96 points. They concluded PRP to be a viable treatment alternative for Achilles tendonitis.

A recent study by de Vos and colleagues was performed on subjects with tendinopathy. Their study was stratified, block randomized, double blind, and placebo controlled. They included subjects age 18 to 70 years old. Diagnosis was made clinically with findings of a painful and thickened tendon in relation to activity and on palpation with symptoms lasting greater than 2 months. The subject base included 27 in the PRP group and 27 in the control group. They used 54 mL of whole blood to derive the PRP that was mixed with sodium bicarbonate to match the pH of tendon tissue. An undisclosed amount of PRP was injected into 5 sites along the injured tendon under ultrasound guidance. Subjects were only allowed to walk short distances indoors in the first 48 hours. In days 3 to 7, subjects were allowed to take walks up to 30 minutes. After 1 week an exercise routine was started with 1 week of stretching and a 12-week daily eccentric exercise program with heel drops off a step. No weight-bearing sports activities were allowed for 4 weeks, and then a gradual return was instructed. They were only to use acetaminophen during the follow-up period. Their results were based on subject questionnaires that quantify pain and activity level. The results showed an improvement in 24 weeks by 21.7 points in the PRP group and 20.5 points in the placebo group. They concluded that there was no significant difference between the groups. This study is limited by several factors. They did not identify any characteristics of the anatomy of the tendon preinjection and postinjection, neither clinically nor with imaging techniques. Their sample size was small. They could not quantify the concentrations of PRP that were used in each subject.

PRP in the form of a fibrin gel (when combined with thrombin) can also be used as a tendon scaffold. It can be used as a bridge and augmentation within the rupture defect, or it can be wrapped around the tendon repair. In most cases, it will be combined with Bone marrow aspirate (BMA) for further enhancement of the PRP matrix. The introduction of PRP in the repair of Achilles rupture has also been evaluated in the rat model. In one study, surgically transected tendons treated with PRP showed a 42% increase in their force to failure, a 61% increase in ultimate stress, and a 90% increase in energy after 2 weeks compared with control. In another study, those tendons treated with PRP had a 30% increase in strength and stiffness after 1 week. Sánchez and colleagues investigated the augmentation of Achilles tendon rupture repair with PRP in athletes (6 in both the PRP group and control group). They used 2 PRP preparations on the primary repair of the Achilles as compared with controls. A total of 4 mL of PRP was mixed with CaCl₂ and after 30 minutes a fibrin scaffold was produced and incorporated into the repair site between the tendon ends. The remaining PRP was again mixed with CaCl₂ but immediately sprayed onto the wound site before closure. Subjects were followed for 1 year by ultrasound imaging and physical examination. They found that as compared with the control, the PRP group was able to return to mild running with earlier range of motion and without wound complication.

Sarrafian and colleagues performed a study to compare a cross-linked acellular porcine dermal patch (APD) against a platelet-rich plasma fibrin matrix (PRPFM) for repair of acute Achilles tendon rupture in a sheep model. The 2 surgically transected tendon ends were re-approximated in groups 1 and 2; whereas, a gap was left between the tendon ends in group 3. APD was used to reinforce the repair in group 2, and autologous PRPFM was used to fill the gap, which was also reinforced with APD, in group 3. Tensile strength testing showed a statistically significant difference in elongation between the operated limb and the unoperated contralateral limb in
groups 1 and 3, but not in group 2. In group 1, all surgical separation sites were identifiable and healing occurred via increasing tendon thickness. In group 2, healing occurred with new tendon fibers across the separation, without increasing tendon thickness in 2 out of 6 animals. Group 3 showed complete bridging of the gap, with no change in tendon thickness in 2 out of 6 animals. In groups 2 and 3, peripheral integration of the APD to tendon fibers was observed. They concluded that the use of APD, alone or with PRPFM, to augment Achilles tendon repair in a sheep model is a viable and strong repair.

The author has used PRP for the treatment of chronic Achilles tendinopathy and rupture repair in many cases (Fig. 4). The treatment protocol is similar to that of plantar fasciitis. Patients are chosen based on the chronicity of their symptoms and the quality of the tendon. Those patients that have failed conservative therapies after 3 to 6 months are good candidates. In addition to pain, decreased activity, and loss of function, most patients present with nodular thickening within the substance of the tendon. Some may even have multiple fibrotic nodules. Patients that have an associated retrocalcaneal exostosis have also been treated with PRP with varying results. Diagnosis is confirmed with ultrasound or MRI. A local anesthetic block is placed well above the site of injection. The PRP is then prepared at the desired concentration from the whole blood collection and activated by calcium citrate. Between 6 and 10 mL of PRP is injected within the substance of the tendon beginning at the site of pathology (pain and any bulbous mass). The medial or lateral aspect of the tendon is approached with patients in a prone position under ultrasound guidance. Several pulsed (peppered) doses of approximately 0.25 mL at a time are injected using a 25-gauge needle, fenestrating the tendon. Patients are then placed in a walking boot on crutches and nonweight-bearing for up to 1 week, and then allowed to bear weight in the boot for the next 1 to 3 weeks. They are then transferred into an athletic shoe with a slow increase in weight-bearing activity over a 4-week period. The author has seen a significant reduction in pain, decrease in the size of fibrous nodules within the tendon, and a sooner return to regular and sporting activity after PRP. Most patients have been able to return to increased exercise and activity within 2 months of the injection. Again, some patients have benefited by a second injection approximately 6 weeks after the first.

**Cartilage Injury**

Many studies have been performed examining the role of PRP in aiding the repair of cartilage in early osteoarthritis (OA). In vitro studies have shown that PRP has the

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**Fig. 4.** Treatment of Achilles tendinosis with PRP under ultrasound guidance.
potential of increasing proteoglycan and collagen synthesis in chondrocytes.\textsuperscript{27} Sun and colleagues\textsuperscript{28} evaluated the effect of PRP on cartilage defects in a rabbit model. They looked at the cartilage specimens after 4 and 12 weeks, macroscopically, with computed tomography, and histologically and found a significant increase in newly formed cartilage and bone as compared with the untreated group. They concluded that PRP improves osteochondral healing in the rabbit model. In vivo studies have also been promising.\textsuperscript{29,30} Sánchez and colleagues\textsuperscript{31} reported results on a retrospective study for human subjects with OA of the knee. They compared PRP injections and hyaluronan injections with 3 injections over 3 weeks. By week 5, the pain scale success reached only 10.0\% for the hyaluronan group and 33.4\% for the PRP group. Kon and colleagues\textsuperscript{32} studied 115 osteoarthritic knees with PRP injections. They found improvements in pain scale at 6 months follow-up. Cugat and colleagues\textsuperscript{33} investigated PRGF on athletes with chondral defects with positive results. As discussed earlier, mesenchymal stem cells can differentiate into chondrocytes and cartilage. Mishra and colleagues\textsuperscript{34} studied the effect of MSC treated with PRP on cartilage regeneration in vitro. They found that a 10\% PRP treatment increased cellular proliferation of chondrogenic differentiation more than 10-fold versus control. Investigation by Wu and colleagues\textsuperscript{35} suggested promising results by using PRP as a chondrocyte carrier to fill acute cartilage lesions in the knee. A scaffold made with PRP and thrombin was used to transfer chondrocytes to the lesion.

The author has not found recent studies that show the effect of PRP on OA of the foot and ankle. Theoretically, however, there is evidence that suggests improvement in pain and cartilage regeneration that could prove effective in the treatment of OA in the foot and ankle. At present, foot and ankle surgeons perform microfractures into cartilage lesions (osteochondral drilling) to initiate fibrocartilage repair. The marrow cells that are presented into the joint after microfracture are similar to those from BMA, MCS, and PRP. It would seem logical that the introduction of such cell products by percutaneous injection or surgical transfer would in fact increase cartilage regeneration and repair.

### Bone Augmentation

PRP can be used in the augmentation of bone or bone grafting. Concentrating platelets will increase the level of growth factors that could stimulate a prematurely terminated bone healing process.\textsuperscript{36,37} Initially, PRP was used for graft augmentation in oral and maxillofacial surgery by Marx and colleagues\textsuperscript{17} finding significant improvements in fusion rates and bone density in the mandible. It has been used as a percutaneous injection for fresh fractures to facilitate healing of nonunions, to augment fresh arthrodesis procedures with and without bone graft, for surgery using autologous or allogenic bone graft, and to fill bone defects. The effect of PRP on bone healing has been studied in great detail both in vitro\textsuperscript{38–41} and in vivo.\textsuperscript{36,37,42} It is thought that the increase in platelets and their growth factors will stimulate and enhance levels of osteoprotegerin, osteopontin, osteoblast differentiation of myoblasts and osteoblastic cells, and osteoclastlike cells.\textsuperscript{39,41,43,44}

BMA has been studied and used for several years and shown to enhance the healing of bone.\textsuperscript{45} There are 2 types of stem cells that originate in the bone marrow: hematopoietic and mesenchymal. It is the hematopoietic stem cells (HSC) that are pluripotent stem cells and give rise to all blood types. HSCs are fond in large numbers in the bone marrow and play a role in hard-tissue formation and differentiate into platelets. Mesenchymal stem cells are multipotent stem cells and are found in human tissues, including synovial tissue, bone marrow, and adipose tissues. They differentiate into cartilage, bone, muscle, and adipose tissue.\textsuperscript{46} Studies have shown MSCs to regenerate articular
cartilage in animal models and in bone for human models. Investigators have shown that PRP and its growth factors and cytokines enhance MSC proliferation. Theoretically, combining BMA and PRP together can create an environment where platelets and stem cells can act together to even further enhance bone healing than when used alone. The efficacy of PRP and BMA in the augmentation of bone and bone-graft healing is divided. There are many studies that show promise; whereas, others show little difference versus control or traditional products.

Gandhi and colleagues used PRP in nonunion fractures of the foot and ankle that were present for 4 months or more. Their findings suggest a decreased level of growth factors around nonunion fracture sites as compared with fresh fracture sites. The addition of PRP in this area could then increase nonunion healing potential through increases in growth factors. They found a 60-day mean resolution of the nonunions after the addition of PRP.

High-risk elective foot and ankle surgical subjects were studied by Bibbo and colleagues. The risk factors included previous poor osseous healing, osteomyelitis, tobacco use, diabetic neuropathy, malnutrition, immunosuppression, and alcohol abuse. Their results showed that 116 fusion sites (94%), using either autogenous or allogenic graft, went on to fusion in a mean of 41 days. They concluded that PRP may aid in union rates for high-risk patients.

Bielecki and colleagues used what they called platelet-leukocyte-rich gel percutaneously in delayed and nonunions of the humerus, femur, tibia, radius, and clavicle. They followed 32 subjects using radiograph and absorptiometry examinations. Results showed a total union in 9.3 weeks for all those delayed union cases treated with PLRG. In the nonunion group, union was seen in 13 of the cases with an average of 10.3 weeks with PLRG. They found that delayed and nonunions that were more than 11 months had the least favorable results. They concluded that percutaneous injection of PLRG into nonunion and delayed union fractures may be sufficient to facilitate union and can replace more invasive bone marrow injections.

Coetzee and colleagues studied the benefits of PRP in the union of the syndesmosis with use of total ankle arthroplasty. The retrospective study compared 66 subjects with the addition of PRP and 114 without augmentation. The control group had a fusion rate of 61% at 8 weeks and 85% at 6 months. The PRP group had a fusion rate of 76% at 8 weeks and 97% at 6 months. They also found and increase in the fusion rate of those subjects treated with PRP that had a history of tobacco use. Similar results were reported by Barrow and Pomeroy who found an 85% union rate at 8 weeks and 100% at 6 months in their prospective study.

The author has been using PRP in conjunction with BMA to facilitate midfoot and hindfoot surgical fusions. Patients are chosen as candidates for augmentation of fusion with PRP based on the patient history and risk factors. Those patients that have a history of tobacco use, alcohol abuse, previous nonunions, diabetic neuropathy, and osteoporosis are good candidates. PRP has been used in conjunction with BMA in cases with or without the need for bone autograft or allograft. The author will harvest the BMA from the calcaneus or the proximal tibial metaphysis. The technique for acquiring the percutaneous BMA from these areas is documented by Schweinberger and Roukis. The whole blood acquired for the PRP and BMA are combined together and prepared in the centrifuge. The final PRP and BMA mixture can be applied as a liquid or a gel. The gel is formed by adding thrombin to the final mixture. Exposure of PRP to thrombin will induce platelet degranulation, increasing the concentration of growth factors. The use of bovine thrombin can lead to the development of antibodies to the clotting factors V, XI, and autologous thrombin, which can lead to multisystem failure. Techniques can now use the same blood sample used to
make PRP to generate autologous thrombin from prothrombin. This generation can be achieved by adding calcium chloride during the processing of the PRP, forming a dense fibrin matrix that traps the platelets resulting in a small amount of thrombin, minimizing activation that leads to a slow release of growth factors over 7 days.9 The fibrin mass that is created is a gelatinous scaffold that is a malleable product that can be introduced between bones to be fused when used with or without a bone graft and introduced into bone defects (Fig. 5). The liquid form can be used to coat a bone graft. The author has seen significant promising results with an increase in bone healing rates with less pain and earlier radiographic evidence of fusion using a combination of PRP and BMA.

Wound Healing

Many foot and ankle surgeons are faced with diabetic, iatrogenic, decubitus, and venous chronic wounds. A plethora of biologic materials have been produced and investigated to aid in the closure of chronic wounds. PRP seems to also have the properties to augment wound healing. During the inflammatory phase of wound healing, an environment rich in cellular proteins form an initial clot. This clot is composed of collagen, platelets, thrombin, and fibronectin. In addition to aiding in hemostasis these products lead to the release of growth factors and cytokines that will stimulate the cascade that ends in a healed wound. PRP full of these growth factors could potentially significantly aid in the closure of chronic wounds. PRP is usually used in conjunction with bone marrow aspirate when applied to wounds.

Several in vitro and in vivo studies have shown PRP can increase the potential of wound-healing cell products. Smith and Roukis4 reviewed several studies investigating PRP used on chronic wounds (diabetic and nondiabetic) of the lower extremities. The majority of these studies found that wounds treated with PRP healed significantly sooner than their control groups. In most of the studies, the control groups were eventually treated with PRP with closure achieved because of its effectiveness. Some studies have shown the ability of PRP to combat wound infection.60–62 Bielecki and colleagues60 found that PRP gel inhibited the growth of Escherichia coli and S aureus.

Lacci and Dardik63 performed a literature review between July of 2008 and March of 2009 to evaluate the number of studies and their outcomes with the use of PRP on

Fig. 5. PRP formulation as fibrin gel with BMA introduced into fusion site at first metatarsal cuneiform joint.
chronic wounds. They found PRP to be effective in several case-control studies and noncontrolled clinical trials. They only found 1 prospective, randomized, controlled clinical trial on PRP in the treatment of diabetic foot ulcers by Driver and colleagues\textsuperscript{64} with significant results. Lacci and Dardik\textsuperscript{63} concluded that there is promise for the use of PRP in chronic wounds of varying etiology and diabetic foot ulceration.

Cervelli and colleagues\textsuperscript{65} performed a study on 30 chronic lower-extremity wounds. They used the theory that MSC is present in adipose tissue, which can accelerate the effects of PRP by using PRP and autologous fat grafts. Their results showed an improvement from minor to moderate in 100\% of subjects after 3 weeks, healing in less than 6 weeks in 47\% of subjects, and complete wound healing in 57\% of subjects within 3 months. They concluded that there is the ability of the combination of PRP and autologous adipose graft to regenerate tissue and epithelialization with wound closure, with a significant healing-time reduction. They found it to be well accepted by subjects with a relative reduction in cost. This group also studied the role of PRP used as an autologous scaffold for cellular growth, in combination with hyaluronic acid as a temporary dermal substitute for chronic wounds with exposed tendon, and found that PRP aided healing of acute and chronic open wounds of the foot and ankle.\textsuperscript{66}

A recent study by Frykberg and colleagues\textsuperscript{67} evaluated the use of PRP gel in the initial wound-healing trajectories of chronic, nonhealing wounds of various etiologies and in different care settings. They followed 65 nonhealing wounds (mean duration 47.8 weeks, range 3.0 to 260.0) at 8 long-term acute care hospitals and 3 outpatient foot or wound clinics and applied PRP gel on their wounds. The majority of subjects had low albumin, hematocrit, or hemoglobin levels. The most common wounds were pressure ulcers, venous ulcers, and diabetic foot ulcers. Following a mean of 2.8 weeks with 3.2 applications, reductions in wound volume area, undermining, and sinus tract/tunneling were observed. For all wound etiologies, 97\% of wounds improved. Their results suggest the application of this PRP gel can reverse nonhealing trends in chronic wounds.

Most patients with chronic lower extremity wounds are good candidates for the use of PRP with BMA. The PRP is prepared with a 60 mL blood draw. The platelet-poor portion is set aside to spray over the inner dressings. The BMA is acquired and prepared with the PRP and thrombin is added to create the gel. While the gel is forming, extensive debridement of the ulcerating is performed to healthy bleeding tissue. The gel is formed into the shape of the wound and placed directly to the wound site. The dressings are applied with a standard wet-to-dry dressing for the first few days, to allow the patch to fully breakdown and begin the healing process. After the first few days (4–6), the dressing should be changed. Mineral oil can also be used to aid in the dressing.

DISCUSSION

Clearly the importance of platelets, their $\alpha$ granules, and their release of growth factors on bone and tissue repair cannot be overstated. The literature is full of studies suggesting the potential for the augmentation of bone, soft tissue, and wound healing with PRP. In vitro and in vivo animal studies have shown PRP to have a positive effect on tissue repair on the cellular level. The safety and risk profile for PRP proves to have low morbidity and associated complications.\textsuperscript{19} It has a low chance of rejection because it is produced from the patients’ own blood. PRP is easy to acquire and apply because it can be produced in the clinical or operative setting at the time it is needed. It is also less expensive than other orthobiologics and modes of tissue augmentation.
The research and use of PRP also has potential limitations. There is a lack of uniformity on several levels. Many different concentrations of PRP are used, although some simply cannot quantify the concentrations used. There is no optimal dose presented for the potential application and uses of PRP. The literature is not standardized on the acquisition, the method of preparation, or the addition of supplements to activate PRP.

There are several studies investigating PRP; however, many are poorly designed and few involve the foot and ankle. Further human, large, consistent, and well-performed prospective studies of PRP and its use in the foot and ankle are critical to better understand and apply its potential and benefits of use. Future studies that investigate the benefits of using PRP in acute versus chronic cases would also be beneficial. It will be important that future studies be able to suggest consistent concentrations of PRP, appropriate dosing, improved technique, and the best postinjection protocol.

SUMMARY

PRP presents promise for the treatment of many foot and ankle pathologies, including tendinopathy (Achilles, peroneal, posterior tibial, flexor hallucis longus, anterior tibial), ligamentous injury (plantar fasciitis, lateral ankle), augmentation of bone intraoperatively with primary fusions, fresh fractures, nonunions, tendon rupture repairs, cartilage injury (ankle, subtalar, metatarsal cartilage lesions), sesamoiditis, and chronic wounds. The author has even seen promising results in a small sample of patients treated for sesamoiditis and chronic lateral ankle pain.

The author has been using PRP over the last 2 years. The results have been increasingly promising with regard to decreased pain, increased activity, improved function, faster recovery, and increased strength. The use of PRP in the clinical setting may be advantageous for its ease of use, relative availability, low side effects, and tolerability, as compared with more invasive techniques. Although the theory behind the use and effectiveness of PRP and some positive clinical evidence have shown promise, it is evident that additional well-designed prospective studies on PRP and its use in foot and ankle pathology are needed to measure its true effectiveness.

REFERENCES


