American College of Foot and Ankle Surgeons®

Proven leaders.
Lifelong learners.
Changing lives.

Autologous Platelets for Treatment of Tendonopathy of the Foot and Ankle

BY ADAM M BUDNY, DPM

This article is written exclusively for Podiatry Management by the American College of Foot and Ankle Surgeons (ACFAS). Founded in 1942, ACFAS is a professional society of more than 6,300 foot and ankle surgeons. The College promotes the art and science of foot, ankle and related lower extremity surgery, addresses the concerns of foot and ankle surgeons, as well as advances and improves the standards of education and surgical skill to ensure the highest level of patient care. For more information on ACFAS, visit acfas.org or circle #152 on the reader service card.

Abstract

While the use of autologous platelet preparations for the treatment of musculoskeletal pathology has been in vogue over the past decade, there is a surprising paucity of literature to justify this, especially in regard to the foot and ankle. A number of studies are available for review; however, the majority are anecdotal case reports or case series with no control group; and those that do employ a more scientific approach often have small sample sizes. While the rationale behind the use of this technology has been thoroughly examined, one must conclude that further evaluation is required before making a final judgment in regard to the efficacy for treatment of tendonopathy in the foot and ankle. The author will review the science behind platelet concentrates, describe commercially available systems, examine existing literature, and provide a few case examples.

The goal in development of PRP products is to achieve a concentration of platelets above the baseline value for the subject.

Introduction

The field of orthobiologics has increased seemingly exponentially over the past few years, with more companies offering bone substitutes, collagen matrices, dermal substitutes and autologous platelet preparations. Specifically of interest to this paper is the advent and development of platelet concentrates, which have gone by a number names including platelet rich plasma (PRP), platelet rich concentrate, platelet releasate, platelet rich plasma-concentrate release (PRCR), and autologous conditioned plasma (ACP). Regardless of the name, the principle remains the same: a patient's whole blood is collected peripherally, then centrifuged to separate the individual components. Subsequently, the platelet rich component is isolated, which can be administered clinically to treat a variety of conditions. The use of this platelet concentrate has been evaluated in oral surgery, plastic/cosmetic surgery, wound healing, orthopaedic surgery (including bone fusion, fracture care, and tendon healing) as well as multiple other areas. Some of the popularity may be due to media coverage of professional athletes receiving this as an alternative choice to surgery or extended rehab and significant time away from their team.

Platelet Physiology

In addition to their role in clotting, platelets have been shown to release many proteins responsible for

Continued on page 92

enhancing tissue regeneration and healing from intracellular alpha granules. These native cytokines include transforming growth factor beta (TGFbeta), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), insulin-like growth factor (IGF) and epithelial growth factor (EGF), among others.[1-5] Based on the concentration of these growth factors, PRP is assumed to stimulate a "supraphysiologic" response in an attempt to jumpstart the healing process in chronic orthopaedic injuries.[1]

TABLE 1
Growth Factors and Their Respective Effects on Tissue

Growth Factor	Function
TGF-beta	Promotes formation of extracellular matrix and regulates bone metabolism
PDGF	Stimulates angiogenesis, promotes cell proliferation and granulation
VEGF	Angiogenesis
IGF	Stimulates fibroblasts ad myoblasts
EGF	Promotes cell differentiation and proliferation

At a more basic level, blood contains three main components: plasma, red blood cells (RBC), and white blood cells (WBC). These are maintained in healthy individuals at a relatively constant ratio of 93%:6%:1% (RBC, Plasma, WBC, respectively).[6] The platelets component of blood is manufactured in the bone marrow; they have a short lifespan of 7-10 days. They require thrombin to be activated (usually precipitated by an injury) which leads to aggregation, clotting, and subsequent release of the growth factors from the alpha granules. These factors then play a variety of roles in tissue healing (Table 1).[1,3]

The goal in development of PRP products is to achieve a concentration of platelets above the baseline value for the subject. There is not yet a standardization for the value of concentration that defines "platelet rich", and the manufacturers of PRP systems all achieve different levels of platelets and growth factors in their centrifugation process (Table 2). The normal concentration of platelets is 150,000/uL to 350,000/uL. Most research suggests at least 1,000,000/uL is needed to promote an increase in healing.[1,4]

Most of the manufacturers of PRP systems achieve an increase of 3-5x in platelets and will use one or two centrifugation cycles to separate the blood products). The system offered by Arthrex, Autologous Concentrated Plasma (ACP) (Arthrex Inc, Naples, FL) is unique in that WBCs and neutrophils are specifically not included while the plasma concentrate administered still contains a supra-physiologic amount of platelets and associated cytokines.[7] Previous literature has suggested that the presence of WBCs and neutrophils may be deleterious to wound healing.[8]

TABLE 2
Commercially Available Platelet Concentration Systems and the Relative Increase in Concentration of Platelets

Platelet Concentration System	Increase in Platelets Above Baseline
Magellan*	2-14x
GPS III∞	Up to 9.3x
Symphony§	3-6x
ACP ¤	2x

* Arteriocyte Medical Systems, Cleveland, OH
∞ BioMet Biologics Inc., Warsaw, IN
§ Depuy Orthopaedics, Warsaw, IN
¤ Arthrex Inc., Naples, FL

Tendon Physiology and Healing

Tendon and ligament injuries can fall into two broad categories of either acute or chronic. An acute injury implies that a tendon will go through the normal three phases of healing: inflammation, cellular proliferation, and remodeling.[8,9] The tendon repair sequence begins after formation of a clot and granuloma at the injury site, followed by fibroblasts forming collagen, mostly type 3.[9] This gradually increases mechanical strength, and as the tendon is loaded through elastic deformation (i.e., muscle contracture/joint movement), a gradual transition to type 1 collagen is made. When a tendon injury becomes chronic, this normal cycle is disrupted, and the tendon is frozen in the proliferative phase. This leads to a degenerative process of tendonopathy characterized by collagen fiber disruption, mucoid degeneration, neo-vascularization, and an ab-

Continued on page 93

sence of inflammation.[2,8] Tendons are, in general, relatively avascular structures with a low basal metabolism that contributes to the prolonged recovery after injury.[10] In vitro studies have confirmed that application of PRCR can lead to accelerated proliferation of tenocytes, as well as Type 1 and 3 collagen.[9,10]

Autologous platelet preparations have the potential to interrupt chronic tendonopathy in several ways. First of all, this process is mediated by the administration of supra-physiologic concentrations of growth factors from the alpha granules contained in the PRP injection. As previously noted, this will introduce an increased amount of cytokines that will subsequently restart the cycle of tendon repair.[3] This, combined with the mechanical injury from injecting in the form of "micro-tenotomy" or "peppering" techniques, will serve to create an inflammatory response to a stagnant healing environment and thus initiate tendon repair.[8]

Literature Review

When a systematic search for PRP (or any of the aforementioned descriptors) is completed, a significant amount of literature can be found in regard to tendonopathy. The search must be narrowed, however, to remain relevant to this article. The number of prospective trials has significantly increased over the past three years to include research in sports medicine, anterior cruciate ligament repair, rotator cuff repairs, Achilles tendonopathy, patellar tendonopathy, lateral epicondylitis and plantar fasciosis.[1, 3,8,10,12,14] Recently, the quality of this research has improved to include prospective controlled trials; however, a number of case reports and series with retrospective data are available as well.

In 2011, Finoff, et al. wrote a two-part paper. Part 1 was a retrospective review. Part 2 of their study was to bring patients back for a prospective diagnostic ultrasound on patients undergoing percutaneous microtenotomy and PRP injection for recalcitrant tendonopathy.[8] Their patients had a variety of involved tendons in both the upper and lower extremities (n = 10 (24.4%) and (n = 31 (75.6%), respectively. Post-procedurally, they found that 83% of subjects were satisfied with the outcome. Although none of their patients achieved a sonographically normal tendon, there were significant improvements in echotexture, resolution of intratendinous calcifications, and a decrease in intratendinous neovascularity.

The study was slightly different from much of the available literature as it did involve a percutaneous tenotomy followed by PRP, while most other trials simply describe three to

Continued on page 94

five injection sites for administration of the PRP into the mid-substance of the tendon.

Another recent randomized controlled trial (RCT) evaluated the efficacy of PRP in arthroscopic rotator cuff repair.[10] This was an RCT of 53 patients divided into a treatment group (PRP) (n = 26) and control group (n = 27), with healing verified via validated scoring systems as well as a follow-up MRI. All patients underwent rotator cuff repair, and the PRP group was found to have lower pain scores at days 3, 7, 14, and 30 days after surgery. Strength in external rotation was also higher at three months.

The follow-up MRI did not demonstrate any significance in healing rate; however, there were nine retears in the PRP group and 12 in the control group, with an overall healing rate of 54% (in agreement with previous literature). Their conclusion was that PRP could decrease pain and accelerate functional recovery. This group used the BioMet GPS system for platelet concentration, and the PRP was administered after completion of the repair by injection into the joint space.

In contrast to the study by Randelli, another group was unable to demonstrate the same accelerated healing in rotator cuff repairs.[5] This was a cohort study of 42 patients, with 19 in the PRP treatment group and 23 in the control. The authors found appreciable differences in pain, range of motion, strength, or functional scores. Differences included the fact that they did not use a commercially available PRP system; instead, they used an automated plateletpheresis system, and they created a platelet gel which was then sutured between the tendon and bone. They do concede that one of the greatest weaknesses between all studies about PRP is the lack of standardization of preparation, concentration, levels of WBCs in the gel, and platelet activation.

A recent paper on the application of PRP in ACL repair was also conducted to evaluate if there was a reduction in anterior knee pain, kneeling pain, and donor site morbidity after patellar tendon graft harvesting.[14] They also evaluated bone healing at the final follow-up via MRI and conducted a clinical exam as well as validated (VISA) questionnaires. Forty athletes (all male) underwent ACL reconstruction with an autologous bone-patellar tendon-bone graft. They found a statistically significant increase in VISA scores in the treatment group in regard to knee pain as well as filling of the bone defect in 85% (only 60% in the control group). The authors conclude that application of PRP can reduce pain in athletes which could otherwise be an obstacle to quick return to high-level sport.

The only paper found which specifically addresses plantar fasciosis was a pilot study by Barrett and Erredge in 2004.[12] This was a case series of just nine patients undergoing PRP injection for recalcitrant plantar fasciosis. The authors did compare pre- and post-procedural ultrasound to evaluate the thickness of the fascia and did find that there was a mean reduction of 2.30mm. Six of the nine had complete resolution after two months, and one had dropped from the study after receiving a corticosteroid injection. This was a very limited study with no control group and very small sample size, which would be difficult to generalize to a larger population. Also no statistical evaluation was performed.

At the most recent American Academy of Orthopaedic Surgeons (AAOS) meeting (February 2012), an abstract was presented by Monto.[16] In this prospective, controlled trial, 36 patients were randomized to an ultrasound-guided corticosteroid or PRP injection. All had failed extensive conservative treatment for approximately five months. The AOFAS score improved from 52 (pre-injection) to 81 at three months, but fell back to 58 at twelve months, whereas in the PRP group, the scores improved from 37 pre-injection to 95 and 94, respectively. The author concluded that PRP was more effective and durable for treating recalcitrant plantar fasciitis.

Treatment of chronic Achilles tendonopathy with PRP has been evaluated by a number of authors.[8,13,15-17] For the most part, there have been favorable results reported in regard to outcomes; however, the patient sample size of all combined studies is still very small and difficult to apply to the general population. Sanchez, et al. were the first to report the use of PRP in a retrospective case control series of Achilles tendonopathy in twelve athletes.[16] The authors found better functional outcomes and an earlier return to training in the PRP group (n = 6) with a 12 month follow-up. They also found a smaller cross-sectional area of the tendons on follow-up MRI. Their series was, of course, limited by a small sample size and retrospective design. The same senior author later reported outcomes associated with two patients treated for revision Achilles surgery due to tissue loss.[18] Both patients were athletes who were able to return to their respective sports at 14 and 28 weeks.

Treatment of chronic Achilles tendonopathy with PRP has been evaluated by a number of authors.

Gaweda, et al. presented a case series of 14 patients (15 Achilles tendons) who had chronic Achilles tendonopathy.[15] Their treatment protocol was 3mL of PRP administered with ultrasound guidance, followed by six weeks with crutches (six patients had to undergo a second injection). They reported significant improvements in VISA and AOFAS foot and ankle scores at 18 months. The AOFAS score increased from 55 to 96 at final follow-up. In addition, they found improvements in the ultrasonic appearance of the tendons with decreased thickness, reduction of interstitial tears, and hypo-echoic foci. Of note, they did report a transient increase in

Continued on page 96

neovascularization for up to three months.

DeVos, et al. performed a level 1 RCT on chronic mid-substance Achilles tendonopathy, in which one group received an ultrasound guided PRP injection vs. a saline injection control group.[13] The original paper reported 24 week outcomes for 54 patients, and the same data was used in a later paper reporting on a one year follow-up.[17] Both the PRP and the saline groups demonstrated statistically significant improvements in VISA scores (21.7 and 20.5 respectively). Both groups received what could be considered a variation of a micro-tenotomy, with 15 perforations during administration of either the PRP or saline. In addition, both groups were treated post-procedurally with an eccentric training program.

Although a level-one RCT, a few questions remain. First of all, was it the micro-tenotomy that caused the improvement in both groups? Secondly, since both groups underwent an eccentric strengthening regimen after the treatment, does this trial simply show that the ideal treatment for Achilles tendonopathy is physical therapy alone? Investigations have indeed shown that both micro-tenotomy and eccentric training are effective for mid-portion Achilles tendonopathy.[8]

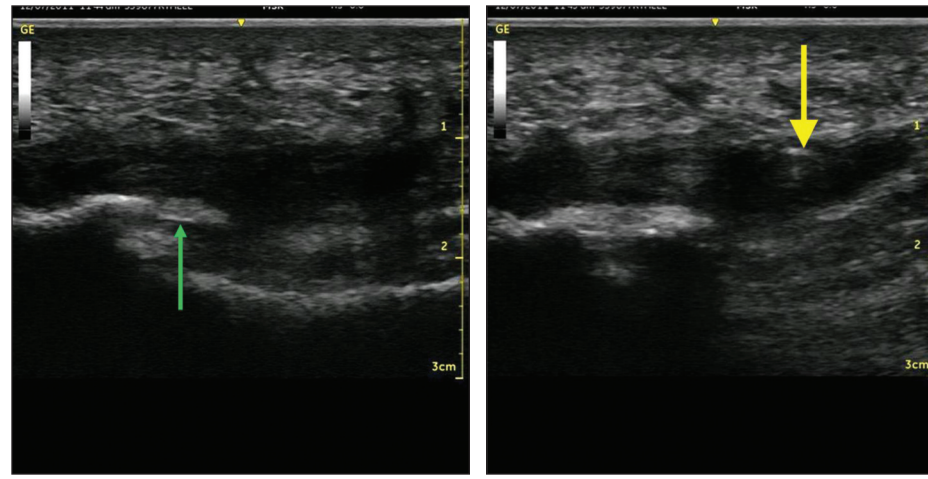

Figure 2: Ultrasound image demonstrates thickening of the plantar fascia (green arrow) with concomitant heel spur. The needle is perpendicular to the long axis of the ultrasound probe (yellow arrow).

Case Examples

The author has used the Autologous Concentrated Plasma system (Arthrex Inc., Naples, FL (Figure 1) for approximately one year for both chronic plantar fasciosis and mid-portion Achilles tendonopathy. In all cases, patients have undergone extensive conservative treatments for their respective conditions, including stretching, strengthening, bracing, orthotics, physical therapy, etc. If the patients fail to respond to the conservative measures, and their next step would be to make a decision for surgery, they are given the option to attempt an ultrasound-guided injection of ACP. The authors preferred technique includes administration of a pre-emptive infiltration with 0.5% bupivicaine proximal to the site of pathology. Subsequently the ACP is injected with a "peppering" technique (approximately 5-10 individual depots) into the tendon or fascia. Post-procedurally, they are to abstain from NSAIDs for at least two weeks, and use tramadol or hydrocodone with acetaminophen and ice for pain. In both scenarios, they are protected with a removable fracture boot and crutches. Gradual transition to shoes and limited activity is allowed at two weeks with an appropriate home exercise program. Return to low-impact aerobic activity/exercise is allowed after four to six weeks.

Figure 1: Arthrex ACP centrifuge system(a) and syringe(b).

Plantar Fasciosis

A 48-year-old female had been treated for plantar fasciitis for six months with no relief. This included plantar fascia-specific stretching, orthotics, NSAIDs, and night splinting. ACP was offered to her as an alternative to surgical fasciotomy. Injection was administered under ultrasound guidance (Figure 2) followed by two weeks in a protective fracture boot. At one month, she was pain free and transitioned to accommodative shoes and activities without limitation.

Achilles Tendonopathy

A 53-year-old female presented with a two-year history of Achilles pain. She had been treated by another provider unsuccessfully and had persistent pain in the left Achilles tendon. After she had gone through physical therapy as well as bracing without further relief, an ACP injection was offered as a last resort prior to surgical intervention. Using the technique previously described, she underwent injection therapy (Figure 3). She was immobilized in a fracture boot for

Continued on page 98

three weeks post-injection, followed by an Achilles support sleeve for three more weeks. At the six week point, she was pain-free and allowed to return to activity. She has not had recurrence of any pain or limitation (now at the five-month follow-up).

Conclusions

The only conclusion that can be made at this time about the use of PRP for chronic tendonopathy in the foot and ankle is that more research is required. The studies that are available represent only a limited number of patients, are poorly designed, or have flaws and cannot be generalized to larger populations. While it is a very promising technology, several questions remain: What is the ideal concentration of platelets? One injection, or weekly, or monthly? Microtenotomy technique or single-dose administration?

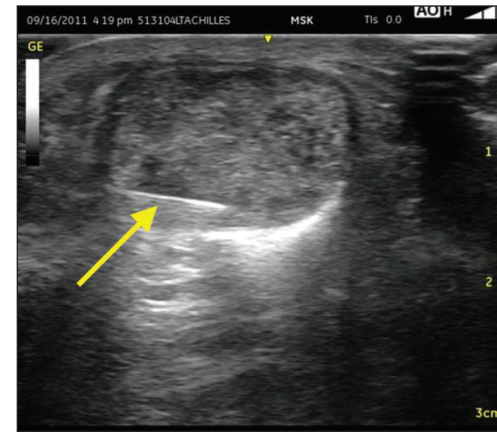

Figure 3: Ultrasound image demonstrates thickening of the Achilles with interstitial tearing and significant tendonopathy. The needle can be seen entering the mid-substance of the tendon (yellow arrow).

The only conclusion that can be made at this time about the use of PRP for chronic tendonopathy in the foot and ankle is that more research is required.

This, of course, opens the door for more research and further investigation into PRP. While the final answer is yet to be revealed, a few things can be inferred for surgeons who would like to offer this to their patients: It is a simple procedure which can be performed in an outpatient setting or the office; it has a brief convalescence; the risks are minimal; and it does not preclude further treatment or surgery if required. The physiology behind the use of autologous platelets should support the theoretical advantages of its use clinically, and there is clearly potential for future research. **PM**

References

[1] Sampson, S., Gerhardt, M., Meandelbaum, B. Platelet rich plasma injection grafts for musculoskeletal injuries: a review. Curr Rev Musculoskelet Med. 2008, Vol. 1.

[2] Paoloni, J., de Vos, RJ., Hamilton, B., Murrell, GA., Orchard, J. Platelet rich plasma treatment for ligament and tendon injuries. Clin J Sport Med. Jan, 2011, Vol. 21, 1.

[3] aylor, DW., Petrera, M., Hendry, M., Theodoropoulos, J. A systematic review of the use of platelet rich plasma in sports medicine as a new treatment for tendon and ligament injuries. Clin J Sport Med. Jul, 2011, Vol. 21, 4.

[4] Soomekh, DJ. Current Concepts for the use of platelet rich plasma in the foot and ankle. Clin Podiatr Med Surg. Jan, 2011, Vol. 28, 1.

[5] Jo, CH., Kim, JE., Yoon, KS., Lee, JH., Kang, SB., Lee, JH., Han, HS., Rhee, SH., Shin, S. Does platelet rich plasma accelerate recovery after rotator cuff repair? A prospective cohort study. Am J Sports Med. Oct, 2011, Vol. 39, 10.

[6] Marx, R., Garg, A.,. Dental and craniofacial applications of platelet rich plasma. s.l. : Quintessence Publishing Co Inc, 2005.

[7] Arthrex Inc. Autologous Conditioned Plasma. Naples, FL : Arthrex Inc., 2011.

[8] Finnoff, JT., Fowler, SP., Lai, JK., Santrach, PJ., Willis, EA., Sayeed, YA., Smith, J. Treatment of chronic tendonopathy with ultrasound guided needle tenotomy and platelet rich plasma injection. PM R. Oct, 2011, Vol. 3, 10.

[9] Chen, L., Dong, SW., Liu, JP., Tao, X., Tang, KL., Xu, JZ. Synergy of tendon stem cells and platelet rich plasma in tendon healing. J Orthop Res. Dec 12, 2011.

[10] Randelli, P., Arrigoni, P., Ragone, V., Aliprandi, A., Cabitza, P. Platelet rich plasma in arthroscopic rotator cuff repair: A prospective RCT study, 2 year follow up. J Shoulder Elbow Surg. Jun, 2011, Vol. 20, 4.

[11] Wang, X., Qiu, Y., Triffitt, J., Carr, A., Xia, Z., Sabokbar, A. Proliferation and differentiation of human tenocytes in response to platelet rich plasma: An in vitro and in vivo study. J Orthop Res. Nov 18, 2011.

[12] Barrett, S., Erredge, S. Growth Factors for Chronic Plantar Fasciitis. Podiatry Today. Nov, 2004.

[13] de Vos, RJ., Weir, A., van Schie, HT., Bierma-Zeinstra, SM., Verhaar, JA., Weinans, H., Tol, J. Platelet rich plasma injection for chronic achilles tendonopathy—arandomized controlled trial. JAMA. 2010, Vol. 303, 2.

[14] Cervellin, M., de Girolamo, L., Bait, C., Denti, M., Volpi, P. Autologous platelet rich plasma gel to reduce donor site morbidity after patellar tendon graft harvesting for anterior cruciate ligament reconstruction: a randomized, controlled clinical study. Knee Surg Sports Traumatol Arthrosc. Jun 16, 2011.

[15] Gaweda, K., Tarczynska, M., Krzyzanowski, W. Treatment of achilles tendonopathy with platelet rich plasma. Int J Sports Med. 2010, Vol. 31.

[16] Sanchez, M., Anitua, E., Azofra, J., Andia, I., Padilla, S., Mujika, I. Comparison of surgically repaired achilles tendon tears using platelet rich fibrin matrices. Am J Sports Med. 2007, Vol. 35.

[17] de Jonge, S., de Vos, RJ., Weir, A., van Schie, HT., Bierma-Zieinstra, SM., Verhaar, JA., Weinans, H., Tol, JL. One year follow up of platelet rich plasma treatment in chronic achilles tendonopathy: a double blind randomized placebo controlled trial. Am J Sports Med. Aug, 2011, Vol. 39, 8.

[18] Sanchez, M., Anitua, E., Cole, A. Management of post surgical achilles tendon complications with a preparation rich in growth factors: a study of two cases. Injury Extra. 2009, Vol. 40.

Adam M. Budny is a foot and ankle surgeon at Blair Orthopedic Associates in Altoona, Pennsylvania where he is also Chief, Section of Podiatry at Altoona Regional Health System. In addition, he is co-medical director of the Wound Healing Program at Nason Hospital in Roaring Spring, PA. He received his DPM from Des Moines University and is a Fellow in the American College of Foot and Ankle Surgeons.