Platelet-rich Plasma for Foot and Ankle Disorders in the Athletic Population

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Abstract: Athletes and their physicians are constantly searching for ways to heal injuries faster and allow for a quicker return to activity and sport. However, reliable and effective means of treating foot and ankle tendon/ligament disorders as well as fracture nonunions, and osteochondral lesions of the talus are limited. In the past, rest/immobilization, corticosteroids/nonsteroidal anti-inflammatory drugs, and rehabilitation were the mainstays of nonoperative treatment. However, results were inconsistent. In addition, anti-inflammatory medications and corticosteroids have been associated with potentially serious side effects. Recently, platelet-rich plasma (PRP) has been heralded as a safe, new therapy with potential for treating both soft and mineralized tissue injuries throughout the body, including the foot and ankle. PRP is a concentrated solution of platelets and other buffy coat elements in plasma that can be activated by collagen or thrombin and calcium. Platelets are known to be rich in growth factors and cytokines that are involved in the healing response, such as platelet-derived growth factor, vascular endothelial growth factor, insulin-like growth factor-1, and transforming growth factor-β. Early reports showed positive results leading to increasingly greater interest. Currently, we recommend using PRP only for injuries/lesions of the foot and ankle that have failed standard therapies. Before use, a thorough history and physical examination should be performed, including a detailed history of allergies and blood disorders. For maximum benefit with minimal risk of complications, injections should be performed under image guidance. Despite the great potential associated with it, evidence regarding the efficacy of PRP has been primarily limited to small case series and anecdotal reports. More rigorous analyses, preferably randomized controlled studies, are needed before PRP may be adopted as a standard therapeutic modality.

Key Words: platelet-rich plasma, PRP, tendon, bone, cartilage, foot, ankle

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HISTORICAL PERSPECTIVE

Foot and ankle tendon or ligament injuries, difficult to heal fractures of the fifth metatarsal, and osteochondral lesions of the talus are common in the athletic population and with the ever improving capabilities of magnetic resonance imaging (MRI) and ultrasound, pathology can be more accurately and quickly diagnosed. Consequently, better ways to treat these disorders are continuously sought by the athlete and physician alike. However, reliable and effective means of treatment have been limited with respect to traditional treatment strategies. In the past, a combination of rest/immobilization, along with anti-inflammatory medications or corticosteroids, and a rehabilitation program have been used with inconsistent results.[1–3] Further complicating matters, anti-inflammatory use has been associated with possible gastrointestinal bleeding in certain predisposed individuals,[4,5] whereas corticosteroids injected directly into tendons/ligaments can adversely affect tendon structure and increase the risk of rupture.[6–8] It is clear then, that new, safer therapeutic alternatives are needed.

New therapies using progenitor cells and specific growth factors and cytokines are emerging. Previous success in characterizing the bone morphogenetic proteins led to revolutionary clinical outcomes[9–15] which have inspired the search for other potent factors and proteins. Yet the pursuit of specific growth factor/cytokine therapies is fraught with difficulties at multiple levels, including identification, isolation, and clinical translation. This has led some investigators to reexamine the macroelements of the healing response. One recent subject of interest has been platelets. Platelets are known to contain multiple anabolic factors, including platelet-derived growth factor, vascular endothelial growth factor, insulin-like growth factor-1, transforming growth factor-β-1, and epidermal growth factor within the α granules present in their cytoplasm.[16] After injury, platelets migrate quickly to the lesion site and are stimulated to release the contents of these granules, which help to initiate the inflammatory/healing cascade.[16] It has also been reported that growth factors released from platelets may also aid in the process of stem cell homing to the host site (signaled, in part, by stromal-derived factor-1α and stem cell factor) and in the multiplication and differentiation of stem cells into new tissue cells.[17]

In the late 20th century, clinicians began experimenting with platelet concentrates in wound and bone healing.[18] The early data demonstrated improved healing of complicated skin wounds, as well as bone defects and grafts.[19,20] These various platelet concentrate products have now evolved into what is often referred to as platelet-rich plasma, or PRP. PRP is an autologous blood product, derived from an individual's whole blood that is spun down into its fractional elements. There are a number of commercially available systems that can be used to prepare PRP, each with their own specific protocol. What is universal among these systems, however, is that the red blood cell fraction is discarded along with the platelet-poor plasma portion, leaving a solution of platelets, buffy coat, and plasma. This solution is then activated at the time of application, thereby stimulating the platelets to release their contents.

After the publication of these initial positive reports, it was not long before clinicians and athletes alike began to recognize the potential benefits of PRP in sports medicine. This lead to an exponential increase in the number of injuries treated with PRP, though a clear understanding of the mechanism(s) of action of PRP or the ideal preparation are still lacking. Recently, however, it was shown that PRP (in the form of a PRP clot releasate) could promote the differentiation of tendon stem cells into highly proliferative and active

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tenocytes that have an abundant collagen production capacity.[21] This is some of the first data to show an effect on tendon stem cells and may potentially provide a springboard for a better understanding at the molecular level.

The clinical effects of PRP have yet to be well characterized in the foot and ankle literature, as studies demonstrate a mixture of both positive and equivocal results.[22,23] Currently, PRP is being used to augment the healing of tendon repairs, as well as to treat tendinopathy, muscle injuries, poorly healing fractures, and osteochondral lesions. The following sections will describe in greater depth our experiences and techniques with PRP for treating these specific injuries.

INDICATIONS AND CONTRAINDICATIONS

Indications

No definite indications for the use of PRP in athletes yet exist as clinical data is still limited. The authors' therefore advocate a conservative approach to its use at this time. Before considering PRP treatment, a thorough and complete history should first be obtained from each patient along with a careful physical examination. This should include questions regarding their particular symptoms (including location, duration, radiation etc.) as well as medical history and comorbidities. Blood disorders such as anemia, polycythemia, thrombocytopenia, factor deficiencies, and leukemias/lymphomas should be inquired about. A history of allergic reactions, particularly to any types of blood products (especially thrombin) in the past should also be elicited.

The following is a list of foot and ankle disorders, which we have treated with PRP:

- Chronic Achilles, peroneal and posterior tibial tendinopathy that have failed conservative treatment modalities
- Plantar fasciitis that has failed conservative treatment
- Surgical reconstruction of the Achilles tendon
- Chronic lateral ankle or deltoid ligament sprains
- Fifth metatarsal fracture nonunions
- Surgical treatment of osteochondral lesions of the talus

Contraindications

PRP is derived from a patient's own blood thus, there appears to be little risk of significant side effects associated with its use. In our experience, we have neither noted any cases of true immunoreaction nor is there evidence in the literature of this. We have, however, noted cases of pain at the site of injection that may persist for several days. This may be a relative contraindication to the repeat treatment with PRP if the initial reaction was severe enough. Patients who have failed PRP therapy (ie, received 2 or more injections without significant clinical improvement) should not undergo further PRP treatment.

PREPROCEDURE PLANNING

Imaging studies to assess the nature of injury before PRP injection are critical. For tendon, ligament, and cartilage injuries, MRI can provide qualitative assessment of the soft tissue injury and may even hold prognostic value. For instance, based on the experience of one of the authors (J.G.K.), a 50% or greater cross-sectional involvement of tendon pathology on MRI is unlikely to respond positively to PRP. Quantitative imaging assessments in the form of a standard relaxation time or region-of-interest analysis can also be useful, particularly when comparing the rate or degree of healing with a postprocedure imaging study. Ultrasound is useful for tendon and ligament injuries as a dynamic imaging modality; it also is typically less costly than MRI. In cases of fracture nonunions and/or osteochondral lesions, computerized tomography scans may be useful.

TECHNIQUE

Several commercial systems are available to produce PRP from a patient's whole blood. Typically, 60 mL of venous blood is collected into a syringe with 6 mL of anticoagulant (acid citrate dextrose-A). It is then spun according to manufacturer recommendations, separating the whole blood into 3 separate layers: platelet-poor plasma, buffy coat, and red blood cells. The buffy coat is isolated and resuspended in plasma, and the solution is then activated with bovine thrombin and calcium chloride.

For lesions of the Achilles tendon or plantar fascia, one of the author's (J.G.K.) will typically perform the injections in the clinic, where fusiform thickening and swelling of the tendon can provide a clinical landmark for the injection site. However, the authors typically perform injections of the posterior tibial and peroneal tendons under ultrasound guidance in the interventional radiology suite. We prefer ultrasound guidance as these tendons are smaller and, therefore, more difficult to accurately target. If a patient had previously received PRP treatment that was performed without the use of ultrasound guidance and results were equivocal, the repeat injection should be performed under direct imaging.

PRP can also be administered intraoperatively during tendon repair. In these instances, we prefer a platelet-rich compound with a fibrin matrix that is more dense than typical PRP products, so that it can be handled during surgery. A platelet-rich fibrin matrix (PRFM) can in fact be sutured at the site of interest, thereby localizing its effects. PRFM is an autologous fibrin matrix formed by activation of the fibrin clotting cascade with the addition of calcium chloride and a second centrifugation step. This process minimizes platelet activation and traps unactivated platelets in the fibrin matrix, allowing for sustained release of the cytokines and growth factors.

Treatment of specific lesions with PRP is described below.

PRP and Achilles Tendon Repairs

Once the repair has been achieved and after irrigation (but before wound closure) PRP is injected above and below the repair as well as along the suture line. In the case of a tendon-splitting approach for a Haglund's deformity resection, one of the author's (J.G.K.) will often consider "sandwiching" PRFM between the tendon halves during suturing of the tendon. The wound is also an area of potential breakdown in Achilles surgery and PRP may be administered at the time of wound closure to take advantage of its potential healing properties.

PRP and Chronic Achilles Tendinopathy

Cases of Achilles tendinopathy that have failed standard conservative treatment measures (including limited physical activity, rehabilitation/modalities, anti-inflammatories, heel lift, night splint, and possibly immobilization) are often indicated for surgery (and therefore a prolonged recovery time). In these scenarios, PRP may be beneficial as a final option before undergoing extensive surgery.

For Achilles tendinopathy, we recommend injecting small depots in multiple locations along the degenerated portion of the tendon, according to the Maffulli technique.[24] Afterwards, the patient is instructed to lay in the prone position for approximately 10 minutes to allow for dissipation within the tendon substance before they are allowed to stand and ambulate.

Typically, a controlled ankle motion (CAM) boot is worn for 2 weeks with a heel raise to decrease the mechanical loading on the tendon during that time. Proper physiotherapy in the form of functional isometric training is then commenced after 2 weeks. The authors have not had success in combining eccentric tendon loading with PRP injection and stress that this theoretically has the potential to induce microtearing within a healing tendon. We recommend avoidance of nonsteroidal anti-inflammatory medications for 10 to 14 days after PRP injection.

PRP and Plantar Fasciitis

Plantar faciitis is usually a self-limiting disorder that will do well when treated with a steroid injection combined with an appropriate physical therapy program.[25] However, in recalcitrant cases, patients are often recommended endoscopic plantar facial release. Although the authors have found this to be a satisfactory treatment with minimal recovery time, PRP can be used as a nonsurgical alternative. In these cases, PRP is injected directly into the plantar fascia. The posteromedial insertion to the calcaneous is peppered with the needle in an attempt to fenestrate the tendon and create neovascular channels, potentially promoting a healing response as well as distributing the growth factors. By doing this we are in essence attempting to simulate an acute-on-chronic injury with an acute inflammatory response in a chronic injury environment. After the injection, the patient is typically placed in a CAM boot for 2 weeks, followed by a functional isometric training program of the Achilles and the plantar fascia.

PRP and Peroneal and Posterior Tibial Tendinopathy

For recalcitrant peroneal tendinopathy and small tears, PRP may be injected, under ultrasound guidance, directly into the degenerated tendon in a manner similar to that described for Achilles tendinopathy.

Posterior tibial tendinopathy is a progressive deformity that can lead to tearing and ultimately loss of arch height and a pronated foot position. In the experience of the foot and ankle surgeon of our group (J.G.K.), patients with grades I or IIa tendinopathy, without loss of arch height, may benefit from a PRP injection and medial heel posting with University of California Berkeley Laboratory type orthotic. Once again, placement in a CAM boot for 2 weeks postinjection is recommended, followed by functional isometric training.

PRP and Ligament Sprains (Deltoid Ligament, Anterior Talofibular Ligament, Calacaneofibular Ligament)

We do not typically treat acute ligament sprains with PRP. These injuries will often heal with simple RICE (rest, ice, compression, elevation) and early functional and proprioceptive rehabilitation.[26] However, in cases of chronic ankle instability, particularly of the lateral side, PRP may be considered. In these cases, PRP can be injected at the repair site to augment a healing response by bringing potent growth factors and cytokines to the area of interest.

PRP and Proximal Fifth Metatarsal Fracture (Jones Fracture) Delayed Unions/Nonunions

Proximal fifth metatarsal fractures have a relatively poor prognosis for healing owing to the occurrence of injury in a vascular watershed area.[27,28] We recommend prompt percutaneous reduction and internal fixation of these fractures in the athletic population owing to the known risk of delayed union, nonunion, and refracture when treated conservatively in this patient subgroup.[29] However, in cases where surgery is not initially indicated, or in those patients who demonstrate delayed healing or nonunion after fixation, PRP may be used to prevent surgery or further revision procedures. In these cases, one of the author's (J.G.K.) has used a single injection of PRP into the fracture site. After PRP treatment, the patient is made non-weightbearing in a CAM walker boot with crutches for assistance. Weightbearing is advanced according to healing demonstrated on radiographs and patient symptoms. However, further information about the role of PRP in bone healing is required, as mixed results have been reported in basic studies.

PRP and Osteochondral Lesions of the Talus

Recently, one of the author's (J.G.K.) has begun to use both PRP and bone marrow aspirate concentrate (BMAC) in combination for the surgical treatment of osteochondral lesions of the talus. The rationale behind using these 2 modalities is that the large number of undifferentiated pluripotent cells in BMAC may benefit from the growth factors in PRP by the process of stem cell homing and differentiation.[17] Furthermore, the transforming growth factor-β superfamily is both osteogenic and chondrogenic and may be particularly useful in these cartilage repair procedures.[30]

The PRP and BMAC are prepared on the back table and can also be "double spun" to produce a more viscous implant, if desired. For arthroscopic procedures, one can inject the BMAC and PRP under a dry scope after excision of the lesion, curettage of the defect site, and bone marrow stimulation. This will typically form a fibrin clot at the defect site, which may increase the amount of type-II collagen and proteoglycan differentiation in the fibrocartilage, possibly increasing its longevity.[31,32] For an open autologous osteochondral transplantation procedure, the graft itself is bathed in the solution and introduced via a syringe into the base of the graft recipient site. The purpose is to provide rapid infill of the bone and cartilage at the graft/host interface, to limit the theoretical potential of synovial fluid inflow that may undermine the graft over time.

RESULTS

The provisional results of our cases treated with PRP are outlined in Table 1. In our experience, the use of PRP with chronic, midsubstance Achilles tendinosis is compelling and must be further evaluated as an alternative to surgery (Fig. 1). By comparison, insertional Achilles, peroneal, and posterior tibial tendinopathy show mixed treatment results and require further refinement of treatment strategies (Figs. 2, 3). Finally, PRP in combination with BMAC may potentially have a beneficial effect in treating cartilage injuries, though this is yet unproven. The authors' stress that high quality, level I studies are needed before any definitive treatment strategies can be discerned.

Complications

Complications as a consequence of PRP injection are rare. As PRP is produced from autologous whole blood, there is little risk of cross-reaction, though bovine thrombin is known to be immunogenic.[33–36] Currently, to the best of our knowledge, there are no case reports of significant reaction to the compound in the literature. Neither have we noted any infections after PRP administration in our practice nor in the literature.

TABLE 1. Preliminary Results of PRP Treatment for Various Foot and Ankle Conditions

Pathology	Indication	Total No. Patients	Duration of Follow Up	Results	Comments
Achilles tendon: mid-substance tendinopathy or partial tear	Failed 6 wk conservative treatment plan; alternative to surgery	32	Minimum 1 y (mean 23 mo)	25 (78%) with complete resolution of symptoms 7 (22%) with no improvement or worsening	Poor correlation between post-PRP MRI findings and symptoms. No correlation between sex and age and outcome in either group
Insertional Achilles tendinopathy	Failed 6 wk conservative treatment plan; alternative to surgery	19	Minimum 1 y (mean 18 mo)	10 (53%) with resolution of symptoms 9 (47%) with no improvement or worsening	Poor correlation between post-PRP MRI findings and symptoms. No correlation between sex and age and outcome in either group
Tibialis posterior tendinopathy or tear	Grade I or IIA, without architectural collapse	30 (26 grade IIa, 4 grade I)	Minimum 1 y (mean 20 mo)	19 (63%) with complete resolution of symptoms; 11 (37%) with no improvement or worsening. 2 cases of recurrence after 8 and 11 mo postinjection – 10 out of 19 patients who did well could perform a unilateral toe raise at 6 mo – 10 out of 11 patients who did poorly required surgery	Poor correlation between post-PRP MRI findings and symptoms. No correlation between sex and age and outcome in either group
Peroneal tendinopathy or tear	Failed 6 wk of conservative treatment plan; alternative to surgery	17	Minimum 1 y (mean 19 mo)	6 (35%) with complete resolution of symptoms (all US guided); 11 (65%) with no improvement (3 of 11 were US guided) 4 patients did well initially but returned to previous symptoms at mean 9 mo; 11 of 11 patients who did not improve with PRP treatment required surgery	Poor correlation between post-PRP MRI findings and symptoms. No correlation between sex and age and outcome in either group
Sesamoid fractures		12	Minimum 1 y (mean 15 mo)	6 (50%) with symptomatic improvement; 6 (50%) with no improvement or worsening	

MRI, magnetic resonance imaging; PRP, platelet-rich plasma; US, ultrasound.

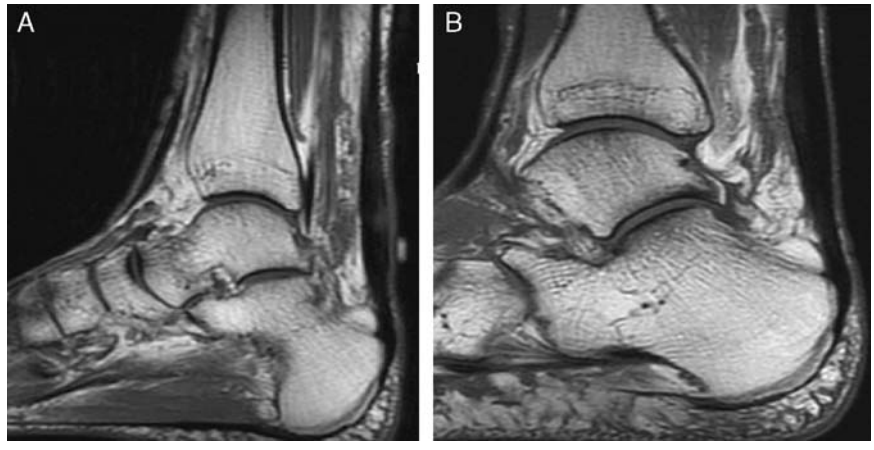

FIGURE 1. A, Case of a midsubstance partial tear of the Achilles tendon before PRP treatment. B, Same patient after PRP treatment. Achilles lesion resolved on MRI to a mild-moderate tendinosis. The patient has returned to sports and is pain free. PRP indicates platelet-rich plasma.

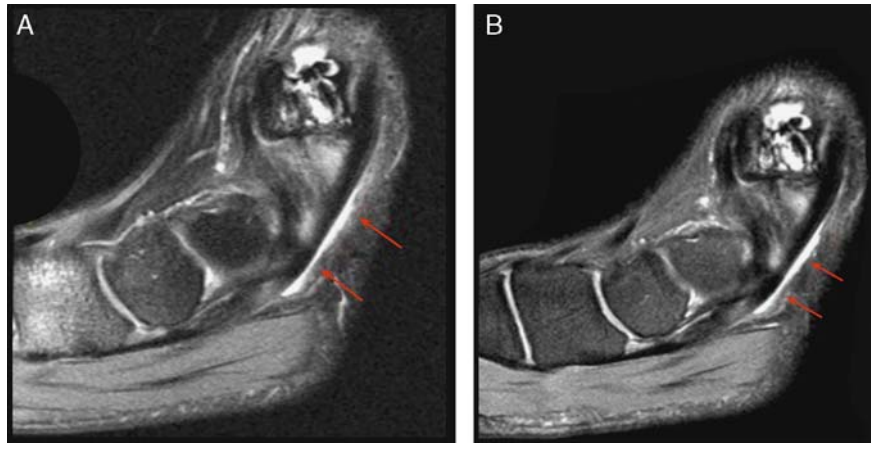

FIGURE 2. A, Case of posterior tibial tendinosis before PRP therapy. B, Same patient after PRP treatment. This patient had no resolution either clinically or on MRI at the 6-month time point. This patient has since gone on to posterior tibialis tendon reconstruction. Arrows indicate pathology. PRP indicates platelet-rich plasma.

Other potential complications, such as vascular thrombosis/embolism and nerve injury secondary to inaccurately placed needle injection, though not reported in the literature, are a theoretical possibility and may be prevented by precise localization using image guidance.

The most common side effect we have noted after administration is local pain. We have found that a certain percentage of patients report pain at the site of injection, which may be greater in severity than the original pain. This pain may take several days to resolve. We treat it symptomatically with rest, ice, compression, elevation, and acetaminophen. We tend not to use nonsteroidal anti-inflammatory drugs owing to the potential to inhibit cytokine activity, possibly limiting the efficacy of the PRP.

Finally, a concern associated with PRP is that it may increase the risk of neoplasia owing to the enhanced levels of growth factors and its effects on progenitor cell proliferation and differentiation.[37–39] However, there is no data to support this and furthermore, growth factors are physiologic proteins that act on the cell membrane rather than the nucleus with no evidence of mutagenicity.[16]

POSTOPERATIVE MANAGEMENT/ POSTOPERATIVE FOLLOW-UP AND REHABILITATION

We recommend follow up at 10 to 14 days after PRP administration. Patients with unusual complaints or a concerning postprocedural course are brought in for evaluation sooner. The operative/injection site is carefully inspected for signs of erythema, cellulitis, ecchymosis, and hematoma. Discharge is noted and appropriately addressed.

Patients who receive PRP injections for tendinopathy undergo a modified rehabilitation program. In the initial period (1 to 2 wk) the patients undergoes stretching and massage with the therapist. Weightbearing of the affected limb is usually protected for several days. After the initial visit, they may begin functional isometric stretching with strengthening. Specific protocols should vary based on the nature of the injury.

POSSIBLE CONCERNS/FUTURE OF THE TECHNIQUE

More clinical data regarding the effects of PRP on foot and ankle disorders is needed; current studies are limited in both

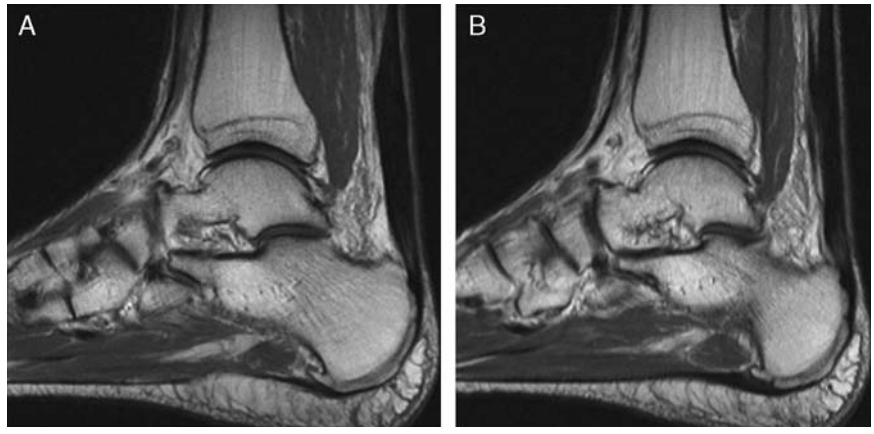

FIGURE 3. A, This patient presented with pain and insertional Achilles tendinosis with partial tear. B, Same patient after PRP treatment. This patient had mild resolution of symptoms for 6 months. At 7 months after PRP injection the patient retore at the same location and required surgery in the form of a Haglund's resection and tendon debridement. PRP indicates platelet-rich plasma.

quality and number. Gaweda et al[40] noted improved outcomes in a cohort of patients with chronic noninsertional Achilles tendinopathy that were treated with PRP. Sanchez et al[22] reported a faster recovery in range of motion and quicker return to activity in athletes with Achilles tendon ruptures treated with surgical repair and preparation rich in growth factors compared with historical controls. Despite the positive results, these studies are limited by small patient numbers and lack of strict study design. More rigorous studies are needed before educated opinions on the efficacy and utility of PRP can be formed. As of this writing, only one randomized-controlled trial in the foot and ankle literature is available. After randomizing 54 patients to receive local PRP or saline injections for their chronic Achilles tendinosis, de Vos et al[23] found no significant differences in mean Victorian Institute of Sports Assessment - Achilles scores between the groups. This study has been criticized primarily for using both an already effective adjunctive treatment (eccentric exercise)[41] and a previously described treatment strategy as a placebo.[24] Nevertheless, it describes the particular difficulties between treating chronic tendinopathy and acute injury, as well as possible differences in PRP efficacy when treating these different entities.

Some of the other difficulties in interpreting the current literature stem from the variety of systems, devices, and protocols in use today. This has made standardization difficult, and a comparison of studies sometimes impossible. Furthermore, the optimal number of platelets has yet to be defined and the specific contents of the various PRP compounds have yet to be identified. Another parameter yet to be well understood is the role of leukocytes in the PRP. Most of the systems that are currently commercially available have variable levels of leukocytes. A recent study noted that the concentration of white blood cells in the PRP was increased compared with baseline levels, with a greater proportion of monocytes to lymphocytes, than is typically found in whole blood.[42] This is due to increased monocyte retrieval compared with lymphocytes. The significance of this is not known. The mononuclear cell fraction may also contain progenitor cells, such as $CD34^+$ cells.

More research into the mechanism(s) of action of PRP is needed and the most optimal delivery vehicle has yet to be discovered. Future studies will undoubtedly provide greater insights and allow for the more educated and specific use of this exciting new therapy.

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