Platelet-Rich Plasma in Football

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Introduction

Platelet-rich plasma (PRP) was first used in maxillofacial surgery with more recent and increasing use in orthopedic surgery [1]. PRP is formulated by centrifuging autologous blood from the patient to obtain a preparation of platelets at least twice the concentration of whole blood. Cellular content includes red blood cells (RBC) and white blood cells (WBCs), the latter consisting of both leukocytes and neutrophils. The alpha granules of platelets have been shown to contain the critical growth factors [2].

Despite the rising interest of PRP research and application, there is no consensus for standardized concentration of constituents or method of preparation. There are differences in blood volume, centrifuge rate and time, PRP volume, WBC and RBC counts, platelet and growth factor concentration, delivery method, and activating agent use. Most systems utilize single-spin or double-spin sequences. Single-spin sequences are typically slower and shorter, yielding products that are two to three times baseline platelet concentration while excluding WBCs (leukocyte poor; LP-PRP). Double-spin sequences can yield greater platelet concentrations and commonly include WBCs in the yielded preparations (leukocyte rich; LR-PRP). There is also a flow cytometry option, which allows for more customizable ratios of platelets and white blood cells [3].

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K. W. Farmer (ed.), *Football Injuries*,
https://doi.org/10.1007/978-3-030-54875-9_12

Commercially available PRP preparation systems utilize either the single-spin or dual-spin methods; dual-spin methods are more time consuming to prepare [4, 5]. LR-PRP has up to three times the number of neutrophils, which contain catabolic enzymes that can degrade collagen and can cause direct injury to muscle via metalloproteinases and reactive oxygen species [6]. Platelets include important growth factors such as insulin-like growth factor 1 (IGF-1) that can affect tissue modulation. PRP enhances proliferation of myoblasts, chondrocytes, and osteoblasts in culture [7]. Platelets can also recruit stem cells in vitro [8]. There can be daily variation in platelet growth factors, serum WBCs, and serum platelets, compromising standardization in study populations. Heterogeneity of preparation and delivery methods can also make results reported in the literature difficult to access and compare clinically [9, 10].

Authors' Preference for Platelet-Rich Plasma Preparation

LR-PRP generally has higher overall concentrations of platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and soluble CD40 ligand [11]. This suggests that LR-PRP may be more beneficial in clinical scenarios that involve areas of hypovascularity, such as tendinopathy in more anatomically susceptible or watershed areas of relative hypovascularity, where stimulation of a vascular response and healing is a priority [12].

However, a 2019 Level I randomized controlled trial in athletes with ultrasound-confirmed patellar tendinopathy treated with an exercise-based rehabilitation program combined with LR-PRP, LP-PRP, or saline showed no significant difference between the groups in outcome measures, including pain scores at 6 weeks, 12 weeks, 6 months, and 12 months [13]. A meta-analysis of 18 randomized controlled clinical trials for treatment of tendinopathy published in 2016 found that patients treated with LR-PRP had a stronger positive effect with changes in pain intensity as a primary outcome measure, when compared with the LP-PRP patients [14]. However, both treatments had an overall positive benefit over placebo, regardless of the leukocyte concentration.

Our preference for PRP preparation is Autologous Conditioned Plasma (ACP, Arthrex, Naples, FL), a plasma-based leukocyte-poor preparation. It is a simple and fast preparation technique that is advantageous when dealing with an athletic population. A total of 15 cc of blood is drawn in a special double syringe (Arthrex, Inc) and centrifuged for a single 5-min spin at 1500 revolutions per minute with the upper yellow plasma layer containing platelets separated from the lower, higher-density red and white blood cell layer (Fig. 12.1). Utilizing the inner syringe, this plasma layer is easily extracted for injection. The platelet count for ACP is 2.40 times normal blood concentration on average. The typical white blood cell count is a mean of 1.3×10^9/L. Generally, 4–6 cc of LP-PRP is obtained from the process. No anticoagulant (like ACD-A in double-spin systems) has to be added to ACP after the single spin, as it is ready for injection after just 5 minutes. This has the potential

Fig. 12.1 An autologous conditioned plasma (ACP) vial, with the leukocyte-poor, platelet-rich plasma separated from the red blood cells.

for reduced pain after the injection, since the low pH of 5 for ACD-A could contribute to increased pain with a soft tissue injection [15]. No activating agents are added; the platelets are activated by the tissue thromboplastin method [16].

Use of Platelet-Rich Plasma in the Treatment of Specific Football Injuries

Platelet-rich plasma has numerous specific applications in football, including treatment for both acute and chronic muscle strain and tendon injuries, as well as inflammatory joint conditions. We have utilized LP-PRP exclusively when appropriate for the treatment of specific football injuries in our Division I program. This is in combination with a comprehensive post-injection protocol, incorporating other treatment modalities to control inflammation and promote mobility to enhance the healing process. Rehabilitation, with a focus on eccentric exercises, is instituted early on in the process. A return-to-play progression plan is customized to each individual athlete based on injury, position, and functional assessment by training staff and team physicians.

Hamstring Strains

Hamstring injuries are extremely common in high-level athletes and can result in significant disability and time loss. Furthermore, recurrence of hamstring strain is not uncommon [17, 18]. Hamstring strains most commonly occur in sports that involve fast or sudden changes in speed or direction. Given the fact the hamstring muscles cross two joints, they are more at risk for strain injury, especially with eccentric loading and deceleration [19–21].

A 2019 retrospective review of 61 NFL players with acute grade 2 hamstring injuries compared outcomes of treatment of a LP-PRP injection versus no injection. Those treated with PRP missed an average of 1.7 games versus 2.7 games in the non-PRP group. Notably, no re-tears were experienced by the PRP group, despite a faster return to play. The authors also highlighted the potential financial benefit of one additional game for a player at this level with PRP treatment [20, 22].

A case control study published in 2013 was based on only ten NFL players with grade 2 hamstring injury, treated with a single injection of LR-PRP under ultrasound guidance. Rettig et al. showed a mean return to play of 20 days in the PRP group and 17 days in the non-PRP group treated with rehabilitation and functional progression alone. A major difference from the Arner study was the use of LR-PRP [23].

In a randomized controlled trial, Hamid et al. demonstrated statistically significant earlier return to play after full recovery and lower pain severity scores in 28 patients treated with a single injection of LR-PRP combined with a rehabilitation program versus a rehabilitation program alone in acute grade 2 hamstring injuries. The PRP group patients also had lower pain interference scores (interference with daily activities, such as general activity, walking, work, mood, enjoyment of life, relations with others, and sleep), but no statistical difference was found [24].

In a more recent LR-PRP study on grade 2 hamstring strain in soccer players, return to play averaged 36.76 days with a reinjury rate of 12%. Although there was no control group, the authors found no difference in their outcomes from untreated hamstring strain patients based on the literature [25].

Our preferred approach for hamstring strains is to offer an ultrasound-guided LP-PRP ACP injection, which is generally administered approximately 24 hours after injury. In many cases, a magnetic resonance imaging (MRI) is done for injury grading purposes. We first discuss the potential advantages of PRP treatment with the athlete, based on the evidence and our experience, along with the risks and complications of this treatment. Therefore, the athlete is better equipped to make an informed decision. In many cases, athletes will request PRP based on discussion with teammates who have undergone the procedure for a hamstring strain with a good outcome. The injection is performed under sterile technique with betadine skin preparation followed by alcohol. The ultrasound is performed with use of sterile ultrasound gel and is used to localize the injection site. After the injection, the affected area is thoroughly massaged to enhance tissue activation. Again, since the ACP injection is easily prepared and administered in under 30 minutes without the use of an anticoagulant, potentially lessening local injection site pain. In severe

grade 2 strains with a large area of involvement or grade 3 injuries, the ACP injection is repeated in 5–7 days. Direct cryotherapy is followed with various training modalities and graduated advancement to full painless knee flexion and hip extension. This is followed initially with concentric and then eccentric light strengthening exercises, focusing on the knee and hip. Fortunately, we have not seen any adverse reactions or consequences to this ACP treatment approach.

From 2009 to 2019, we treated 41 Division I football players with 44 total hamstring injuries with LP-PRP injected in the zone of injury. The average age was 20.36 years with an average of 10.5 days (SD 4.37) to full return to play from date of treatment. There were 10 Grade 1 injuries with average of 9 days (SD 4.69) to full return to play from date of treatment, 29 Grade 2 injuries with average of 11.25 days (SD 4.4) to return to play from date of treatment, and 5 Grade 3 injuries with an average of 16.80 days (SD 6.14 days) to return to play from date of treatment. The increased time to full return to play with increased severity of the injury is expected. Our average return to play of 10.5 days is within the lower ranges what has been reported for hamstring strains [26, 27]. LR-PRP with a graduated rehabilitation and return-to-play protocol has been utilized at our institution for over a decade with excellent results.

Inflammatory Knee Conditions

Inflammation in the knee can have a multitude of etiologies. In football, it is not uncommon to have generalized knee inflammation while adjusting to workload changes, learning a new position, recovering from a previous injury, or rehabilitating from surgery. Intra-articular injections can be part of the treatment armamentarium for such knee inflammation issues, but it should be emphasized that any intra-articular joint injection for in-season management can lead to suboptimal results if the underlying causative disease process is not addressed by other means.

Corticosteroids are commonly used to treat pain and inflammation in the knee. They recently have been implicated in promoting cartilage volume loss in the treatment of knee osteoarthritis, although the clinical relevance of this finding for other joint conditions is unclear [28]. Certainly, in a young athletic population from a joint injection standpoint, an "arthroprotective" injection is desired. Hyaluronic acid (HA) viscosupplementation would be a potential option if knee osteoarthritis is the underlying problem in an athlete.

PRP, particularly LP-PRP, has been well documented in multiple level 1 studies to be efficacious and safe when treating knee osteoarthritis, which does affect young football players due to chondral injury [29, 30]. Furthermore, in head-to-head studies, LP-PRP has outperformed HA [31–36]. However, based on mechanism of action, PRP has the advantage of also reducing joint inflammation even when osteoarthritis is not the primary etiology. Specifically, PRP helps to stimulate chondrocyte proliferation and inhibit pro-inflammatory cytokines through growth factor mediation [37–41]. Additionally, LP-PRP ACP when compared to LR-PRP has been shown in a laboratory study to decrease metalloproteinases (MMP-9) and

interleukin-1β (IL-1β), which are powerful cytokines that promote inflammation and matrix degradation [42]. Also, an in vitro tissue model study showed ACP actually increased endogenous HA production from synoviocytes compared to HA itself (SYNVISC; Sanofi-Aventis, Paris, France), as well as decreased MMP-13 production, which is a known powerful cytokine for knee arthritis [43]. Finally, a laboratory study showed ACP significantly stimulated secretion of superficial zone protein or lubricin from articular cartilage and synovium, which is a very important substance for joint health and lubrication [44]. From the clinical standpoint, Smith showed both the safety and efficacy of knee joint ACP injections for osteoarthritis [29].

ACP has been very helpful in our experience in managing a number of inflammatory knee conditions in football players, and we feel it is both safer and more efficacious than corticosteroids, given the above documented scientific evidence. For instance, ACP has helped reduce reactive joint swelling in players returning to play after anterior cruciate ligament (ACL) reconstruction or meniscal surgery. Also, ACP has also been helpful in athletes who sustain isolated traumatic bone contusions with associated swelling. Our approach is to decompress the joint with an aspiration prior to the ACP injection. Compression and icing are utilized along with an early emphasis on isometric quadriceps exercises. In some cases, a second ACP treatment is administered 5–7 days later if needed.

Patellar and Achilles Tendinopathy

PRP and its growth factors can stimulate angiogenesis, cell migration, collagen synthesis, and matrix formation. These attributes seemingly make PRP ideal for use in the treatment of tendinopathy conditions, given these are areas generally with limited blood supply and slow cell turnover. Controversy exists over the WBC content of the preparation that is preferred, along with number and timing of injections. WBCs promote inflammation, and an argument could be made that an inflammatory response is what is needed to stimulate healing in a chronically avascular and degenerative tendon [45]. In a meta-analysis of randomized controlled trials of PRP in the treatment of tendinopathy, Fitzpatrick et al. found that the most significant reductions in pain were found in patients treated with leukocyte-rich PRP injections [14]. However, studies involving both leukocyte-rich and leukocyte-poor PRP injections have shown promise in the setting of tendinopathy [45–49].

Patellar tendinopathy is a common problem in American football players, possibly related to heavy squatting and eccentric overload. When symptoms persist despite standard conservative treatment measures, which include eccentric quadriceps strengthening exercises, PRP can be helpful.

Charousset et al. published results on a case series of professional and semiprofessional athletes treated with three consecutive ultrasound-guided LP-PRP injections for the treatment of chronic patellar tendinopathy (jumper's knee). At 2-year follow-up, 75% (21 out of 28) were able to return to pre-symptom sporting level at a mean of 3 months, and 57% had healing and return of normal structural integrity of the tendon demonstrated on follow-up MRI at 3 months. These athletes were in a

variety of sports that involved explosive movements, such as high jump, basketball, soccer, gymnastics, volleyball, judo, tennis, and badminton. They were permitted to return to sport as tolerated at 8 weeks from the last injection following a rehabilitation program that included eccentric exercises on a board. Three patients eventually underwent surgical intervention. This series shows the potential for clinical benefit from a series of LP-PRP injections for patellar tendinopathy in athletes [50].

Vetranoet et al. published a study utilizing two injections of LP-PRP versus extracorporeal shock wave therapy for patellar tendinopathy and found LP-PRP was significantly better at both 6 months and 12 months with PRP based on the Victorian Institute of Sports Assessment (VISA) validated outcome questionnaire [46].

In a double-blind randomized control trial with 23 patients who had failed previous nonoperative treatment, Dragoo et al. demonstrated improvement in VISA outcome scores in the treatment of patellar tendinopathy with a one-time LR-PRP injection (GPS III, Biomet Inc., Warsaw, IN, USA) compared with a dry needling group, who also received an injection of bupivacaine. All patients in the study were also given instructions on a standardized eccentric exercise program coordinated by physical therapists [47].

Our approach for refractory patellar tendinopathy includes an MRI to confirm that the diseased patellar tendon involves at least 50% of the posterior half of the tendon. Frequently, there is associated increased signal in the fat pad and sometimes bone edema with the inferior pole of the patella (Fig. 12.2). Ultrasound guidance for optimal needle placement is routinely done under sterile conditions with skin preparation with betadine and alcohol and then use of sterile ultrasound gel. After the ACP injection, the area is massaged thoroughly. Generally, two injections are given, typically 5–7 days apart. Rehabilitation progresses from isometric to eccentric quadriceps strengthening.

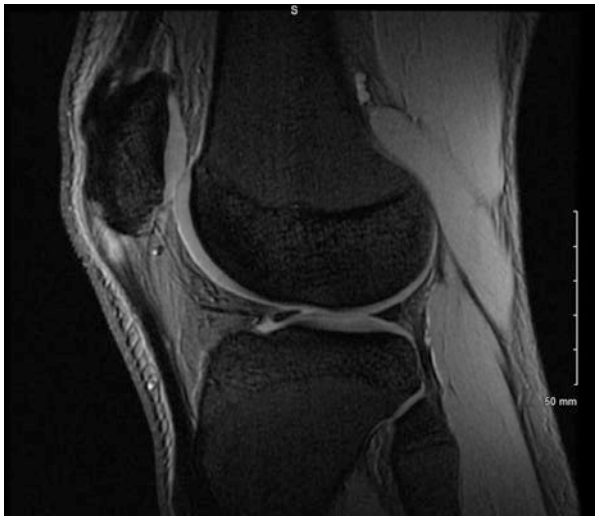

Fig. 12.2 A sagittal MRI demonstrating high-grade patellar tendinosis and partial-thickness tearing

Achilles tendinopathy is also seen in American football players. Gaweda, in 2010, reported significant improvement in both clinical scores and ultrasound with LP-PRP treatment [51]. In 2010, DeVos also reported no difference between the use of LR-PRP and saline injections in a group of 54 randomized patients with Achilles tendinopathy [52].

In a case series of 30 patients who had failed conservative management for at least 6 months with noninvasive measures for Achilles tendinosis, Monto found an increase in American Orthopedic Foot and Ankle (AOFAS) score at both 6 months and 24 months after injection of LR-PRP; patients also had resolution of pre-treatment imaging pathology noted on MRI and ultrasound in 93% of patients [53].

Acute Ankle Injuries

We have found PRP particularly useful in the treatment of acute low-grade syndesmotic injuries and lateral ankle sprains for reducing initial injury pain and swelling to enhance rehabilitation efforts. The results in the literature have shown some benefit, but results are not conclusive as studies include a low number of patients, thus increasing the chance of not detecting significant changes with small effect sizes [54].

In a cohort-controlled pilot study of ten rugby players, Samra et al. demonstrated that the time to return to play from acute syndesmotic injury was significantly less in the group that had a single ultrasound-guided LR-PRP injection into the anterior inferior tibifibular ligament (ATFL). The intervention group also demonstrated a higher vertical jump than the nonintervention group. However, in a double-blind, randomized controlled study of LR-PRP use in 37 patients for ankle sprains in the emergency department, Rowden et al. demonstrated no difference in pain scores or validated outcomes (Lower Extremity Functional Scale) over placebo [55].

Conclusion

Platelet-rich plasma can be an effective adjunctive treatment measure along with training room modalities and a comprehensive rehabilitation program for football injuries. The value of returning to play even a few days earlier after injury can have significant implications for each athlete that can be difficult to quantify. The science behind PRP continues to evolve as more research is performed, and clearly the current clinical use and application of PRP is ahead of high-level data for many injury patterns. There is still uncertainty related to whether LR versus LP-PRP preparations are preferred for certain conditions. Our preference for LP-PRP, and specifically ACP, is based on the available basic science, in combination with published clinical studies and our own anecdotal evidence. In this chapter, we have reviewed the current literature for use of PRP in some of the more common injuries seen in college football players. We have provided our clinical data on ACP treatment for hamstring strains, which is our most common use, and has represented a paradigm shift in our treatment of this very common football injury. Unfortunately, we do not have a control group for comparison, but that may not be a practical or realistic

approach with a Division I football team. Nonetheless, PRP has been a safe treatment intervention with no known complications in the ACP injections that we have performed to date. Above all, our primary goals with PRP treatment are minimizing overall injury time and facilitating return to play, while doing so safely.

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