CHAPTER 12

Infiltrations of PRGF to Treat Ligament and Tendon Injuries in the Hip and Pelvis

AUTHORS

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SUMMARY

In recent years, platelet-rich plasma (PRP) has gained popularity within the orthopaedic community as a treatment modality to enhance tissue healing. This chapter aims to concisely present the current indications for PRP injections in the treatment of hip and pelvic pathologies and to describe some novel applications for PRP which have not yet been reported in the literature. With regard to hip and pelvic pathologies, PRP injections are used most commonly as a non-operative intervention, and have been described in the literature to treat osteoarthritis of the hip joint as well as tendinopathy of the hamstrings, adductor longus, and gluteus medius. In contrast, most of the surgical applications of PRP for the hip are novel, with few reported studies in the literature. Because of the increasing awareness of PRP's beneficial effects on musculoskeletal healing and thus the growing number of indications for its use, this review also describes some novel applications for PRP, including osteitis pubis, post-microfracture of the hip, tears of the rectus femoris, and avulsion of the sartorius muscle.

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1. INTRODUCTION

Platelet-rich plasma (PRP) has gained popularity within the last decade among the orthopaedic community as a treatment modality to enhance tissue healing. The term platelet-rich plasma may be applied to any fraction of autologous blood that contains a higher concentration of platelets than baseline[1]. Thus, this term is non-specific and factors such as the concentration of platelets and leukocytes as well as centrifugation methods have differed between studies. DeLong et al[2] developed the PAW classification system to aid in comparing different protocols of PRP preparation. This classification system is based on the absolute number of platelets (P), the method of platelet activation (A), and the presence/absence of white cells (W).

Recently, PRP has been utilized for numerous musculoskeletal indications such as rotator cuff repair[3,4], patellar tendinopathy[5], knee osteoarthritis[6], lateral epicondylitis[7], osteochondral lesions of the talus[8,9], and many other orthopaedic conditions. PRP induces musculoskeletal healing through a number of effects. As a treatment modality for tendon healing, PRP enhances the mobilization of circulation-derived cells[10]. This may include inflammatory cells that secrete cytokines and growth factors as well as fibroblast-like cells that synthesize matrix. Compared to serum, PRP has been shown to significantly increase the deposition of a collagen-rich extracellular matrix[11], with higher collagen I content compared to placebo[12]. Interestingly, PRP-treated tendon tears have actually been shown to contain fewer blood vessels compared to placebo[12], possibly indicating a more physiological healing process. Once PRP enhances the early phase of regeneration, mechanical stimulation is required to promote organized collagen synthesis and remodeling during new tendon development[13].

With muscle strains or contusions, the hematoma that originates contains approximately 94% red blood cells, 4% platelets, and < 1% leukocytes[14]. Compared to whole blood, PRP contains higher concentrations of certain growth factors, in particular platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β)[15]. Thus, PRP is theorized to replace the hematoma with a high concentration of platelets and growth factors to promote healing. Furthermore, PRP has been shown to promote angiogenesis through activation of PRP-releasate (PRP-r)[16]. In comparison to tendon and muscle healing, little is known on the mechanisms of PRP in promoting healing of articular cartilage, though this likely involves multiple biological processes including apoptosis, extracellular matrix synthesis, angiogenesis, and inflammation[17]. Because of the increasing awareness of PRP's beneficial effects on musculoskeletal healing and thus the growing number of indications for its use, we present a chapter of the current indications for platelet-rich plasma injections to augment the conservative and surgical treatment of hip and pelvic ligament and tendon pathologies and describe some novel applications for PRP[18]. Although several studies have described the use of PRP for some of these pathologies, other indications for PRP discussed in this chapter have not been published previously. As such, these indications are not yet evidence-based.

2. DECISION-MAKING

After performing an appropriate patient history and physical examination, advanced imaging is typically obtained to better characterize the suspected pathology. With muscle or tendon tears, magnetic resonance imaging (MRI) or ultrasound (US) should be used to determine the exact location and extent of the injury. Depending on the pathology, PRP may be used as a conservative treatment measure or as adjunctive treatment during surgery. When used as a conservative treatment option, PRP may be applicable for tendinopathic changes or partial tendon tears in which the tendon ends are not retracted[1].

The cost of platelet-rich plasma treatment is certainly a factor in the decision-making process. In-

surance companies still do not recognize PRP as standard of care, and thus PRP must be paid by patients out of pocket. It has been estimated recently that the cost of PRP is $500 to $1,500 per application[19]. It is important to have an open discussion regarding the cost of PRP injections, given that it may be prohibitively expensive for some patients.

3. PREPARATION AND APPLICATION TECHNIQUES

A sample of whole blood is collected in a sodium citrate tube in order to delay clotting of the blood sample. Once the whole blood sample is collected, centrifugation allows separation of the sample into its component cells and serum. Either one or two centrifugation steps may be used depending on the final product desired. A "soft" spin separates the whole blood sample into three layers: an upper layer consisting mainly of plasma and platelets, a very thin middle layer known as the "buffy coat" that is highly concentrated in WBCs, and a bottom layer consisting mainly of red blood cells (RBCs)[20]. A second, "hard" spin may be used to further concentrate the platelets[20,21]. Following centrifugation, approximately 10% of the initial whole blood volume remains as PRP concentrate[1]. The platelets in the PRP concentrate are activated with calcium chloride and/or autologous or bovine thrombin. These additions are used to initiate the clotting cascade, the release of growth factors from the platelets, and the formation of a fibrin scaffold[21]. Autologous thrombin has been shown to have a lower clot strength compared to bovine thrombin or calcium chloride, with bovine thrombin having the quickest clot initiation time[22]. In an equine model, calcium chloride activation of PRP has been shown to result in greater release of platelet-derived growth factor compared to autologous or bovine thrombin[23]. Calcium chloride also provides the advantage of not using bovine or other non-autologous materials.

Therapeutic doses of PRP require 2.5-5 times the baseline concentration of platelets[24,25], though higher concentrations than this have an inhibitory effect on healing[26]. The white blood cell concentration may also be controlled, with leukocyte-rich PRP (L-PRP) and leukocyte-poor PRP (P-PRP) both being used in the literature. For production of L-PRP, the entire layer of the buffy coat and few RBCs are transferred to an empty sterile tube, while the upper layer and only the superficial buffy coat are transferred for production of P-PRP[20]. Plasma rich in growth factors (PRGF) is a term used to describe a leukocyte-poor PRP which is separated manually (direct visualization using a fine pipette) from the lower fraction of the plasma containing the highest concentration of platelets and growth factors, avoiding the thin WBC layer. PRGF techniques have been shown to produce lower concentrations of growth factors compared to standard PRP kits by 3-4 fold[27] which, according to many studies, may serve as the optimal ratio for tissue healing.

When a tendon or muscle is injured, healing proceeds through three processes: inflammation/degeneration, regeneration, and fibrosis[1]. Although L-PRP has been shown to contain the highest levels of growth factors and cytokines[28], it induces catabolic effects and a significantly greater acute inflammatory response and thus may actually prolong the healing process[28-31]. Thus, the inclusion of white cells defeats the purpose of PRP. On the other hand, P-PRP induces mainly anabolic changes, and while this is generally a beneficial outcome, it could also result in scar tissue formation due to these anabolic effects[28,31]. Still, no randomized or prospective clinical studies have been performed to compare outcomes between leukocyte-rich versus leukocyte-poor PRP.

4. NON-OPERATIVE APPLICATIONS

Platelet-rich plasma injections are used most commonly as an adjunct to conservative treatment. In cases of chronic tendinopathy or osteoarthritis, PRP is typically indicated when first-line treatment (physical therapy, rest) fails. For professional athletes, in-season PRP may be used to reduce pain and improve function as an interim solution until the offseason when the athlete can undergo surgical intervention. This is particularly true for hip labral tears and chronic tendinopathies.

As detailed below, PRP injections have been used to treat tendinopathy of the hamstrings, adductor longus, and gluteus medius. These injections are typically performed under US guidance in the clinic. The number of injections used differs by study, though most reports describe the use of a single PRP injection for a variety of hip pathologies. Prior to injection, patients should fast for a minimum of three hours and should limit water intake to 8 ounces. In addition, patients should avoid the use of non-steroidal anti-inflammatory drugs (NSAIDs) for at least two days prior to and five days following injection, as these medications have been shown to impair platelet function[32].

Hamstring tendinopathy

Chronic tendinopathy or partial tears of the proximal hamstring tendons are common injuries among athletes. These injuries often occur while running, particularly when accelerating. Following severe hamstring injuries, many high level athletes may struggle with sitting on a bike or returning to running. Corticosteroid injections should be avoided as they may result in further tendon weakening and progression to high-grade tearing. PRP injections can be used to facilitate healing when there is partial thickness involvement or tendinosis without retraction. Complete tears, especially if chronic and retracted, are best treated with surgical repair.

A Hamid et al[33] conducted a randomized controlled trial to compare PRP therapy plus a rehabilitation program versus rehabilitation alone in patients with acute hamstring injuries (table 1). Patients in the PRP group were given a single intra-lesional injection of PRP, without addition of an activating agent, under US guidance at an average of 4.6 days following injury. Time to return to play was significantly lower in the PRP group (mean 26.7 days) versus the control group (mean 42.5 days). In addition, the PRP group had significantly lower pain severity scores at all time points up to 7 weeks following intervention.

STUDY	LEVEL OF EVIDENCE	PATHOLOGY	CONTROL GROUP(S)	OUTCOMES MEASURED
A Hamid et al, 2014[33]	II	Acute hamstring injuries	Rehabilitation without PRP	Return to play time, pain severity score, pain interference score
Hamilton et al, 2015[34]	I	Hamstring injuries	Platelet-poor plasma, no injection	Return to play time, reinjury rate
Fader et al, 2015[35]	IV	Chronic proximal hamstring tendinopathy	N/A	VAS pain
Wetzel et al, 2013[36]	III	Proximal hamstring injuries	NSAIDs, physical therapy	VAS, NPRS
Davenport et al, 2015[37]	I	Proximal hamstring tendinopathy	Autologous whole blood	MHHS, Hip Outcome Score-ADL, IHOT-33
Dallaudière et al, 2014[39]	IV	Upper and lower limb tendinopathy	N/A	WOMAC, ultrasound lesion size
Mautner et al, 2013[42]	IV	Chronic tendinopathy	N/A	VAS, assessment of functional pain, overall satisfaction

TABLE 1.CLINICAL STUDIES ON PRP TREATMENT FOR HIP AND PELVIC PATHOLOGIES.
VAS = visual analog scale, NSAIDs = non-steroidal anti-inflammatory drugs, NPRS = Nirschl Phase Rating Scale, MHHS = Modified Harris Hip Score, ADL = activities of daily living, IHOT-33 = International Hip Outcome Tool 33, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, OA = osteoarthritis, HA = hyaluronic acid, HHS = Harris Hip Score, AVN = avascular necrosis.

In another randomized controlled trial, Hamilton et al[34] compared PRP, platelet-poor plasma (PPP), and no injection in professional athletes with MRI-positive hamstring injuries. All patients underwent a standardized rehabilitation program. Time to return to sport was found to be significantly lower in the PRP group (mean 21 days) compared with the PPP group (mean 27 days). No significant difference in re-injury rate was noted between the three groups at 2 months or 6 months following intervention.

Fader et al[35] performed a retrospective case series of 18 patients with chronic proximal hamstring tendinopathy. Each patient received a single PRP injection by US guidance. Patients had chronic hamstring pain symptoms for an average of 32.6 months prior to their injection and all patients had attempted other non-surgical treatments such as cortisone injections and physical therapy prior to injection. Based on a visual analog scale (VAS) for pain, patients had an average improvement in pain of 63% at 6 months following PRP injection.

In another study, Wetzel et al[36] performed a retrospective cohort study comparing twelve cases of proximal hamstring injuries treated by a single PRP injection and five patients treated with traditional conservative treatment (TCT) consisting of NSAIDs and physical therapy. Patients in the PRP and TCT groups presented at an average of 9.6 and 7.8 months after injury, respectively. At an average follow-up of 4.5 months, the PRP group demonstrated significantly improved VAS ($p < 0.01$) and Nirschl Phase Rating Scale (NPRS) scores ($p < 0.01$) compared to pre-treatment. At an average follow-up of 2 months, the TCT group did not show the same degree of improvement in VAS ($p = 0.06$) or NPRS scores ($p = 0.06$). However, due to the small sample sizes and differences in follow-up times, it is difficult to discern these outcome differences.

Davenport et al[37] conducted a double-blind, randomized controlled trial comparing a single injection of PRP versus autologous whole blood (WB) for the treatment of proximal hamstring tendinopathy. At follow-up times of 2, 6, and 12 weeks and 6 months, no significant differences were observed between groups with regard to the Modified Harris Hip Score, Hip Outcome Scores for activities of daily living (ADL) and sport-specific function, and International Hip Outcome Tool 33 (IHOT-33). However, compared to baseline, the PRP group demonstrated significant improvements in ADL and IHOT-33 scores, whereas the WB group showed significantly decreased pain with 15-minute sitting at 6 months.

Although conflicting results exist, the majority of published studies have reported successful outcomes of PRP injections for hamstring injuries. The authors use PRP injections for acute hamstring injuries including, in rare cases, complete tears with a small amount of retraction in patients with low activity levels or when patients opt out of surgery.

Adductor tendinopathy/athletic pubalgia

Adductor tendinopathy typically presents with groin pain and is often seen in soccer players due to the frequency of running and cutting movements involved in this sport[38]. Athletic pubalgia is a more general term involving groin pain, often in athletes, with adductor tendinopathy being a frequent concomitant pathology in these patients. Good outcomes have been shown following adductor tenotomy with and without hernioplasty[38], though PRP provides a non-operative treatment option for this pathology.

Adductor longus tendinopathy is a common indication for PRP treatment. Dallaudière et al[39] performed a retrospective case series of 408 consecutive patients treated by a single ultrasound-guided PRP injection for tendinopathy of upper (medial and lateral epicondylar tendons, i.e. golfer's and tennis elbow, respectively) and lower (patellar, Achilles, hamstring, adductor longus, and peroneal tendons) limbs. Patients with hamstring and adductor longus tendinopathy demonstrated significantly improved Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores at 6 weeks and a mean 20.2 months following injection ($p < 0.001$). Ultrasound was also used to assess lesion size at baseline and 6 weeks post-

injection, with hamstring and adductor longus tendon lesion size decreasing from an average of 21.2 mm to 2.6 mm during this time ($p < 0.001$).

Interestingly, there is a high incidence of athletic pubalgia symptoms in patients with symptomatic femoroacetabular impingement (FAI)[40]. Hammoud et al[40] showed that 39% of professional athletes presenting with concomitant AP and FAI experienced symptom resolution with surgical treatment of FAI alone. Larson et al[41] demonstrated a return to unrestricted activity in 89% of patients with surgical management of both athletic pubalgia and intra-articular hip pathologies, compared to only 25% in patients undergoing surgical treatment of athletic pubalgia alone.

The authors inject the origin of the adductor longus (AL) tendon for chronic tendinopathy or acute tears (fig. 1). We first exclude the pubic symphysis as the source of the pain (using a lidocaine test) due to its anatomical proximity to the AL. It is also important to conduct full range of motion (ROM) evaluation of the hip joint to exclude concomitant FAI. FAI results in reduced ROM which in turn places increased stress on the AL origin and may result in chronic microtears and tendinopathy. In these cases, PRGF may not be a beneficial long-term solution as the offending mechanism is still present.

When electing to perform PRGF injections for adductor tendinopathy, it is important to have the patient shave the groin area a few days prior to injection for ease of US guidance. These injections can be very painful, though due to the superficial location of the pathology, lidocaine cannot be used. It is recommended that nitric oxide be used as an inhaled anesthetic if possible.

Gluteus medius tendinopathy

The literature is currently lacking in reported outcomes of PRP injection for gluteus medius tendinopathy. However, in a multicenter, retrospective review of 180 patients with chronic tendinopathy[42], 16 patients underwent US-guided PRP injections for gluteus medius tendinopathy with 13 patients demonstrating moderate improvement to complete resolution of symptoms at an average follow-up of 15 months post-injection. However, the PRP injection methodology of this study was non-uniform in that 60% of all patients received one injection, 30% received two, and 10% received three or more injections.

The authors use a series of three injections of PRGF for chronic indications[8] such as gluteus medius or minimus tendinopathy (fig. 2). It is important to

FIG. 1
Ultrasound-guided PRP injection of the adductor longus near its origin on the pubic body.

FIG. 2
Ultrasound-guided PRP injection of the gluteus medius near its insertion on the greater trochanter.

conduct a comprehensive physical examination to determine that the reported pain is not referred from the lower back or hip joint. In some cases, a lidocaine test can help to confirm or exclude the gluteus as the primary pathology. It is instrumental to review a high resolution MRI of the region and to determine pre-injection if gluteal bursitis is causing the patient's pain or if tendinopathic changes/tears are present. It is also important to note which tendons are involved, as the minimus tendon is deeper and thus requires proper US guidance during injection. From our experience, the majority of gluteal tendon tears are in the medial/deeper side of the tendon.

As mentioned with hamstring tendinopathy, many practitioners would use steroid injections for greater trochanteric bursitis. However, this is usually a misdiagnosis or a secondary pathology as gluteal tendon tears are often the primary pain source. Although steroid injections can improve pain for a few months, they can also result in atrophy and weakening of the gluteal tendons.

Sartorius avulsion

The sartorius originates on the anterior superior iliac spine (ASIS) apophysis, which begins to ossify between the ages of 13-15 years and fuses with the ilium between the ages of 21-25 years. An ASIS apophyseal avulsion injury occurs most commonly during running with the hip in extension and knee in flexion, or during a kicking motion[43]. Pain and a tearing sensation are the most common symptoms.

Recently, a 16 year old male presented to our clinic with anterolateral left hip pain following a lacrosse injury in which the patient made a cut while sprinting and felt and heard a pop around his hip. MRI showed a proximal sartorius avulsion with a few millimeters of distraction and significant soft tissue and bone edema in the surrounding area (fig. 3). The patient underwent US-guided PRGF injection (fig. 4) and reported complete resolution of symptoms within a week. He returned to full activity with our clearance at five weeks post-injection. A similar technique can be used for other apophyseal avulsion injuries such as that of the hamstrings or rectus femoris.

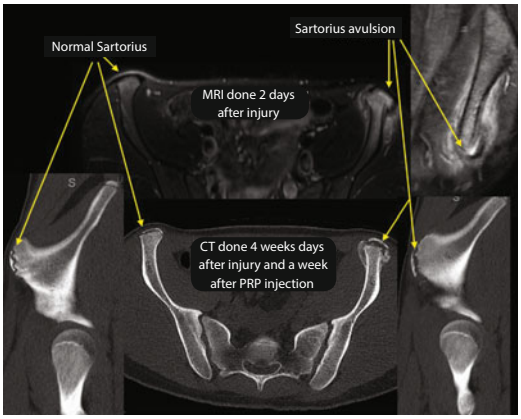

FIG. 3
MRI demonstrating avulsion of the sartorius muscle from its origin on the anterior superior iliac spine (ASIS, top images). CT images comparing a normal sartorius origin on the ASIS (bottom left) and a sartorius avulsion (bottom right).

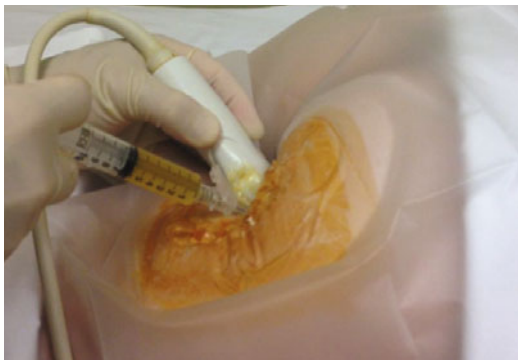

FIG. 4
Ultrasound-guided PRP injection of Hamstrings near its origin on the anterior superior iliac spine.

5.SURGICAL APPLICATIONS

As described above, when used in a non-operative setting, platelet-rich plasma is applied as a liquid injectable. However, in an intraoperative setting, PRP may be injected as a liquid or gel[44], or delivered as a fibrin matrix (platelet-rich fibrin matrix, PRFM)[45]. Most of the surgical applications of PRP for hip and pelvic pathology are novel, with few studies currently in the literature.

Adjuvant therapy for tendon repair

Platelet-rich plasma has been shown to improve healing in patients with acute ruptured Achilles tendons[12,46]. Sánchez et al[46] showed an earlier recovery of range of motion, return to gentle running, and return to training activities in 12 athletes who underwent open suture repair of a complete Achilles tendon rupture with PRP versus standard open suture repair. Alsousou[12] compared biopsy samples of acute ruptured Achilles tendons treated with PRP versus a control group receiving no treatment. The PRP group demonstrated significantly higher collagen I content and a significantly lower modified Bonar score, which indicates improved early tendon healing.

The authors use PRGF injections in patients undergoing surgical repair of the hamstring tendons when the tendon tissue is found to be of low quality and enhancement of the surgical repair is required. Another common indication for PRGF within our practice is in professional athletes for whom there is a need for an expedited recovery and return to play. This is most commonly indicated for the hamstrings, rectus femoris, or a sartorius avulsion.

6. CONCLUSIONS

This chapter describes some of the established as well as novel applications of platelet-rich plasma or plasma rich in growth factors (PRGF) for the treatment of hip and pelvic pathologies. Although the outcomes of many of these applications have not been described in the literature, particularly in high-level studies, from our experience we have found that symptomatic and functional outcomes are successful in the majority of patients. As indications for PRP continue to expand, it will become increasingly important for future studies to state specific methodologies used in the preparation of PRP in order to recognize ideal preparation techniques and the ideal number of PRP injections for each pathology. Leukocyte-poor PRP has the advantages of a reduced inflammatory response and mainly anabolic changes compared to leukocyte-rich PRP, though further, high quality studies are necessary to determine outcome differences between these two PRP preparations.

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