Treatment of Muscle Injuries with Platelet-Rich Plasma: a Review of the Literature

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Abstract

Purpose of Review This review discusses the current literature regarding the use of platelet-rich plasma (PRP) in the treatment of muscle strain injuries. Case series as well as experimental trials for both human and animal models are covered.

Recent Findings Multiple studies have examined outcomes for the use of PRP in the treatment of muscle strain injuries. PRP has been shown to promote muscle recovery via anabolic growth factors released from activated platelets, and in doing so, potentially reduces pain, swelling, and time for return to play.

Summary In vitro studies support the regenerative potential of PRP for acute soft tissue injuries. Multiple clinical case series for PRP injections in the setting of muscle strains demonstrate imaging evidence for faster healing, less swelling, which can decrease time for return to play. These studies, however, are retrospective in nature, and few randomized controlled studies exist to demonstrate a clear clinical benefit. Additionally, there is tremendous heterogeneity regarding the injectant preparation, optimum platelet concentration, presence of leukocytes, and volume of PRP which should be administered as well as number of and timing of treatments.

Keywords Platelet-rich plasma · PRP · Sports medicine · Muscle injury · Return to play

Introduction

Muscle injury is relatively common in the context of athletic participation and can occur by a variety of mechanisms. Overall muscle strain prevalence in athletes is approximately 12–16% [1•]. Certain muscle groups are prone to strain and are more commonly seen on examination. These include muscle groups that cross two joints, such as the hamstrings, quadriceps, gastrocnemius, and

hip flexor units, which often sustain eccentric contractile loads [2]. Hamstring strain injuries represent 29% of all injuries in sports and are seen in up to 50% of sprinters. Reinjury can often occur with a frequency between 12 and 21% [3]. Opar and colleagues performed a literature review looking at hamstring strain injuries and factors that lead to injury and reinjury. They collected studies from 1966 to 2011. Track and field hamstring injuries accounted for 26% of all injuries, while football was 12% and rugby was 15%. Moreover, they noted that 27% of all hamstring injuries were recurrences of previous injuries in the Australian Football League and 32% in American Football [4]. As athletes are the main recipients of muscle strains, there are many studies evaluating return to play as well as the treatment involved in expediting return to sport. Studies demonstrate the tremendous cost of lost days due to hamstring and muscle strains [5, 6].

With the prevalence and associated competitive and financial loss of acute muscle injuries, there is increased interest in optimizing treatment modalities. Platelet-rich plasma (PRP) has been utilized as an adjunctive measure to possibly improve the healing process, modulate inflammation, and

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expedite return to sports and activities of daily living. We will review the pertinent basic science concepts and clinical outcome studies on this topic.

PRP Production and Usage

PRP is produced by obtaining autologous blood and centrifuging it to separate the layers based on density of the contents. Platelets and leukocytes are separated from erythrocytes and further centrifuged to increase the concentration of each component to a presumed therapeutic level, although there is significant variability between preparation methods and patients. There is also inconsistency in the desired concentrations. Additionally, activating agents such as thrombin and calcium can be added to serum to begin the release of growth factors as opposed to inactivated PRP, which is activated upon administration and exposure to collagen and thromboplastin [7]. Platelets, one of the main components in PRP, mediate the release of several growth factors that are essential in the healing process. Various preparations of PRP and vendors providing the algorithm for PRP fabrication are on the market, each with the ability to produce serum with different concentrations of platelets and leukocytes. Some data exists to suggest optimal concentrations of platelets are at four to five times the normal level of serum [7]. Conversely, it has been described that concentrations greater than two times normal may actually be catabolic and detrimental for healing. There is speculation regarding the benefit of leukocyte-rich (LR) versus leukocyte-poor (LP) PRP. It is thought that tendon to bone healing would benefit from LR PRP, as inflammation is a required stage for tendon healing. However, recent work comparing LR and LP formulations for tendinopathy has shown a better histologic healing response with LP, perhaps due to the higher concentration of catabolic cytokine IL-6 in LR preparations [8]. Moreover, although the inflammatory phase of healing is important, excessive inflammation can cause increased pain, intramuscular fibrosis, and scar [1•]. The optimal platelet and leukocyte concentrations for the treatment of acute muscle injuries remain unclear.

PRP has been used in various disciplines of medicine, from maxillofacial surgery to stimulating hair follicles. In orthopedics, PRP has been shown to have benefit in treating conditions such as lateral epicondylitis, knee osteoarthritis, rotator cuff tendinopathy, patellar tendinopathy, Achilles tendinopathy, and plantar fasciitis [9–15]. Conversely, surgical techniques such as anterior cruciate ligament reconstruction, rotator cuff repair, Achilles tendon repair, and fracture healing have not shown a clear benefit when augmented with PRP application [16–20]. Muscle injury is an attractive avenue for treatment with PRP because of the relatively non-invasive means in which it is administered and the potential for restoration of muscle architecture after injury.

Basic Science

Basic science research has demonstrated that muscle regeneration and myogenesis are dependent upon paracrine healing and growth factors, namely insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), fibroblast growth factor 2 (FGF-2), transforming growth factor β 1 (TGF β -1), tumor necrosis factor- α (TNF- α), platelet-derived growth factor (PDGF), and prostaglandins (PG). In vitro, IGF-1 has been shown to stimulate proliferation and differentiation of myoblasts and improve muscle regeneration in mouse skeletal muscle [21, 22]. In vivo, FGF-2 has been shown to enhance both the diameter and number of regenerating muscle fibers. In animal models, HGF activates quiescent satellite cells, while TGF β -1 supports additional growth factors such as PDGF which can also stimulate satellite cell activation. A balance between TGF β -1 and PG E-2 is required to prevent fibrosis of skeletal muscle, as TGF β -1 has been shown to stimulate fibrotic scar tissue formation. PRP offers a concentrated release of these growth factors which theoretically can expedite the healing process [1•]. One study demonstrated that the addition of an antifibrotic agent, such as Losartan, can be added in with PRP to enhance muscle healing by stimulating muscle regeneration and angiogenesis and preventing fibrosis [23]. Additionally, PRP releasate has been shown to promote skeletal muscle cell proliferation in association with the up-regulated protein expressions of PCNA, cyclin A2, cyclin B1, cdk1, and cdk2 [24].

Hammond et al. investigated the healing response of 72 rats with PRP comparing maximal isometric contraction injury and multiple lengthening contraction injury models [25]. The multiple lengthening injury model paradoxically resulted in a longer healing time, and PRP injection resulted in significant functional improvement in the single lengthening injury model at day 3 and the multiple lengthening protocol at days 7 and 14. MyoD and myogenin messenger RNA transcripts, markers for satellite cell activation, were elevated after injury but more so in the PRP group. Wright-Carpenter et al. looked at 108 mice with a contusion injury to the gastrocnemius muscle treated with autologous conditioned serum injections at 2, 24, and 48 h post injury compared to those in a control group treated with saline injection at those intervals. Histologic analysis demonstrated that satellite cell activation between 30 and 48 h after injury was accelerated by approximately 84% and the diameter of the regenerating myofibers was increased in the PRP group versus the controls within the first week. By day 14, however, the difference between control and treatment groups was eliminated completely [26].

In addition to tissue healing, PRP has been suggested to play a role in the modulation of inflammatory cells and pain control. The mechanism is likely through regulation of inflammatory pathways. PRP does show quantifiable amounts of interleukins (IL) 1, 6, 7, and 10, which can be specifically

pro or anti-inflammatory in nature. A recent laboratory study examined the effect of PRP releasate on the treatment of gastrocnemius muscle tears in Sprague-Dawley rats. Muscle healing was assessed at 2, 5, and 10 days. Cellular apoptosis was also examined following PRP treatment. The results revealed that PRP can not only enhance the muscle healing process but also decrease pro-inflammatory CD68-positive and apoptotic cells [27].

Diagnosis and Imaging

Diagnosis of muscle injury is based on clinical exam as well as imaging. Magnetic resonance imaging (MRI) and ultrasound (US) have become the mainstay for imaging confirmation of muscle injury and do an excellent job at localizing edema and structural abnormality. US is operator dependent and may be subject to user error; however, both modalities have demonstrated good specificity and sensitivity for diagnosing injuries such as tendinopathy or tendon tear [2, 28–31]. Although US has the added benefit of a Doppler study which can demonstrate neovascularization in soft tissues, MRI remains the mainstay modality for the diagnosis, localization, and grading of these injuries as well as qualifying the recovery [2]. The information gleaned from this advanced imaging has been shown to correlate with return to play and clinical outcomes. A study looking at Australian Rules Football players with hamstring strains seen on MRI demonstrated a mean of 27 days missed from competition when edema was found versus 16 days missed when no edematous changes were seen [32]. In addition to the presence of edema, injury location and extent of muscle volume involved are also important factors. Proximal avulsion injuries and strains involving a higher cross-sectional area of muscle are predictive of a longer recovery time and higher risk for recurrence [30, 32].

Various studies have used longitudinal imaging to correlate with healing. A study by Bubnov et al. comparing PRP administration versus control in 30 professional athletes demonstrated accelerated regenerative processes diagnosed with US in the PRP group [33]. At 7 days after treatment, 20% of the PRP group showed a significant difference in regenerative process on diagnosed with US compared to none in the control group ($p < 0.05$). At 14 days after treatment, regenerative processes were seen on US in 80% of the PRP group compared to 20% in the control group ($p < 0.01$). At 3 weeks after treatment, all subjects in the PRP group had imaging evidence of a regenerative process, compared to 73% in the control group ($p < 0.05$). By 28 days post treatment, all patients in both groups had regenerative healing. Findings on longitudinal MRI for hamstring strains treated with PRP have also been reported in the literature. Hamilton et al. published a case report of a 42-year-old male with a grade 2 hamstring injury diagnosed on MRI [34]. He was treated with ultrasound-

guided PRP injection and had repeat MRI at 9 and 17 days post treatment. MRI at 9 days after treatment initiation demonstrated mild resolution of edema but clinically the patient had pain-free full range of motion. At 17 days post treatment, the patient had no signal changes or edema on MRI and clinically had no pain with motion or with contraction and was able to return to regular activities by 3 weeks. Zanon et al. reported a case series where 57 professional European Football players were followed for 31 months and a total of 25 grade 2 hamstring injuries were treated with autologous PRP injection [35]. They divided grade 2 injuries into groups a, b, and c with group a having partial tear involving less than 1/3 of the muscle diameter, group b involving 1/3 to 2/3 of the muscle diameter, and group c involving 2/3 but less than 100% of the muscle diameter. Group a received 2 PRP injections at day 0 and day 7. Groups b and c had three injections at days 0, 7, and 14. US and MRI were performed within 24 to 72 h of the initial injury. Follow-up MRI was performed at days 14 and 21 for group a and days 14, 21, and 28 for groups b and c. Twenty-one of the 25 hamstring strains involved the long head of the biceps femoris. Mean sports participation absence (SPA) was 36.7 days overall, 31.7 days for grade 2a, 61.3 days for grade 2b, and 49.3 days for grade 2c. Fifteen of 25 injuries involved the myotendinous junction. Reinjuries occurred in three players (12%). In each player, the study demonstrates minimal scarring, lack of edema, and tissue healing at the last MRI. Wright-Carpenter et al. performed a non-randomized, non-blinded study of 18 professional athletes with hamstring injuries treated with autologous conditioned serum (ACS) versus 11 in the control group treated with Actovegin and Traumeel, which are a deproteinized dialysate from bovine blood and a homeopathic anti-inflammatory drug with extracts of arnica, calendula, and chamomile among others, respectively [36]. All patients were treated within 3 days of the injury and received 2.5-mL injections into the lesion every other day until return to play. The ACS group had an accelerated return to play at 16.6 days versus 22.3 days in the control group which was statistically significant ($p = 0.001$). MRI at 14 to 16 days in each group demonstrated nearly complete regression of edema and bleeding in muscle with restitution of the muscle structure compared to only a mild regression of the edema and bleeding in the control group at the same time.

Clinical Outcome Studies

PRP has been advocated as a minimally invasive intervention to facilitate healing and decrease inflammation. Multiple clinical studies show PRP to be a potential adjunct to the conservative treatment of muscle injuries with regard to healing, pain control, and return to play.

Rossi et al. compared the time for return to play and risk for recurrence after acute grade 2 muscle injuries in recreational and competitive athletes who were treated with conservative measures with or without PRP. The PRP group contained 34 patients and the control group had 38, and all athletes subsequently had progressive rehab consisting of agility and trunk stabilization. Mean time to play was 21.1 days for PRP and 25 days for the control group, which was found to be significant ($p = 0.001$). Pain, as assessed with the VAS, improved for both treatment regimens, without a significant difference between the two. While PRP shortened time to sports after acute grade 2 muscle injury versus control, the rate of recurrence was not significantly different between the groups [1•]. Conversely, Delos et al. described in their study the results of PRP injections with US guidance for muscle injuries. They reported no complications from PRP injections and stated that their athletes had full functional recovery in half the time compared to athletes not treated with PRP; however, no control group was available for comparison [37]. A single-blinded randomized controlled trial by Hamid and colleagues in 2014 examined outcomes for the use of PRP in the treatment of acute grade 2 hamstring injuries [38]. Twenty-eight patients with hamstring injuries were included in the study. Return to play was 26.7 days for the PRP group and 42.5 days for the control groups, which was found to be statistically significant. There were also lower overall VAS pain scores in the PRP group; however, this did not reach statistical significance. Several studies have looked at PRP for the treatment of hamstring injuries in NFL players. Mejia and Bradley reported on a case series of PRP injections given to National Football League (NFL) players with acute hamstring injuries within 24–48 h of injury [39]. They noted that there was an earlier return to play by 3 days for grade 1 hamstring strains and 5 days for grade 2 hamstring strains, which was equivalent to a one game difference. They also noted that there was a 0% recurrence rate in this population. A recent systematic review looked at return to play for conservative treatment with or without PRP as an adjunctive modality for acute muscle injuries in athletes across different sports. The study collected 268 participants with muscle injuries in five studies with the mean age 25 years old and follow-up 12 months. They noted that soccer was the most common sport for acute muscle injury at 69.2%. The difference in time to return to sport with the PRP versus control groups favored PRP by 6 days. However, a subgroup analysis of PRP in acute grade 1 or 2 hamstring strains revealed no difference in return to sport with PRP versus control. Moreover, there was no difference in return to sport between PRP and control groups for all acute grade 2 muscle strains. The overall pooled reinjury rate was 14.3% and 17.1% with PRP and control, which was not significant. The authors found that PRP may reduce time for return to sport with all types of grade 1 or 2 muscle strains without increase risk of rerupture at 6 months, but subgroup

analysis specific to hamstring strains did not show this reduced time to play [40•].

Although some of the aforementioned studies suggest a healing benefit to PRP, there are additional studies which challenge the clinical utility of this treatment [41]. Hamilton and colleagues reported on the results of three treatment groups for hamstring injuries—PRP injection, PPP (platelet poor plasma) injection, and no injection [42•]. They found that the median time of return to sport was 21 days in PRP group, 27 days in PPP group, and 25 days in the no injection group. In comparing the PRP and PPP groups, there was a significant difference in favor of PRP ($p = .01$); however, in comparing the PRP and no injection groups, there was no significant difference ($p = .210$). Reinjury rate at 6 months post treatment was 2 of 26 in the PRP group, 3 of 28 in the PPP group, and 3 of 29 in the no injection group, without a difference between the groups. There was also no difference in isokinetic strength testing at 6 months. Rettig et al. published a case control retrospective study where 10 NFL players with grade 1 or 2 hamstring strains were treated with PRP and rehabilitation versus rehabilitation alone [43]. Median return to play was 20 days in the treatment group and 17 days in the control group, which was not shown to be significantly different. They speculated that the degree of strain and edema on MRI cross section were the strongest predictors of recovery time. There were no injury recurrences at 6 months in either group. A meta-analysis by Grassi et al. looked at six studies, two of which were randomized control trials, and analyzed the effect of PRP for the treatment of acute muscle injuries versus at least one control group including patients treated with placebo injection or physical therapy. The outcomes evaluated were time to return to sport, reinjuries, complications, pain, muscle strength, range of motion and flexibility, muscle function, and imaging [44•]. The time to return to sport evaluated in all six studies was significantly shorter in patients treated with PRP with a mean difference of -7.17 days ($p < 0.05$). Looking at only the double-blind studies ($n = 2$) or studies including only hamstring injuries ($n = 3$), there were no significant differences however. Reinjury and post treatment complications demonstrated relative risk of -0.03 and 0.01 , respectively, and were also statistically not significant between the two groups ($p > 0.05$). Nor were any substantial differences found regarding pain, muscle strength, ROM and flexibility, muscle function, and tissue integrity on imaging. The performance bias was high due to the lack of patient blinding in four studies. One of the additional theoretical clinical benefits of PRP for muscle injury is improved healing and reduced risk for subsequent reinjury. Reurink et al. reported on 42 patients who underwent PRP injection for acute muscle

injury versus 42 patients with placebo. No significant difference in reinjury rate was noted with 16% reinjury in the PRP group and 14% in the placebo group [45].

The published outcomes of PRP in the treatment of acute muscle injuries, not including the hamstring, are fewer in number. Loo et al. reported on a case of a 35-year-old male body builder with an ultrasound confirmed adductor longus strain [46]. Autologous PRP with calcium was administered each week for 3 weeks. The patient was able to return to competitive training 1 week after the last injection. Important to note, the authors did not disclose the injury grade, timing of the injection, or if rehabilitation treatment was also provided. Borriane et al. conducted a retrospective observational study to evaluate functional recovery following exercise following PRP for muscular lesions of the distal musculotendinous junction of the medial gastrocnemius head [22]. All lesions were grade 2 or 3 of distal junction medial gastrocnemius head, and patients received three ultrasound-guided PRP injections. There were 31 total patients in both the treatment and control

groups, which followed the same rehabilitation program consisting of isometric exercises for the gastrocnemius/soleus complex, ankle muscles, biking, and eccentric muscle strengthening. Control groups started the second phase of exercise in delayed fashion compared to the PRP group at 17 days versus 9 days, respectively. This was mainly due to pain. VAS decreased for the PRP group from 7.8 to 2.3 after 1 week, 1.2 at the end of active exercise therapy, and 0.38 after 3 months. The control group started with pain at 8.2 and decreased to 5.1 after 1 week, 2.8 at the end of active exercise therapy, and 1.95 after 3 months. Progression to the third phase of exercise rehabilitation was delayed in control group versus PRP at 43 days and 27 days respectively. Time to walk without pain was 24 days in the PRP group and 52 days in the control group. Time to return to sport was 53 days in the PRP group and 119 in the control group.

A summary of conclusions from the available level I and II studies on the use of PRP in the treatment of acute muscle injuries is included in Table 1.

Table 1 A summarized review of level I and II clinical studies on the outcomes of PRP for the treatment of muscle injuries

Authors	Summary	Conclusion	Level of evidence
Grassi et al. Sports Med, 2018 [44•]	• Meta-analysis of randomized controlled trials and prospective studies assessing functional outcomes after PRP injection vs placebo or control	PRP shortened return to play by over 7 days; however, subgroup analysis of randomized control trials showed no difference as did isolated hamstring injuries.	Level I
Rossi et al. Knee Surg Sports Traumatol Arthrosc, 2017 [1•]	• Randomized controlled trial comparing effect of PRP and rehabilitation versus rehabilitation alone after acute grade 2 muscle injury with a 2-year follow-up	PRP shortened time to return to sports after acute grade 2 muscle injury vs control, but the rate of recurrence at 1 year was not significantly different.	Level I
Hamilton et al. Br J Sports Med, 2015 [21]	• Randomized three-arm double-blinded parallel group trial consisting of 90 professional athletes with MRI positive hamstring injuries	There was no benefit of a single PRP injection over intensive rehabilitation in athletes who sustained acute hamstring injuries. There was a statistically significant difference between PRP and PPP regarding return to play.	Level I
Reurink et al. N Engl J Med, 2014 [24]	• Randomized double-blind, placebo controlled 3 center clinical trials of 80 recreational athletes in the Netherlands with acute muscle injuries diagnosed with MRI. Compared a PRP group which received 2 injections (first within 5 days of injury and second 5–7 days after the first) versus a placebo group which received an isotonic saline injection	Median time for return to sports was not different between the groups (42 days)	Level I
Sheth et al. Arthroscopy, 2018 [19]	• Meta-analysis of 5 studies including 268 participants comparing return to sport with PRP versus control	PRP may reduce time to return to sport for acute grade 1 or 2 muscle injuries; however, subgroup analysis did not demonstrate a significant return to sport with acute grade 1 or 2 hamstring injuries.	Level II
Hamid et al. Am J Sports Med, 2014 [17]	• Single-blinded randomized controlled trial investigating time to return to sport after acute grade 2 hamstring injuries.	Single autologous PRP injection combined with rehabilitation program was significantly more effective in treating hamstring injuries than a rehabilitation program alone.	Level II
Bubnov et al. Med Ultrasound, 2013 [26]	• Randomized prospective trial assessing outcomes in 30 consecutive professional athletes with acute muscle injury for single PRP injection under ultrasound guidance combined with a conservative rehab program versus rehab only	The PRP group demonstrated a significantly higher level of pain relief, quicker return to sport by a mean difference of 12 days and faster muscle strength recovery compared to the control group	Level II

Conclusions

PRP has been suggested as a treatment adjunct for muscle injuries; however, few level one studies exist demonstrating a clear benefit. Outcome comparisons between studies are limited due to significantly variability in study design and PRP preparation and application techniques. Additional study is needed to identify and standardize the optimal PRP preparation and content for the treatment of acute muscle injuries. A large proportion of studies mentioned in this review are neither blinded nor randomized controlled trials. The majority of studies included in this review report main outcomes as return to play and pain scores, and they do not report on muscle strength or flexibility. Reinjury rates are reported in some studies but the main objective outcome scores are return to play and days until return to play. Follow-up imaging studies are evaluated qualitatively looking at edema, scar formation, and muscle architecture. High-quality randomized controlled studies are also necessary to determine the clinical efficacy of PRP for the treatment of these injuries.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

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35 initially treated in the PRP group had recurrence of muscle strain (5.7%) versus 4 of 40 in the control group (10%) but was not found to be statistically significant. This study ultimately showed that a single injection of autologous PRP with a rehabilitation program significantly shortened time to return to sports after and acute grade 2 muscle injury when compared with control group; however, the rate of recurrence was not significant between the two groups.

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not significant ($p = 0.189$). The time to return to sport between PPP and control was 2.8 days, which was not significant ($p = 0.210$). There was no difference in reinjury rate between any groups. In conclusion, this study found that there was no benefit of a single PRP injection over rehabilitation program in athletes who have sustained acute MRI positive hamstring injuries.

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- muscle strength, range of motion and flexibility, muscle function, and imaging. Six studies were included with a total of 374 patients. Time to return to sport was significantly shorter in patients treated with PRP (mean difference -7.17 days), but if only double-blind studies or studies involving only hamstring injuries were analyzed, non-significant differences were found. The rate of reinjury and complications was similar between the two groups ($p > 0.05$), nor was any differences in pain, muscle strength, flexibility muscle function, and imaging. The authors did note that the performance bias was a high risk due to lack of blinding in four studies. Due to the bias in the studies, heterogeneity of the findings, and limited sample size, the authors found that the evidence should be considered a low quality despite promising biological rationale, positive preclinical findings, and early successful clinical experience of PRP.**
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