Platelet-rich plasma for muscle injuries: game over or time out?

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Abstract Muscle injuries are common and may be associated with impaired functional capacity, especially among athletes. The results of healing with conventional therapy including rest, ice, compression, and elevation (RICE) are often inadequate, generating substantial interest in the potential for emerging technologies such as platelet-rich plasma (PRP) to enhance the process of soft-tissue healing and to decrease time to recovery. In vitro studies and animal research have suggested that PRP may have benefits associated with the increased release of cytokines and growth factors resulting from supraphysiological concentrations of platelets that facilitate muscle repair, regeneration, and remodeling. Despite the promise of basic science, there is a paucity of clinical data to support the theoretical benefits of PRP. The only double-blind controlled clinical trial was recently reported and showed no benefit of PRP in the time to resume sports activity among athletes with hamstring muscle injury. This review examines the current evidence and the theoretical framework for PRP and muscle healing. Scientific gaps and technological barriers are discussed that must be addressed if the potential promise of PRP as a therapeutic modality for muscle injury is to be realized.

Keywords PRP · Biologics · Muscle injury · Muscle regeneration · Sports medicine

Introduction

Platelet-rich plasma (PRP) is a potentially promising but unproven therapy for musculoskeletal soft-tissue injuries. A high prevalence of sports-related and occupational injuries has led to a burgeoning interest in the potential application of bioaugmentation techniques such as PRP to enhance the healing process of skeletal muscle. Despite technological advances and the growing use of PRP in orthopedic practice, a recent Cochrane review of platelet-rich therapies for musculoskeletal soft tissue injuries concluded that scientific evidence was insufficient to support their use for treating several common ligament and tendon injuries [1•]. The evidence base to guide the use of PRP in the treatment of contusion injuries and muscle strains is very limited. An International Olympic Committee (IOC) consensus paper on the use of PRP in sports medicine indicated there is little scientific support for PRP in the treatment of muscle strain injury and suggested further investigation utilizing this technology is needed to develop practice guidelines [2].

The first double-blind, randomized, placebo-controlled clinical trial of PRP in the treatment of acute hamstring muscle injuries was recently published in a letter to the editor of the New England Journal of Medicine and showed no benefit for PRP in the time to resume sports activity among athletes, raising the question if the game is over for PRP to treat muscle injury or if the null result is a limitation of current science and technology [3•]. The purpose of this paper is to review the scientific evidence and theoretical framework for the potential benefits and possible adverse effects of PRP in acute muscle injuries. The critical need to develop standardized preparations and to conduct high quality research regarding the

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optimal timing, dosing, frequency, and customization of PRP for targeted tissues will be discussed as a priority to establish the evidence base necessary to draw definitive conclusions regarding the use of PRP to treat musculoskeletal injuries. The studies reviewed in this article were identified through a PubMed search on PRP and muscle injury. Relevant references were systematically reviewed to identify any further original research on the topic of PRP and muscle injury in humans or in controlled animal studies.

PRP preparation and injection procedures

PRP is a concentrated autologous blood product with purported benefits derived from its high concentration of platelets rendering it rich in growth factors and cytokines that may facilitate tissue repair, regeneration, and remodeling [4]. Preparation procedures for PRP are not standardized and therefore may result in significant variability in the concentrations of platelets, red blood cells, white blood cells (WBCs), and growth factors depending on the separation process and commercial system utilized [5•, 6]. PRP is harvested by phlebotomy and processed by centrifugation or obtained via apheresis. Centrifugation is a simpler technique and may yield platelet concentrates three- to eightfold higher than whole blood depending on spinning techniques [7]. Apheresis is a more expensive procedure that requires filtration of blood circulating from patient to machine. PRP obtained from apheresis results in a more consistent platelet concentration, typically five times that of whole blood [8].

The potential healing benefits of PRP may be correlated with several variables, including final volume, platelet concentration, platelet activation, fibrin clot formation, and leukocyte concentration [4]. Variation in concentrations of cell types and growth factors in PRP may have a differential impact on the natural healing stages of muscle (inflammation, proliferation, and remodeling) compared to other soft tissues. For example, platelet-derived growth factor (PDGF) stimulates myogenesis and is found in significantly different concentrations in PRP produced by different commercial systems [5•]. Likewise, it has been suggested that transforming growth factor-beta (TGF- β), found in higher concentrations with certain preparations, stimulates fibrosis and thus may have a detrimental effect as it may promote greater fibrotic healing of muscle [9]. Apheresis preparations are theoretically less desirable for muscle therapy considering the concentration of PDGF is lower and TGF- β is higher compared to PRP obtained via centrifugation [8].

WBC concentration and distribution was also found to vary significantly by preparation system [6]. Higher concentrations of lymphocytes and neutrophils may have negative effects on healing due to their pro-inflammatory effects; however, the clinical relevance of this is unknown. Leukocyte-rich PRP

may provide a positive anti-microbial effect, which could be advantageous in the setting of a surgical procedure, but may not offer advantages for treatment of muscle injuries [5•].

PRP protocols may range from the use of fresh concentrate prepared and activated at the bedside to application of frozen and thawed PRP stored under a variety of conditions. A number of agents (e.g., bovine-thrombin, calcium chloride) are used to activate platelets before injection into injured tissue [10]. PRP injections may be performed unaided or under ultrasound guidance. Multiple injection techniques have been employed including intramuscular delivery of a singular bolus, multiple depots at the site of maximal injury, or a single injection into the muscle insertion site. The dose, timing, and frequency of PRP muscle injections that have been reported are also highly variable.

Pathophysiology and mechanisms of muscle healing

The healing phases of an injured muscle involve destruction characterized by hematoma and necrosis of myofibrils, phagocytosis of damaged tissues upon arrival of platelets, neutrophils, and macrophages [11, 12]. This is followed a few days later by the start of the regenerative process. Progressive remodeling of the healing tissue begins during the second week of healing.

Initially, the aggregation of platelets at the site of injury serves a primary role in hemostasis. Platelets are also an important source of a wide range of biologically active metabolites that modulate inflammation, cellular proliferation, migration and adhesion, angiogenesis, vascular remodeling, microbicidal functions, and synthesis of extracellular matrix [13]. Once activated, the alpha granules of platelets release cytokines signaling a cascade that promotes inflammation and neovascularization [4, 9]. The release of growth factors including PDGF, TGF- β , insulin-like growth factor-1 (IGF-1), basic fibroblast growth factor (b-FGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), endothelial cell growth factor (ECGF), and vascular endothelial growth factor (VEGF) are believed to play potentially important roles in the healing response of soft tissue [4, 9]. Substances released from the dense granules of platelets (e.g., serotonin) may also have a positive effect on local pain [9]. The amplification of the biological effects of platelets stimulated by injury in conjunction with the supraphysiologic concentrations of platelets in PRP injected into injured muscle tissue has the potential for both positive and adverse effects as outlined in Fig. 1.

During the initial phase of muscle healing, neutrophil accumulation begins as early as 1–2 h after injury; despite their role in the phagocytosis of damaged tissue, the beneficial effects of neutrophils in muscle healing are debated [11]. Neutrophils have been shown to contribute to oxidative damage and impair the resolution of contraction-induced muscle

Fig. 1 Platelet-rich therapies: theoretical mechanisms in soft tissue healing. *b-FGF* basic fibroblast growth factor, *ECGF* epidermal growth factor, *HGF* hepatocyte growth factor, *IGF-I* insulin-like growth factor-1, *IL-1* interleukin-1, *MMP*

matrix metalloproteinase, *NGF* nerve growth factor, *PDGF* platelet-derived growth factor, *PRP* platelet-rich plasma, *TGF-β* transforming growth factor beta, *TNF-α* tumor necrosis factor-alpha, *VEGF* vascular endothelial growth factor

injury in mice [14]. Leukocytes secrete cytokines and other mediators that increase catabolism by promoting inflammatory responses via tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), and by decreasing extracellular matrix synthesis [15]. Heightened catabolism is associated with decreased sheer/tensile strength of soft-tissue and has been correlated with decreased recovery and healing. The potential for PRP to augment the negative effects of neutrophils in the initial stage of healing lends support to the recommendation to avoid its use in the first 24 h following muscle injury and/or to use leukocyte-poor PRP preparations [16]. Because neutrophils may exacerbate original muscle damage some have suggested this provides further rationale to consider leukocyte-poor PRP for muscle healing [17, 18].

As muscle begins to regenerate, macrophages are recruited to the site of injury and play an anti-inflammatory role in addition to their secretion of growth factors and prevention of apoptosis [11]. The regeneration of muscle is regulated by multiple biological pathways that involve myogenesis, re-innervation, and revascularization [19]. Myogenic precursor cells are derived from muscle satellite cells that rapidly proliferate and have significant regenerative capacity. As they differentiate into myofibers and fuse together, remodeling and

reorganization begins. As fibroblasts invade the gaps created by fused myofibers, they produce an extracellular matrix that restores tissue architecture, but may also lead to formation of dense scar tissue which can mitigate complete recovery [12]. The myogenic response is believed to play a critical role in the recovery of contractile function of skeletal muscle. Lovering et al. demonstrated that inhibition of myogenesis prevented recovery of function following injury with multiple lengthening contractions in a rodent model; however, a similar result was not observed after single lengthening injury, suggesting mechanisms of repair may vary by type of muscle injury [20].

Growth factors released at the injury site are believed to play specific roles during muscle regeneration. Menetrey et al. have shown b-FGF, IGF-1, and nerve growth factor (NGF) stimulate myoblast proliferation and fusion in vitro [12]. The researchers also demonstrated that serial injections of b-FGF and IGF-1 were associated with enhanced muscle regeneration, and increased fast-twitch and tetanic contraction strength in a controlled study of mice with lacerations of the gastrocnemius muscle. The role of activated satellite cells and growth factors in muscle regeneration is further supported by the finding that injection of neutralizing antibodies against b-FGF and IGF-1 into

muscle reduced the number of regenerating myofibers in a rodent model [21].

In a contusion model in mice, Wright-Carpenter et al. showed that a form of PRP, autologous conditioned serum (ACS), injected into injured gastrocnemius muscles increased satellite cell activation and accelerated regeneration compared to controls [22]. ACS was obtained similar to whole blood centrifugation methods used in humans and was associated with significant elevations in b-FGF (460 %) and TGF-*B* (82 %). Treatment with ACS was associated with an 84 % increase in satellite cell activation within 30 h of muscle injury. At the end of 1 week after injury, histological evidence of a greater percentage of newly generated centronucleated myofibers was evident in treated vs. control mice. The authors concluded that the efficacy of ACS was largely due to the increase in b-FGF.

Hammond et al. studied the effects of PRP on the recovery of contractile function in Sprague-Dawley rats injured by a single large strain or multiple small strain lengthening contractions of the tibialis anterior muscles (TA) [23]. The high repetition model demonstrated significant improvements in measures of satellite cell activation and quantification of myogenesis in PRP vs. control groups that peaked at 2 weeks. The PRP group also resulted in marked improvements in contractile function and shortened the time to full recovery from 21 to 14 days. In contrast, PRP showed little impact in the single high-strain protocol group. The authors concluded that the likely mechanism of benefit of PRP is related to enhanced myogenesis and that efficacy may be dependent on the type of injury (acute strain vs chronic overuse injury) based on discordant findings from the different strain models they tested. Improved muscle regeneration was also documented in a rat model by Gigante et al. who compared the efficacy of a platelet-rich fibrin matrix as a source of growth factors on longissimus dorsi muscular lesions compared to untreated controls [24]. The researchers also documented an increase in neovascularization and a slight reduction in fibrosis compared to controls.

A recent study conducted by Terada et al. found that the combination of PRP with an antifibrotic agent significantly improved healing when compared to PRP alone [25]. The researchers hypothesized that healing from a contusion injury could be significantly enhanced by preventing fibrosis in addition to stimulation of muscle regeneration and angiogenesis with PRP. Injured tibialis anterior muscles of mice were treated with PRP alone or in combination with the anti-fibrotic agent losartan. The PRP used in the study contained a 5.5-fold platelet concentration compared to whole blood, and the concentration of TGF-*B* was 16.5 times higher than in the platelet-poor plasma. Combination therapy significantly decreased TGF-*B* gene expression and increased expression of VEGF, CD31 (mediator of cell adhesion), and follistatin (regulator of muscle growth) in injured mice compared to PRP alone. At 2 weeks, the number of regenerating myofibers was

significantly higher than baseline in both groups but did not differ between the PRP treatment alone or in combination with losartan. The combination was associated with a reduction in the development of fibrosis and improved functional measures of muscle function at 4 weeks after injury. The authors concluded that blocking the expression of TGF-*B* with an anti-fibrotic agent resulted in improved effectiveness of PRP on muscle healing after injury that was likely mediated through enhancement of angiogenesis.

Clinical studies of PRP and muscle injury

Over a decade ago, a pilot study was conducted among 18 professional sportsmen with moderate muscle strain injuries who were treated with ACS within 2 days of injury; injections were repeated every second day until complete recovery (mean treatments=5.4) [26]. ACS was prepared from patients' whole blood using a centrifugation technique that yielded significant increases in FGF-2 (750 %), TGF-*B* (31 %), HGF (hepatocyte growth factor) (35 %), and IL-1Ra (interleukin-1 receptor antagonist) (600 %). The subjective time to recover was an average of 16.6 days compared to 22.3 days among a historical control population of 11 professional sportsmen who had been treated with Actovegin/Traumeel, a combination anti-inflammatory treatment used in Europe. The authors concluded that the increase in growth factors associated with the PRP was consistent with what had been observed in animal models and suggested that treatment of strain injuries with ACS may be a promising method to improve recovery time and return to full activity. The data provided proof of concept of PRP in humans but were inconclusive due to the non-randomized, non-concurrent controlled nature of the study, as well as the non-blinded subjective nature of clinical outcomes and lack of objective data on muscle strength and function.

Subsequent studies as outlined in Table 1 included a variety of designs and methods of PRP preparation and outcome measures. Two case reports published in 2009 and 2010 highlighted a potential beneficial effect of platelet-enriched plasma in the treatment of a right adductor longus rupture and a grade II hamstring strain, respectively [27, 28]. The initial case study described a 35-year-old male professional body builder who underwent three weekly injections of autologous plasma that had been centrifuged then activated with calcium to trigger the formation of a fibrin matrix [27]. Repeat ultrasound showed muscle healing, and the athlete returned to competitive training within 1 week of completion of treatments. The latter case study involved a 42-year-old male with coronary artery disease who was prescribed antiplatelet agents (clopidogrel and aspirin) and experienced a sudden onset of posterior thigh pain during a wave surfing accident; MRI confirmed a grade II semi-membranous hamstring muscle strain injury [28]. The patient received ultrasound-guided injection of PRP into the

Table 1 Designs and methods of PRP preparation and outcome measures

Author (year) reference	Design	Population	Injury types	PRP preparation	Injection procedures	Control group	Measured outcomes	Results
Wright-Carpenter (2004) [26]	Non-randomized, non-blinded, retrospective controls	18 professional sportsmen and 11 historical controls in Europe	Moderate, second degree muscle strains—7 muscle types diagnosed by MRI	Autologous conditioned serum from whole blood incubated, and centrifuged, stored at -20°C	Initial injection at 2 days then every second day until full recovery, 2.5 ml via palpation into injury	Actovegin/Traumeel	Ability to participate to 100 % competition in respective sport (subjective athlete decision and physiotherapist)	Time to recovery in PRP group 16.6 days vs. 22.3 days in controls
Loo (2009) [27]	Case report	35-year-old Chinese male professional body builder	Right adductor longus rupture with hematoma diagnosed by ultrasound	Whole blood centrifugation, no buffy coat, activated with calcium	3 weekly injections	N/A	Repeat ultrasound, and time to return to activity	Muscle healing, organized hematoma, good pain relief, return to training 1 week after 3 injections
Hamilton (2010) [28]	Case report	42-year-old physically active male from Qatar with coronary heart disease on anti-platelet agents	Grade II hamstring strain	Commercial prep with Biomet Recover [®]	Ultrasound-guided injection (3×1 ml depots) into injury then immediate icing	N/A	MRI of muscle healing, time to return to activity	Mild resolution at 9 days, complete at 17 days, return to activity 3 weeks
Wetzel (2013) [29]	Retrospective case-series	15 patients (12 females) in Chicago practice who failed traditional therapy, 12 hamstrings treated with PRP, 5 only traditional therapy	Proximal hamstring injuries	55 cc of PRP prepared from patient's whole blood	Single 6 cc bolus of PRP from office whole blood draw injected into muscle origin	N/A	Visual analog scores (VAS), and Nirschl Phase Rating Scale for pain, return to sport	PRP within group decrease in pain scores, no between group difference, all athletes returned to sport
Bubnov (2013) [30]	Randomized, unblinded	30 male professional athletes from Ukraine	Acute local muscle injury (thigh, shoulder, foot and ankle)	Whole blood centrifugation, preparation included buffy coat, no activation	Single freshly prepared PRP injected under ultrasound guidance	Conventional conservative therapy	Visual analog scale, muscle function, subjective global function, ultrasound muscle regeneration, time to return to sport	PRP group faster pain relief, muscle function, and regenerative changes, no differences at 28 days except PRP better range of motion and subjective global function. Time to return to sport 10 days vs 22 days in PRP vs. controls
Bernuzzi (2014) [31]	Clinical experience summary	53 recreational athletes (36 men, 17 women) seen in emergency room in Italy	Grade I–III muscular or myotendinous lesions—7 types	Whole blood centrifugation, platelet concentrate stored at -40°C	Concentrate activated with thrombin, 1 mL injected every	N/A	Pain reduction, muscle function recovery, return to sports activity, ultrasound-	Progressive decline in pain, all patients returned to sports after a mean of

Table 1 (continued)

Author (year) reference	Design	Population	Injury types	PRP preparation	Injection procedures	Control group	Measured outcomes	Results
Reurink (2014) [3•]	Randomized, double-blind, controlled 3 center clinical trial	80 competitive and recreational athletes (76 males, 4 females) from the Netherlands	Acute hamstring muscle injuries confirmed by MRI	Commercial prep with Arthrex®	7 days × 3 weeks 2 injections—first within 5 days of injury, then 5–7 days later, 3 × 1 mL depots into injury	Placebo injection with isotonic saline	imaging tissue healing Time to resume sports activity	30 days, at 1 year 3 new, 1 re-injury Median time to return to sports was not different between groups (42 days)

area of maximal tenderness and muscle injury on day 1 with no change observed in pre- and post-injection MRI. Following comprehensive physical therapy, a repeat MRI showed mild resolution after 9 days and complete resolution at 17 days. Analysis of growth factor levels in the patient's activated plasma demonstrated increased concentrations consistent with what was expected for PRP. The clinical recovery of the patient was complete at 3 weeks with return to recreational activities. Based on this single report, the authors suggested that a single bolus of PRP may be effective, but it is clear that further study is required to address the optimal timing and dosing of autologous growth factors.

Wetzel et al. also evaluated PRP as an adjuvant therapy for hamstring injuries in a retrospective case-series of 15 patients treated for 17 proximal hamstring injuries that failed conservative treatment [29]. Among 10 patients who received a single PRP injection (one patient had a repeat injection at 6.5 months), there was a significant reduction in mean visual analog pain scores (VAS) and Nirschl Phase Rating Scales (hamstring specific pain rating scale) pre- and post-treatment; however, when compared to a group of five patients who received traditional therapy alone, there was no significant difference in scores between the groups after respective treatments (mean follow-up was 4.5 months in the PRP group and 2 months in the traditional treatment group). Despite the equivocal results, the authors suggested PRP might be a non-operative option for proximal hamstring injuries that have failed conservative therapy, and acknowledged the inherent biases in their study with respect to retrospective design and limited sample size. Noteworthy was the large number of hamstring injuries that were considered refractory (71 %) to conservative treatment, underscoring the need for further research into optimal methods to enhance muscle healing.

The efficacy of ultrasound-guided PRP treatment for acute muscle injuries (thigh, shoulder, foot, and ankle trauma) was compared to conservative therapy (immobilization, physiotherapy, and anti-inflammatory therapy) in a randomized non-blinded study of 30 male professional athletes [30]. Status at presentation, 24 h, and 7, 14, 21, and 28 days was evaluated by a pain VAS, physical assessment, self-reported global function, and ultrasound criteria for regeneration of injured muscle. Patients who received targeted PRP injections had better pain relief in early assessments compared to the conventionally treated group, but at 28 days, there was no difference between groups. Some physical assessments and ultrasound measurements showed greater beneficial effects in the PRP group at earlier time points, but the groups did not differ at 28 days. Range of motion and subjective global function was improved in the PRP-treated athletes relative to conventional therapy at 28 days; mean time to return to sports was also shorter in the treated vs. control groups (10 ± 1.2 vs 22 ± 1.5 days). The data lend support for PRP in pain control and to hasten recovery; however, the small and highly select sample, non-blinding,

and lack of adjustment for multiple statistical testing limit the conclusiveness and generalizability of the findings.

Recently, Bernuzzi et al. reported their experience with ultrasound-guided injections of PRP among 53 recreational athletes with grade I, II, and III lesions in diverse muscle groups [31]. Participants received three total treatments (one injection every 7 days) of autologous platelet concentrate that was activated at the bedside and injected directly into the tissue lesion. The authors noted a progressive decline in the VAS pain score within 2 weeks of the conclusion of treatments and all patients returned to their regular sporting activity within 30 days. No infections or other major complications were reported. The 1-year clinical experience documented one recurrent injury and three new muscular injuries. The study is informative due to the more robust clinical experience with heterogeneous muscle injuries among recreational athletes with longer term follow-up. The lack of a control population, MRI validation of tissue healing, and lack of supporting data on growth factor levels in the PRP are significant limitations.

In 2014, Reurink et al. reported the results of a double-blinded, placebo-controlled randomized three-center study of 80 competitive and recreational athletes (95 % male) with acute hamstring injuries [3•]. Participants received intramuscular injections of PRP or isotonic saline as a control within 5 days after injury and a second injection was repeated 5 to 7 days later; in addition, all patients received standard rehabilitation. PRP was prepared with a commercial system and was injected at the site of maximal injury, similar to the control-injection, using ultrasound-guided technique. Patients were followed for 6 months for the primary outcome, which was time to resume sports activity (days between injury and unrestricted sports activity in training or competition). The intention to treat analysis showed the mean time to sports resumption was similar between the groups (42 days). The re-injury rate was 16 % in the PRP group and 14 % in the control group; no serious adverse events were noted.

The authors interpreted the null results of the study as demonstration of no benefit for PRP in hamstring muscle injuries, although a small chance of a clinically relevant benefit could not be ruled out given the 95 % confidence interval for the hazard ratio for the primary outcome ranged from 0.61 to 1.5. The study was designed to detect a difference of 20 % in the number of days to return to play with 80 % power. The strength of the study was the randomized control design; however, methodological concerns should be considered when interpreting the results. The mean time to return to sports activity in the control group was longer than planned in the study design (42 vs 27 days), suggesting poor adherence to standard rehabilitation or refractory injuries. Differences in baseline characteristics of patients were not taken into consideration in the statistical analysis that in aggregate could lead to confounding factors. At baseline, the control group had 10 subjects (26 %) that exercised <3 times/week compared to 6 (15 %) in

the PRP group, raising the possibility that an uneven distribution of athletes (competitive vs. recreational) could bias the results. If competitive athletes were more likely to return to play sooner than recreational athletes, the finding could have been biased in favor of the control group in a small study. Moreover, the PRP group had a larger number of subjects with a history of prior hamstring injuries, raising the potential for an interaction between treatment and outcomes by type of athlete and prior muscle injury. No information was provided if there were between-group differences at study conclusion in use of NSAIDs or other therapies for muscle injury. The study did not assess the composition of growth factors in PRP; therefore, it could not be correlated with clinical outcomes.

A study is underway in Malaysia to assess the clinical efficacy of a single injection of PRP with a different commercial preparation on grade II hamstring injuries compared to a control group after 16 week [32]. The researchers used a blinded, randomized assessor design to evaluate a combination of objective and subjective assessments of return to play. Additional data is expected related to growth factor levels and standardized measures of strength following PRP vs. control intervention.

Table 2 Platelet-rich plasma (PRP) and muscle injury: research limitations

Variability in PRP preparation methods and reporting of injection procedures
Platelet concentration and growth factor levels inconsistent
Optimal timing, frequency, and dose–response not established
Small sample sizes in animal and human studies
Type (acute vs. repetitive) and location of injury variable
Poor correlation between rodent and human models of injury
In vivo mechanisms of healing more complex than in vitro
Majority of clinical data uncontrolled or retrospective
Selection bias in clinical studies (e.g., lack of randomization)
Detection bias in animal and human studies (e.g., non-blinded outcome measurements)
Limited generalizability in clinical studies (e.g., predominately male athletes)
Attrition and reporting bias in clinical studies (e.g., differential loss to follow-up)
Confounding (e.g., degree of injury, comorbidities, use of anti-inflammatory agents)
Variability in control groups (e.g., injections: anti-inflammatory drugs vs. saline)
Functional measures (e.g., subjective, lack sensitivity)
Primary outcome not defined a priori and lack of correction for multiple statistical testing
Cost-effectiveness rarely reported
Lack of data on concomitant use with other biologic augmentation techniques
Comparative effectiveness data lacking with evidence-based interventions

Limitations of current research and future directions

There are numerous limitations to current research outlined in Table 2 that have a significant impact on the ability to draw definitive conclusions related to the efficacy of PRP in the treatment of muscle injuries. A priority is to establish the optimal composition of PRP with respect to platelets and other constituents to yield the greatest benefit to risk ratio with respect to specific muscle injuries. Ideally, this “customization” will be determined in vitro and in animal models before further testing is conducted in humans, given the lack of proven benefit and costs associated with therapy. Once standardized preparations and methods are available, further research should establish optimal protocols for the timing, dosing, and frequency of PRP administration for muscle injections.

If PRP is determined to be efficacious for the treatment of muscle injuries in controlled animal and human studies, it will be imperative to compare the cost-effectiveness of therapy with conventional and emerging therapies. In addition, ethical issues will need to be addressed related to use of PRP to speed recovery among athletes, as concerns related to performance enhancement and doping have been raised [33].

Conclusion

Despite the theoretical benefits of PRP to regenerate muscle tissue and speed return to activity, there is little scientific support for this intervention. Recent controlled clinical trial data provide minimal support for the use of PRP for the treatment of muscle injuries. Whether PRP treatment is inherently ineffective or the current state of science is the limiting factor remains to be determined.

Compliance with Ethics Guidelines

Conflict of Interest Michael J. Mosca was supported by a Harvard College Research Program fellowship award.

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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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