

Review Article

The Regenerative Medicine Potential of PRP in Elite Athlete Injuries

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Received: 13 January 2020; **Accepted:** 20 February 2020; **Published:** 20 March 2020

Citation: Alex Pontes De Macedo, José Fabio Santos Duarte Lana, Carolina Masini Pedrozo, Ivan Corrêa Bottene, Jose Renan Moyses De Medeiros, Letícia Queiroz Da Silva. The Regenerative Medicine Potential of PRP in Elite Athlete Injuries. Fortune Journal of Rheumatology 2 (2020): 016-026.

Abstract

Despite the health benefits of sports and physical activities, sports injuries rank among the major public health problems due to the important social and economic impact on society. A significant proportion of these injuries remain difficult to treat, and many athletes suffer from decreased performance and longstanding

pain and discomfort, especially the high-performance athletes. Non-surgical alternatives have been studied, and the use of the Platelet-Rich Plasma (PRP) is one of the most popular solutions due to its chemotactic, proliferative and anabolic responses through the delivery of growth factors. However, there are many

unanswered questions concerning the composition of PRP, the individual blood product characteristics, the distinct protocols of production, and the different methods of application, all of which compromise the real evaluation of PRP efficacy. In addition, not much is known about its response in professional athletes and how these differ across sports. This review discusses the current literature regarding the use of PRP in the treatment of sports-related injuries in athletes competing at the highest levels. On the basis of the current evidence, few studies attempt to standardize or report the use of PRP in a high-performance athlete, and only 38% of the studies use a control group and discuss platelet concentration. Besides, only 1 study performed growth factor evaluation. To our knowledge, this is the first review introducing the use of PRP in elite athletes, and as in other areas, it is clear that PRP demands regulations and further studies regarding its function and application.

Keywords: Platelet-rich plasma; Sports medicine; Musculoskeletal injury; Elite athletes; Regenerative medicine

1. Introduction

Sports injuries are considered disorders of the musculoskeletal system or concussions [1] that are generally caused during sportive activities such as football, netball, basketball, combat sports, wheeled motor sports, ice and snow sports, water sports, skateboarding and roller sports, equestrian sports, amongst many others. In economic terms, similar to all other injuries, sports injuries have a significant impact upon society, including health care resources, personal disability and activity restriction [2]. In Australia, for example, 36,000 people were hospitalized in 2011-12, with an estimated cost of \$1.8 billion each year [3]. It is important to consider that these conditions exert direct costs such as medical specialist (e.g., orthopedic

surgeon); physiotherapist; use of hospital care; medications and indirect costs, such as those related to loss of productivity due to absenteeism from paid or unpaid work [4]. Being the professional sports category most affected, the loss of training or competition leads to a cost of approximately €500,000 [5]. Muscle injuries are a heterogeneous group of different injury types, locations, severity, and size, which renders the prognoses regarding healing time and rehabilitation difficult. The most common injuries related to the sport are acute muscle tears (involving hamstrings, adductors, and calf muscles) and muscle strains [6, 7], being acute hamstring injuries have one of the highest recurrence rates that can lead to prolonged absence from sports [8, 9]. In football, for example, 25 players in the squad have approximately five hamstring injuries each season, equivalent to more than 80 lost football days [6].

Current general sports injury management includes ice, rest, compression, elevation, physiotherapy [10-12], nonsteroidal anti-inflammatory drugs [8, 13], corticosteroid injections [14] and cell therapies [15]. In the cell therapy field, chondrocyte and tenocyte are indicated for tendon conditions in patients with less than 50 years old with focal chondral defects, whereas mesenchymal stem cells (MSc) therapies can assist tissue regeneration through paracrine interactions [16, 17]. However, these are not the only biological therapies available. Blood-derived products, especially Platelet-Rich Plasma (PRP) [18], aims to improve the process of tissue repair through the delivery of growth factors that provide chemotactic, proliferative and anabolic responses [19, 20]. This product has grown in popularity over the past few years in several fields of medicine, including aesthetics [21], dentistry [22], autoimmune disease [23] and orthopedics [24]. Despite the widespread unregulated use, the efficacy of PRP therapy has yet to be established. There are many unanswered questions concerning the composition of PRP, the

individual blood product characteristics, the distinct protocols of production, and the different methods of application, all which compromise the real evaluation of PRP efficacy. The aim of this review was to evaluate the use of PRP to treat sports-related injuries in athletes competing at the highest levels.

1.1 PRP

The term PRP is described by platelet concentration 3-8 times above the baseline number, in low levels of plasma [20, 25]. These cells are commonly known for their role in hemostasis, however due to their capacity to release growth factors from their α -granules, they play a key role in mediating the healing of the damaged tissue [25-27]. These growth factors include vascular endothelial growth factors (VEGF), epidermal growth factors (EGF), platelet-derived growth factors (PDGF), transforming growth factor-beta 1 (TGF- β 1), basic fibroblast growth factors (FGF), hepatocyte growth factors (HGF), insulin-like growth factors (IGF-I), hepatocyte growth factors (HGF), amongst others [28, 29]. Together, the growth factors influence chemotaxis, cell migration, mitosis, angiogenesis and tissue repair [30-32]. In addition, PRP contains an adhesive substrate for cells, such as fibrin, fibronectin, thrombospondin, osteocalcin, and osteonectin. Considering these properties, PRPs are crucial for wound healing, and in process of repair of tendons, muscles, cartilage [31, 33].

1.2 Classifications of PRP

Currently, classifications are basically based on the type of activation, platelet concentration, growth factors and the presence or absence of leukocytes or fibrin [34]. Classifications include plasma rich in growth factors (PRGF) [35], pure platelet-rich plasma (P-PRP called PRGF by Anitua), leucocyte- and platelet-rich plasma (L-PRP), pure platelet-rich fibrin (P-PRF), leucocyte- and platelet-rich fibrin (L-PRF) [36, 37]. The 4 families of products present different biological signatures and

clinical applications, for example, the L-PRF family is employed in odontology surgery [38] and PRF is specifically applied for skin wound ulcers [39].

1.3 Preparation of PRP

In the past few years, several commercial PRP kits have been developed, and the method used to produce PRPs determines the composition and concentration of leukocytes and platelets. Blood is obtained by phlebotomy and centrifuged to achieve a high concentration of platelets in plasma by differences in specific gravity [25]. Single spinning yields a 1-3-fold change in platelet concentration over baseline levels, and double spinning yields a 4-8-fold change in platelet concentration over baseline levels [33]. A consistent manual PRP preparation method that yielded a product with cytokines and growth factors proposed by Amable et al. in 2013, which has been frequently used in subsequent studies, is composed by two centrifugation steps being the first one at $300 \times g$ during 5 minutes at 18°C and the second at $700 \times g$ during 17 minutes at 18°C [40]. Whereas the technique to produce PRGF uses single-spinning method through PRGF-Endoret System at $580g$ for 8 min [43, 44].

Currently, there are automated machines and commercial kits for PRP obtainment, such as Harvest SmartPrep (2500 ± 150 RPM \times 1-3 min; 2300 ± 140 RPM \times 6-9 min), Biomet GPS III (3400 RPM for 15 min) [41], Magellan APS (2800 RPM \times 17 min; 3800 RPM \times 17 min) [42]. However, despite the fact that those technologies have less blood manipulation, the misinformation regarding the preservation of PRP and the high cost are methodologic disadvantages. Products of the PRF family can be produced by Fibrinet and Choukroun's, however the product is used only as a real solid material for other applications due to their strong fibrin matrix [43]. In addition, among the differences between PRP preparation protocols, it is important to

consider that PRP can also differ as to the inclusion or exclusion of activation factors (e.g. calcium, thrombin), the presence or absence of leukocytes, the volume of application and the type of site. Apparently, one suitable way to solve the particular problem of PRP production would be using the freeze-drying process, as this technique can provide a large-scale PRP production with increased shelf life and minor technical variability and could furthermore be achieved following a single process of production [44, 45]. However, this process has not yet been applied in sports medicine.

1.4 PRP and sports injury

In the 1990s platelets were introduced into maxillofacial surgery as potent adhesives known as fibrin glues [20]. Since then, the use of PRP has spread to many other clinical areas, for example in injuries due to sportive practices. Several studies have been performed in order to evaluate the efficacy of PRP treatment in athletes with knee and hip osteoarthritis [46, 47], lateral epicondylitis [48], and patellar and Achilles tendinopathy [49]. The majority of results indicate that PRP treatment improves the outcome in this population, with pain relief and healing recovery. The use of PRP is widely disseminated especially amongst high-performance athletes, however little is known regarding how team physicians use this treatment modality. To define the use of PRP from professional sports leagues, in 2018 Kantrowitz et al. distributed an institutional review board evaluation to team physicians in elite athletes. Indeed, the majority (93%) use PRP in their practices, despite a lack of consensus regarding PRP production and its characterization [50].

Even with positive results, as shown in table 1, it remains unknown the PRP characterization and its standardization. In 13 studies, only 5 of them show the platelet concentration after PRP production, being only 1 concerned about growth factor recovery [51]. It was demonstrated higher levels of VEGF, PDGF-BB, PDGF-AB, EGF, IGF, and TGF- β when compared to whole blood, which is related to great outcomes at the end of the study. However, the major limitation of this and other studies (8 of 13), is the absence of a control group. When using a control group, a study consisted of 16 elite athletes (mostly soccer players), treated with ultrasound-guided PRP injections for high ankle sprain injuries, showed early return to play and less pain when compared to a control group, which was treated with immobilization, physiotherapy and anti-inflammatory therapy [52]. Same results were observed in rugby players, with also a single autologous PRP injection [53]. Ideally, studies should be similar to the 2015 study conducted by Hamilton et al., which investigated PRP in 90 professional athletes (mostly football players) with a hamstring injury (Grade I and II), in a randomized three-arm parallel-group trial, investigating the effects of PRP, PPP and without injections. The results showed that the pain relief was faster after PRP treatment, however, they observed no benefit of a single PRP injection over intensive rehabilitation [54]. No growth factor measurement was performed. Since platelet-derived preparations were removed from the prohibited list of the World Anti-doping Code [55], and this therapy is currently considered as a treatment before referring for surgery, it is expected an increasing number of PRP use in sports injury in high-performance in athletes for next years.

Authors	Type of study	Sample amount	Age (years)	Type of sport	Area of injury	Type of PRP and application	Is the PRP obtainment described?	Is the platelet concentration described?	Is the PRP activated?	Number of applications	Return to play/training
Mei-Dan O et al. [56]	Case report	1	30	Judo	Complete rupture of MCL	US-guided injection of PRGF without WBC	No, only referenced	No	N.R	3	5 months post-trauma
Scholten MP et al. [57]	Case report	1	20	Lacrosse	Distal rectus abdominis tendinopathy, with refractory groin pain	US-guided injection of PRP (with WBC) and tenotomy	Yes, Magellan Autologous Platelet Separator	No	N.R	1	6 weeks post-injection, without residual symptoms
Eirale C et al. [58]	Case report	1	27	Football (Soccer)	Complete rupture of MCL	PRP, infiltrated using a 23-gauge needle at the highest tender point	Yes, Biomet Recover	No	No	3	3.5 weeks post-injection, without residual symptoms
Bagwell M et al. [59]	Case report	1	30	Wrestling	Complete rupture of MCL	US-guided injection of PRP (with WBC) and laser therapy	No, only referenced	No	N.R	3	1-month post-injection
St-Onge E, MacIntyre IG, and Galea AM [60]	Case report	1	31	Ice Hockey	Inguinal disruption, with recurrent groin pain	US-guided injection of PRP	No	Yes, 5.4-fold	N.R	2	3 weeks post-injection
McCrum CL et al. [61]	Case series	3	25.6	Ice Hockey	Ulnar Collateral Ligament	US-guided injection of PRP without WBC	Yes, ACP	No	N.R	2	1-month post-trauma
Zanon G et al. [62]	Case series, prospective	25	24.2	Football	Hamstring injury (Grade II)	US-guided injection of PRP without WBC	Yes, in-house obtainment	No	Yes	2 to 3	1-month post-trauma
Hamilton B et al. [64]	Randomized three-arm parallel-group trial	90	26.6	Differ categories, mostly football	Hamstring injury (Grade I and II)	PRP infiltrated using a 25-gauge needle through three injection sites into the site of the muscle	Yes, GPS III Biomet	Yes, 3.2-fold	No	1	3 weeks with PRP, 3.8 weeks with PPP and 3.5 weeks without injections

						injury					
Charousset C et al. [51]	Case series, prospective	28	27	Differ categories, mostly jumpers	Chronic patellar tendinopathy	US-guided injection of PRP without WBC	Yes, ACP	Yes, >2-fold. Also, describe GF concentration	No	3	21/28 at 3 months post-injection
Bubnov R, Yevseenko and Semeniv I [63]	Case-control	30	24	N.R	Acute muscle injury	US-guided injection of PRP with WBC and anti-inflammatory therapy	Yes, in-house obtainment	No	N.R	1	1.4 week with PRP and 2 weeks without PRP
Laver L et al. [52]	Case-control	16	22.3	Differ categories, mostly soccer	Antero-inferior tibiofibular ligaments	US-guided injection of PRGF without WBC	Yes, in-house obtainment	Yes, 2.5-fold	Yes	2	1.3 month with PRP and 2 months without PRP
Samra D et al. [53]	Case-control	21	20	Rugby	Ankle syndesmosis	US-guided injection of PRP	Yes, in-house obtainment	Yes, 3.3-fold	No	1	1.6 month with PRP and 2.3 months without PRP
Rettig AC, Meyer S and Bhadra AK [64]	Case-control	10	23	Football	Hamstring injury	US-guided injection of PRP	Yes, GPS III Biomet	No	Yes	1	3 weeks with PRP and 2.5 weeks without PRP

*PRP-Platelet-rich Plasma; PRGF-Platelet-Rich Growth Factors; PPP-Platelet-Poor Plasma; ACP-Autologous Conditioned Plasma; US-Ultrasound; MCL-Medial Collateral; NR-Non-reported

Table 1: Review of studies evaluating the use of PRP in high-performance athletes.

2. Conclusion

The incidence of injury in high-performance sport is an important concern, especially regarding demand in time to return to the field and the costs associated. Injuries, e.g. anterior cruciate ligament, brings lower shortest career length and sustained decreases in performance that requires careful consideration in the type of treatment. While good outcomes have been previously reported in sports injury, including the use of PRP, its response in professional athletes and how these differ across sports still remains unclear. To our knowledge, this is the first review introducing the use of PRP in elite athletes, and as in other areas, it is clear that PRP urge for regulations and further studies regarding its function and application. The absence of a control group, quantification of platelet and growth factor concentration; different time and type of PRP application; and the lack of standardized targets considering the healing process are warranted.

Acknowledgments

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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