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Platelet-Rich Plasma in Athletics: A promising therapeutic concept ?

By Stéphane Bermon

ABSTRACT

The use of autologous blood-derived growth factors and particularly platelet-rich plasma are gaining popularity among professional athletes and sports physicians. This innovative therapeutic concept relies on the use of various growth factors than can be obtained after centrifugation of the patient's whole blood. This part of so-called Regenerative Medicine could have some practical applications in the treatment of muscle, tendon, ligament, fibrocartilage and joint disease. Although case report studies sometimes show spectacular results in terms of healing and shortened time of recovery after injury, well designed randomised clinical studies remain scarce. The purpose of this article is to provide basic and updated scientific knowledge and practical application concerning the use of autologous blood-derived growth factors in musculoskeletal injuries. Potential benefits and risks related to this therapeutic concept as well as possible interference with the current antidoping rules are considered.

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Introduction

The increasing use of autologous blood-derived growth factors (ABGF) in injured professional sportsmen has recently been reported in the media. Although this concept is not new, it has been accelerated by the availability of new biomedical devices that make the preparation of these growth factors easier and safer. In athletics, the high incidence of muscle or tendon injuries[1] and the quest for an early and optimised return in competition explain the growing popularity of this innovative therapeutic approach. While promising, these new techniques are still under the scope of investigation. The basic biological and clinical aspects of treatments with ABGF are covered in biology and sports medicine publications, but are not always referred to in the relevant coaching literature.

The purpose of this article is to provide simple, updated and practical references concerning the use of ABGF for coaches, athletes and their medical entourages. The benefits, risks and possible limitations of these treatments will also be discussed with special emphasis on the latest anti-doping regulations.

What are Autologous Blood-Derived Growth Factors?

The use of blood-derived products to seal wounds and stimulate healing started with the use of fibrin glues, which are constituted of concentrated fibrinogen and were first described 40 years ago. The use of platelets as a source of growth factors was fortuitous given that the main initial interest was to take advan-

tage of the adhesive and haemostatic properties of fibrin. The clinical value of platelet-rich therapies arose from observations such as enhanced bone formation, anti-inflammatory function and lower incidence of secondary infection after maxillofacial applications[2, 3]. These anti-inflammatory and anti-bacterial effects are attributed mainly to the presence of platelets in these preparations[4, 5]. Platelets are anucleate cells produced in large numbers in the bone marrow, which play an important role in primary haemostasis. Upon coagulation (or activation), platelets secrete a pool of growth factors and cytokines involved in healing.

There are four basic types of ABGF treatment, each used for different purposes. All four are briefly introduced hereafter but the present article will mainly focus on the Platelet-Rich Plasma (PRP) technique.

Whole Autologous Blood Injection

This is the oldest and also the simplest type of ABGF under liquid form. A few millilitres of blood are withdrawn from the patient's vein and immediately re-injected on the wound site. Although it has shown some positive results in the treatment of chronic tendonitis[6, 7], this method is actually less used because there is a lower platelet concentration when compared to PRP method.

Autologous Conditioned Serum

Autologous conditioned serum is obtained after incubating the blood with glass beads and spinning the blood down to extract the serum containing the released growth factors. This method produces a lower amount of growth factors than PRP methods[8] and it was originally described for the production of high amount of inflammatory cytokines such as Interleukin-1 receptor antagonist, Interleukin 4, and Interleukin-10. It has been showed to have some positive effects on muscle lesion healing and control of acute exacerbation of knee osteoarthritis[9, 10].

Platelet-Rich Fibrin

This kind of ABGF is obtained by using similar technique than for PRP (see below), but no anticoagulant agent is added to the syringe before withdrawing the blood. Hence, a sort of fibrin gel containing high amount of platelets is obtained after centrifugation and can be shaped and used as a patch on a graft or a wound. This technique is mainly used in maxillofacial and orthopaedic surgical events.

Platelet-Rich Plasma

PRP is a method 3 that requires a sample of blood to be obtained and then the addition of an anticoagulant, such as anticoagulant citrate dextrose A, in order to prevent platelet activation and clotting before therapeutic use. The sample is spun once or twice (depending on the device used), to separate the red blood cells from the plasma, and to concentrate the platelets in the plasma (see Figure 1). This centrifugation results in the formation of two layers within the plasma – a platelet-poor component, and a platelet-rich component (buffy layer) – the so-called PRP. Thirty millilitres of whole blood provides approximately four millilitres of PRP, depending on the type of preparation system used. Within this final volume of PRP, the final platelet concentration varies from four to eight times the whole blood platelet concentration[11].

The platelets are activated at the time of injection with the addition of Calcium and/or Thrombin. This PRP is then re-injected inside the damaged tissue or joint to be treated. The aim is to enhance healing through delivery of growth factors and theoretical optimisation of the healing process. The main tissues or lesions that can benefit from a PRP treatment are tendon (chronic tendonitis or partial rupture), ligament (medial knee ligament for instance), muscle (recent torn muscle), fibrocartilage (meniscus or labrum) or joint (chondritis or arthritis).

It has been shown that PRP contains the following main cytokines or growth factors[11]:

- Platelet-Derived Growth Factor (PDGF),
- Vascular Endothelial Growth Factor (VEGF),
- Transforming Growth Factor Beta-1 (TGF-b1),
- Epidermal Growth Factor (EGF),
- Basic Fibroblast Growth Factor (bFGF),
- Hepatocyte Growth Factor (HGF),
- Insulin-Like Growth Factor-1 (IGF-1).

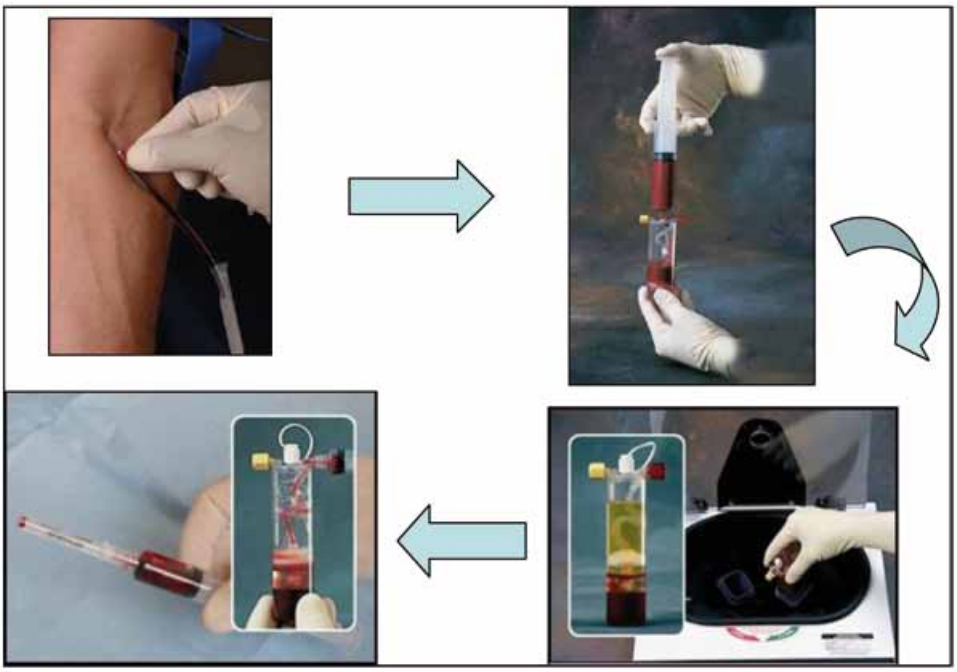

Figure 1: Overview of a Platelet-Rich Plasma making (GPS Device, Biomet®, Warsaw, USA)

The last two of these are plasma-derived whereas the others are platelet-derived factors. These growth factors concentrations appear to be four to 10 times higher in PRP than in whole blood[12].

Laboratory Evidence

Evidence about PRP has been through cell culture or animal studies carried out in the laboratory. Key points are briefly summarised hereafter and in the Table 1.

Tendon

Several studies have reported increased collagen expression, VEGF and HGF production in human tenocytes treated with PRP[13, 14]. PRP also stimulates the mobilisation of circulation-derived cells around the area of injection[15]. Several authors have also reported greater cell proliferation and angiogenesis in animal tendon models treated with PRP[16].

Skeletal Muscle

PRP-derived growth factors have been shown to regulate the inflammatory phase of a muscle injury model and improve healing[17]. IGF-1 and bFGF have also proven to facilitate muscle healing, whereas TGF-b1 plays a pivotal role in the control of the fibrotic response during the muscle healing process[18].

Clinical Evidence

Although further well designed clinical studies are still needed, there is a growing amount of clinical evidence attesting to the efficiency of PRP treatment in musculo-skeletal diseases. For an updated review we strongly advise the reading of the recent articles from HALL et al.[12] and from SAMPSOM et al.[19].

Tendon

Very recently, two articles proved some significant positive effects of PRP in chronic tendonitis. After a gold standard double blind randomised controlled trial, PEERBOOMS et al.[20] reported the results of the first comparison of an autologous platelet concentrate with a corticosteroid injection, as a treatment for lateral epicondylitis in patients who have failed non-operative treatment. They showed that a single

Table 1: Biological roles of the main growth factors concentrated in PRP

Growth Factor	Biological Effect
Platelet-Derived Growth Factor	Stimulates cell replication and angiogenesis, mitogen for fibroblasts
Vascular Endothelial Growth Factor	Angiogenic
Transforming Growth Factor Beta-1	Regulates balance between fibrosis and myocytes regeneration
Epidermal Growth Factor	Proliferation of mesenchymal and epithelial cells, antifibrotic
Basic Fibroblast Growth Factor	Stimulates proliferation of myoblasts and angiogenesis
Hepatocyte Growth Factor	Angiogenic, mitogenic for endothelial stem cells, antifibrotic
Insulin-Like Growth Factor-1	Stimulates myoblasts and fibroblasts, help growth and repair of skeletal muscle

injection of PRP improves pain and function more so than corticosteroid injection and that these improvements were sustained over time with no reported complications.

Similarly, FILARDO et al.[21] used PRP for the treatment of 15 refractory jumper's knee patients who had failed previous nonsurgical or surgical treatments. Following multiple PRP injections into the site of patellar tendinopathy performed on three occasions two weeks apart and physiotherapy, the patients showed significantly higher improvement in pain and physical activity level scores when compared to matched controls.

Muscle

Although case reports seem very promising, randomised double blind human studies are clearly lacking in this field. However, in one study, after ultrasound guided injections of PRGF in 22 muscle injuries of 20 high-level professional athletes, full recovery of functional capabilities was restored in as early as half of the expected recovery time. Furthermore, fibrosis did not appear in any of the treated cases and no re-injuries occurred in any athlete after resuming their normal sports activities[22].

Cartilage

Recently, KON et al.[23] reported interesting preliminary results on 115 chronic degenerative knees treated with three consecutives intra-articular injections of PRP. The authors concluded, for the first time, that the treatment with PRP injections is safe and has the potential to reduce pain and improve knee function and quality of life in younger patients with low degree of joint degeneration. This therapeutic potential must still be confirmed by further, well-conducted randomised studies.

How to Process During and After a PRP Treatment?

Extensive study of the available literature leads to some conflicting opinions regarding the number of injections that should be performed in order to treat musculoskeletal injuries. Although currently there is no consensus, it seems that tendon and muscle injuries should require one to three local injections at one or two week intervals. This interval length is explained by the observation that platelets are viable for seven days and able to release growth factors for approximately one week after concentration and on site injection[24].

As far as joint and cartilage PRP treatment is concerned, it appears from the available publications that at least three intra-articular injections should be proposed to the patient.

Currently, there is a lack of validated protocols for post PRP injection rehabilitation. To the best of our knowledge, there are no studies published so far concerning this aspect. From our experience, we ask our patients for:

- Two weeks of tendon immobilisation (with an articular brace) after an intratendinous injection of PRP and a classical tendonitis rehabilitation programme to be initiated after this period if control imaging gives positive healing result
- To refrain from sports training and light daily physical activity within the course of PRP treatment for muscle or joint pathologies. This period of rest can be extended according the severity of the lesion, the natural evolution of the disease, the imaging control results and the type of rehabilitation protocol.

Risks

Biological risks

Because they are autogenous preparations, ABGF are inherently safe and therefore free from concerns over transmissible diseases such as HIV, hepatitis, West Nile fever, and Creutzfeldt-Jakob disease. ABGF are therefore, well accepted by patients as soon as they receive relevant information and explanations. All modern platelet concentrate devices available on the market are very convenient and simple to use, hence reducing the risk of blood manipulation and contamination by pathogen agents. Although these commercially available devices are more expensive, we strongly encourage athletes or physicians to use them (should they need ABGF treatment), for obvious security and possible legal issues. There were some concerns about the use of bovine thrombin as the clotting initiator owing to the potential development of antibodies against the bovine thrombin. However, bovine thrombin is no longer used in western countries.

A potential local complication of growth factor administration is induction of excessive fibrosis in the healing tissue. Indeed, muscle healing takes place in four overlapping stages (see Figure 2): degeneration, inflammation

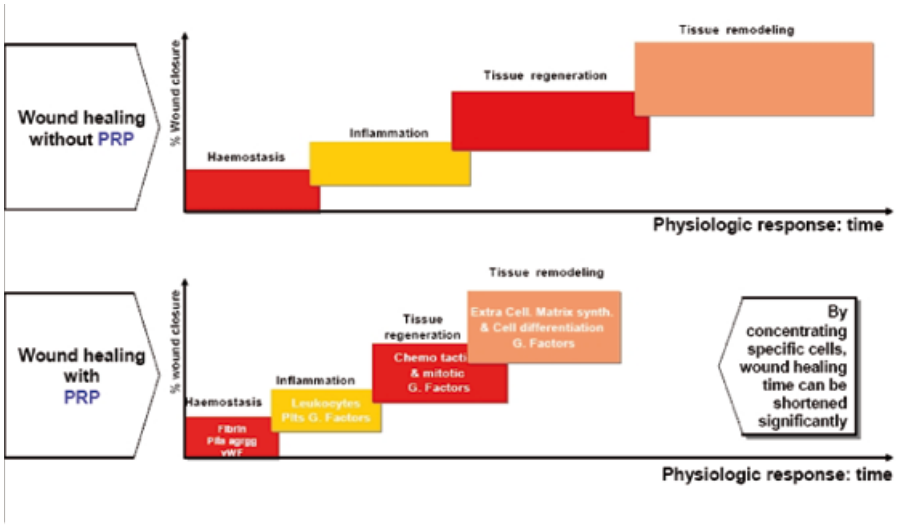

Figure 2: Normal and PRP-improved healing cascade

(first few days), regeneration (beginning day 5, peaking at day 14) and fibrosis (beginning in 2nd week). This last process may become an overly aggressive healing response in extensively injured muscles. Excessive fibrosis is problematic since complete muscle regeneration cannot occur in the presence of fibrosis[25]. TGF-β1 being a key regulator of the fibrotic process (in balance with regeneration), one can speculate that multiple PRP injections in muscle injury may result in increased fibrosis and an impaired final result.

There are no reports in the literature concerning a possible carcinogenic effect of ABGF in humans.

Although not a significant risk, pain can be the main side effect of PRP treatment, especially when injections are performed intratendinous. For tendon repair and treatment, local anaesthesia should be systematically proposed as well as class II pain killers within the 24 hours following the injection.

Cost

The cost of treatments can vary a lot according to the type of platelet concentrate method used and the country. A single treatment can be between 200 and 600 □ and is normally not covered by health insurance.

Antidoping policies

The World Anti-Doping Agency has partly clarified the status of platelet-derived preparations on its 2010 list[26]. Indeed, in paragraph S2 it can be read under the title 5 that Growth Hormone (GH), Insulin-like Growth Factor-1 (IGF-1), Mechano-Growth Factors (MGFs), Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factors (FGFs), Vascular-Endothelial Growth Factor (VEGF) and Hepatocyte Growth Factor (HGF) as well as any other growth factor affecting muscle, tendon or ligament protein synthesis/degradation, vascularisation, energy utilization, regenerative capacity or fibre type switching are substances and methods prohibited at all times (in- and out-of-competition).

Moreover, title 6 says that Platelet-derived preparations (e.g. Platelet Rich Plasma, “blood spinning”) administered by intramuscular route requires a Therapeutic Use Exemption while other routes of administration require a Declaration of Use in accordance with the International Standard for Therapeutic Use Exemptions.

It is very unlikely that the PRP obtained from current techniques and commercial kits produce systemic anabolic effect when injected locally and no scientific data support such a hypothesis. However, addressing a controversy concerning the so-called intramuscular route, the IAAF Medical and Antidoping Commisssion has recently published a position on the ABGF (Figure 3).

Conclusions

ABGF and particularly PRP techniques seem to be of major interest in sports medicine and traumatology. Despite extensive of laboratory evidence, clinical trials proving PRP to be an effective therapeutic concept are scarce. However, many randomised human studies are ongoing with some promising preliminary results. Should clinical efficiency be proven, a lot of work will have to be performed in order to define the optimal PRP devices and protocols as well as specific rehabilitation programmes and recommendations before the athlete can return on the field of play. PRP use still remains an expensive and not widely spread therapy. For these reasons ABGF is mainly used by top-level or professional athletes, most of whom are living or training in developed countries.

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IAAF Position on Platelet-Derived Preparations

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The World Anti-Doping Agency has clarified the status of platelet-derived preparations on its 2010 list. These preparations hereafter are called ABGF (Autologous Blood-Derived Growth Factors) include Platelet-Rich Plasma, (PRP), Platelet-Rich Concentrate (PRC), autogenous platelet gel, platelet releasate or blood-spinning). Intramuscular route for systemic use is prohibited. Local injections for treatment of tendon, muscle, bone and joint injuries are allowed but require a Declaration of Use.

The IAAF Medical and Anti-Doping Commission believes that the use of ABGF reintroduced in PRP or PRF (Platelet-Rich Fibrin) to treat musculotendinous, osteo-articular, bone or orthopaedic injuries under proper medical supervision is not to be considered a doping method. There is no actual evidence that this will enhance oxygen transfer as in „blood doping“ and that it will exert systemic anabolic effects.

The Commission would like to remind athletes and their medical entourage that evidence-based therapeutic alternatives should be used first. These may include but are not limited to rest, physiotherapy, eccentric rehabilitation protocol, electrotherapy, and shockwave treatments.

ABGF is considered investigative treatment but there is growing scientific evidence that this may either decrease healing time and/or lead to a better result. Well-designed, controlled clinical trials are under way and are necessary to determine the therapeutic added value of ABGF.

The Commission warns that iatrogenic risks including infection, inflammation, degeneration, and excessive fibrosis or other untoward effects may occur, when using ABGF.

The IAAF Medical and Antidoping Commission will continue to monitor this procedure. In the future, the IAAF position on ABGF might change accordingly.

Figure 3: IAAF Position on Platelet-Derived Preparations

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