Platelet-rich plasma in sports medicine: hot favourite or non-starter?

Platelet-rich plasma is not a new therapy – it is has been used in clinical medicine for almost 30 years. However, it has only recently come to prominence in the world of sports and musculoskeletal medicine with use in high profile sporting cases. This article examines the basic science and current evidence behind its use.

In the field of sports injury, musculoskeletal injuries require prompt treatment to allow a quick return to the pre-injury level of function. Ideally, any given treatment should, among other factors, be minimally invasive and highly effective, with minimal side effects. One emerging strategy to accelerate tissue healing is the use of platelet-rich plasma. Platelet-rich plasma has been used in clinical practice since the 1980s, in dentistry, maxillofacial surgery and dermatology (Margolis et al, 2001). The treatment developed because platelet-rich plasma is seen as a preparation of growth factors which facilitate rapid healing of damaged tissue. There have been wide variations in agreeing a definition of platelet-rich plasma. It has been defined as a mixture containing at least 1 000 000/μl platelets in 5 ml of plasma, which has a 3–5-fold increase in growth factor concentrations (Marx, 2001). Other studies have accepted platelet-rich plasma to be 400% of the peripheral platelet blood count (1600 x 10^9/litre), although some studies have tried to demonstrate the clinical effectiveness of platelet-rich plasma with still smaller concentrations (634 x 10^9/litre) (Creaney and Hamilton, 2008).

Controversies also exist regarding the method of preparation and delivery of platelet-rich plasma. Further to this, while some in-vitro and animal studies have demonstrated the clinical efficacy of platelet-rich plasma injection, results in human studies have been disappointing, largely as a result of the lack of robustly-designed clinical trials.

This review analyses published studies for the evidence in support of the use of platelet-rich plasma, both in pre-clinical and human studies, in the treatment of sporting musculoskeletal injury.

Platelet physiology and function

In the bloodstream, platelet counts normally range from 150 000–450 000/μl. Platelets contain two types of secretory vesicles that aid clotting function:

- Dense granules contain calcium, histamine and serotonin, which are important in the inflammatory stage of healing
- Alpha granules contain von Willebrand factor, adhesive proteins such as fibrinogen and fibronectin, and various growth factors; the latter play a crucial role in applications of platelet-rich plasma.

Platelet function involves the clotting cascades. Following injury to the vascular endothelium, collagen from the vessel wall is exposed to circulating platelets. von Willebrand factor facilitates platelet adhesion to collagen with platelet glycoprotein receptors. This is helped by adhesive proteins and growth factors activating platelets to participate in the intrinsic coagulation pathway, producing thrombin that converts fibrinogen to fibrin and thus helping to develop the blood clot (Farndale et al, 2007). Alpha granules in platelets store growth factors responsible for the tissue-healing potential of platelet-rich plasma. These are detailed in *Table 1* (Foster et al, 2009). These growth factors have important roles in the healing process and have synergistic function with factors contained in the dense granules of platelets.

Following tissue damage, platelets secrete the contents of these granules. Histamine and serotonin increase capillary permeability, allowing greater access to the wound sites for inflammatory cells. In development of the clot, cell recruitment allows wound healing to continue as the clot forms a scaffold to which cells adhere. These growth factors contribute to further elements of healing, including fibroblast recruitment and synthesis of extracellular matrix proteins, allowing tissue healing (Bennett and Schultz, 1993).

Table 1. Growth factor function

Factor	Function
Platelet-derived epidermal growth factor	Cell growth and recruitment, cytokine secretion, skin closure
Platelet-derived growth factor A and B	Cell growth and recruitment, angiogenesis, growth factor secretion, matrix formation with bone morphogenetic protein
Transforming growth factor β1	Angiogenesis, collagen synthesis, apoptosis, growth inhibition, cell differentiation and activation
Insulin growth factor 1 and 2	Cell growth and differentiation, collagen synthesis
Vascular endothelial growth factor, endothelial cell growth factor	Cell growth and migration, angiogenesis, anti-apoptosis
Basic fibroblast growth factor	Cell growth and migration, angiogenesis

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Studies involving growth factors and tissue repair

Bone

Following bone fracture, growth factors present in platelet-rich plasma are involved in bone healing. A review by Simpson and colleagues (2006) evaluated current theories of the mechanisms involved and concluded that growth factors such as insulin-like growth factor 1, platelet-derived growth factor and vascular endothelial growth factor act to promote osteoblast activity and angiogenesis during fracture repair.

Tendon

Platelet-rich plasma is thought to stimulate tendon repair through pathways involving matrix metalloproteinases (enzymes that degrade the cell matrix). de Mos et al (2008) showed human tenocytes cultured in platelet-rich plasma had increased expression of matrix metalloproteinase-1 and matrix metalloproteinase-3, coupled with increased cell proliferation and total collagen production. Compared with a platelet-poor plasma culture, cell number and total collagen production were equal, although the amount of vascular endothelial growth factor and platelet-derived growth factor was higher in platelet-rich plasma and there was no increased matrix metalloproteinase expression in the platelet-poor plasma culture, leaving uncertainty regarding the exact mechanisms involved.

Muscle

Muscle healing is potentiated by cytokines found in platelet-rich plasma. Menetrey and colleagues (2000) showed that, in a mouse gastrocnemius model, injection of basic fibroblast growth factor and insulin-like growth factor 1 into lacerations enhanced muscle healing and showed increased strength through growth factor-stimulated proliferation of myoblasts, myofibre protein synthesis and activation of satellite cells within muscle fibres.

In-vitro and animal studies of growth factor or platelet-rich plasma injection

Bone

Han and colleagues (2009) investigated the potential of bone healing with platelet-rich plasma in vitro. When added to a demineralized bone matrix, a substrate with its own osteoinductive properties, platelet-rich plasma stimulated a dose-dependent increase in osteosarcoma and marrow stromal cells. These effects were not reproduced when thrombin was added to the cell culture system. Therefore, while platelet-rich plasma could increase osteoinductivity, its effects were inhibited with prior activation with thrombin, limiting its potential clinical application in stimulating fracture healing.

Tendon

Yasuda and colleagues (2004) used a canine model to show how the use of growth factors within platelet-rich plasma can affect biomechanical properties of patellar tendon grafts in anterior cruciate ligament repairs. In ten dogs, anterior cruciate ligament reconstruction was augmented by transforming growth factor β1, epidermal growth factor and a fibrin sealant in the left knee. In a further ten dogs, a fibrin sealant alone was used in the left knee, with no additional treatments made to the right knees of either group. At 12 weeks, through load testing, it was demonstrated that knee repairs receiving growth factor application were significantly more robust than sham and control groups (Yasuda et al, 2004). Weiler et al (2004) used platelet-derived growth factor in the reconstruction of the anterior cruciate ligament in sheep. Mechanical analysis of specimens after 12 weeks, along with histology and electron microscopy, demonstrated that those receiving platelet-derived growth factor had significantly higher tensile strengths and collagen fibril counts than controls, supporting the use of growth factors in aiding mechanical restitution of a healing ligament substitute.

Muscle

Hammond et al (2009) investigated platelet-rich plasma injection for healing in muscle strains. Following either single or multiple injuries to rat tibialis anterior, injections of platelet-rich plasma, platelet-poor plasma and no treatment were compared for return to full contractile function in damaged muscle. Platelet-rich plasma injection resulted in greater muscle regeneration and a faster return to function in the multiple injuries group, but not the single strain group, compared to platelet-poor plasma or no treatment. This was thought to be because growth factor-stimulated myogenesis is not required in single strains.

Human studies of platelet-rich plasma

Chronic Achilles tendinopathy

A double-blind study by de Vos and colleagues (2010) investigated platelet-rich plasma injection in improving outcome in chronic Achilles tendinopathy. They combined an eccentric exercise programme with either platelet-rich plasma or saline injection as a control and used an outcome questionnaire at 6, 12 and 24 weeks that factored in pain improvement and increased activity. They showed that, following injection into the site of pain, both groups showed a significant improvement in scores, implying better function in pain control and activity. However, there was no difference between injection with platelet-rich plasma or saline.

Epicondylitis

Mishra and Pavelko (2006) investigated platelet-rich plasma injection to treat chronic elbow tendinosis. In a group of 140 patients with epicondylar elbow pain, 20 had failed to settle following 15 months of analgesia and physical therapy. Of these 15 then received a single platelet-rich plasma injection compared with five control patients receiving local anaesthetic. After 8 weeks, the platelet-rich plasma group had significantly improved pain scores compared with control studies (60% *vs* 16%). The

platelet-rich plasma group also reported improvement at 6 months of 81% and 93% at final follow up on average 2 years post injection. No complications were reported and no patient complained that the pain had worsened.

Peerbooms and colleagues (2010) compared injection of platelet-rich plasma with corticosteroid in patients with chronic lateral epicondylitis. After 1 year, using visual analogue and the Disabilities of the Arm, Shoulder and Hand (DASH) scoring systems, 73% of the platelet-rich plasma group had a 25% improvement in scores, compared with 51% in the corticosteroid group managing the same level of improvement. This statistically significant improvement prompted the authors to hold platelet-rich plasma injection as a more superior intervention than the gold standard of corticosteroid injection for treating lateral epicondylitis. In this study, platelet-rich plasma was given as a single injection while corticosteroid was used with a 'peppering technique'; this highlights similar issues with other studies in that no single injection technique has been reproduced consistently.

Rabago and colleagues (2009) performed a systematic review comparing platelet-rich plasma to other injection therapies. Collecting data relating to treatment of lateral epicondylitis, the group appraised existing evidence for:

- Prolotherapy, involving an injection of an irritant substance into tissue to stimulate healing via an inflammatory response
- Polidocanol, a vascular sclerosant that exerts its effects by negatively impacting upon neovascularity, one of the main underlying mechanisms thought to be associated with overuse tendinopathies
- Whole blood, acting in the same way as platelet-rich plasma by providing growth factors to induce healing
- Platelet-rich plasma.

Existing data were promising for each of the four modalities in effectively treating refractory lateral epicondylitis, although this was limited by the lack of large definitive trials. In addition, there were no comparative studies to show that one injection therapy was superior to the others (Rabago et al, 2009).

Muscle strains

Wright-Carpenter and colleagues (2004) injected 29 professional athletes who had suffered muscle strains with either serum with similar properties to platelet-rich plasma or a control of Actovegin, a substance thought to improve tissue regeneration. Those receiving platelet-rich plasma-like serum returned to full participation in activity in a significantly shorter time period than controls, although heterogeneity existed regarding the types of muscle strain injected.

Operative uses

Silva and Sampaio (2009) investigated platelet-rich plasma in enhancing repair of the ruptured anterior cruciate ligament. They recruited 40 patients with acute anterior cruciate ligament rupture for arthroscopic reconstruction with hamstring tendon grafts. Patients were sequentially organized into four groups to have surgery and:

- No platelet-rich plasma (group A)
- Platelet-rich plasma in femoral tunnels at the end of surgery (group B)
- Platelet-rich plasma in femoral tunnels at the end of surgery with intra-articular knee injections at 2 and 4 weeks post-surgery (group C)
- Thrombin-activated platelet-rich plasma in femoral tunnels at the end of surgery (group D).

Magnetic resonance imaging graded signal intensity from the area between graft and tunnel wall, termed the fibrous interzone, in healing grafts in comparison to patella tendon, with healing composition graded 0 (tendon density) to grade 3 (fluid density). Following standard rehabilitation, imaging 3 months postoperatively showed that signal intensity in femoral canals relating to the fibrous interzone was equal among all groups, inferring that platelet-rich plasma gave no accelerated healing benefits with respect to graft fixation. In addition, no clinical outcome data were recorded, nor any rates of graft failure (Silva and Sampaio, 2009).

Use of platelet-rich plasma in sports and doping concerns

Platelet-rich plasma came to the forefront of sports medicine when an article in the *New York Times* highlighted that two American footballers had been treated with platelet-rich plasma for their respective injuries before winning the Super Bowl (Schwarz, 2009). However, anecdotal and isolated case reporting aside, there is no trial-based evidence for use of platelet-rich plasma in athletes. One of the main reasons is uncertainty regarding classification of platelet-rich plasma as a banned substance; insulin-like growth factor 1, a constituent of platelet-rich plasma, is on the World Anti-Doping Agency prohibited list, as are platelet-derived growth factor, fibroblast growth factor, vascular endothelial growth factor and hepatocyte growth factor. The concentration of each of these growth factors is within physiological ranges in platelet-rich plasma preparations. In addition, there has been controversy surrounding the use of platelet-rich plasma injections in muscle injury, with its use first being placed on the prohibited list before being removed in 2010, so clarification from the World Anti-Doping Agency is needed for regulation guidelines before robust studies in athletes can be performed (Mei-Dan et al, 2010).

Preparation of platelet-rich plasma

There are currently several machines available on the market that centrifuge patient blood to separate the platelet-rich plasma for therapeutic use; this can be performed within minutes in the clinic or operating room. Different spinning programmes yield different concentrations of platelet-rich plasma. The preparations are then activated with the addition of calcium chloride or human thrombin which activate the clotting cascade (Mei-Dan et al, 2010).

Conclusions

The evidence for the use of platelet-rich plasma injection therapy in sports medicine is scarce and controversial. It is universally accepted that platelets have an important role in wound healing and tissue growth. Platelet-rich plasma is believed to exert its benefits through its higher concentration of platelets and growth factors to promote cell recruitment and healing activity in bone, muscle and tendon. In addition, some studies have shown that this may accelerate healing in rudimentary animal models. Unfortunately, human trials to date have not shown this to be the case. In treatment of Achilles tendinopathy and epicondylitis, platelet-rich plasma has not shown a more favourable healing result compared to other injection therapies. Platelet-rich plasma has also not been shown to accelerate healing following intraoperative use. Finally, while reports emerge of the success of platelet-rich plasma in athletes in the lay press, there is no convincing trial evidence to support its use in athletes.

It is important to consider why we have no definitive answers on the efficacy of platelet-rich plasma in treating sporting injuries. In the arena of sports medicine, where injured elite athletes rely on new methods to expedite healing and a return to top-level activity, the latest technology is often embraced with great enthusiasm. However, particularly in the case of platelet-rich plasma, it would appear that the uses for this technology are outpacing the basic science and clinical evaluations required to validate its efficacy.

Future researchers looking to make definitive conclusions on the benefits of platelet-rich plasma in sports medicine have much to establish:

- What is the optimal protocol for preparation and injection of platelet-rich plasma? In many studies, the volumes of injection, injection technique, timing in relation to injury, optimal post-injection rehabilitation programme and number of injections have all varied, thus creating heterogeneity of methods among studies
- For which type of tissue, and therefore injury, could platelet-rich plasma have the most benefits?
- Should injection therapy replace or augment current standard rehabilitation programmes?

It is only when these questions have been answered with well-designed clinical trials that platelet-rich plasma could claim to have a recognizable role in sports medicine.

KEY POINTS

- Platelet-rich plasma has emerged as a therapeutic strategy in sports medicine in the past decade.
- The perceived benefit of platelet-rich plasma involves using higher-than-physiological concentrations of platelets to enhance soft tissue healing.
- In-vitro and animal studies have demonstrated faster tissue healing and quicker return to function.
- Human studies have failed to convincingly show a clear benefit of platelet-rich plasma over other injection therapies.

In spite of trials promoting the basic science of its growth factors, there remains little robust evidence to support the use of platelet-rich plasma injection therapy in sports medicine. **BJHM**

Conflict of interest: none.

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