INTERNATIONAL
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COMMITTEE

IOC Consensus Statement on the use of platelet-rich plasma (PRP) in sports medicine

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1. Introduction

Acute and chronic musculoskeletal injuries in sports are common and problematic for both athletes and clinicians. A significant proportion of these injuries remain difficult to treat, and many athletes suffer from decreased performance and longstanding pain and discomfort.

In 2008, the International Olympic Committee (IOC) published a consensus document on the importance of molecular mechanisms in connective tissue and skeletal muscle injury and healing. This document predicted an increase in the use of autologous growth factors, as it has indeed happened following that publication.

Platelet Rich Plasma (also referred to as platelet-rich in growth factors, platelet-rich fibrin matrix, platelet-rich fibrin, fibrin sealant, platelet concentrate) is now being widely used to treat musculoskeletal injuries in sports and draws widespread media attention despite the absence of robust clinical studies to support its use. Of the few studies on the effectiveness of PRP in clinical settings have been published, only very few are of sufficient methodological quality that would enable evidence based decision making.

PRP and its variant forms were originally used in clinical practice as an adjunct to surgery to assist in the healing of various tissues. PRP has also been used in prosthetic surgery to promote tissue healing, implant integration, and to control blood loss. Furthermore, the application of activated PRP has an effect on pain and pain medication use following open sub acromial decompression surgery.

Initially, PRP was mainly used in oral surgery. Subsequently, PRP has also been used at the time of surgery involving shoulder, hip, and knee joint procedures, including anterior cruciate ligament reconstruction, and it has been used to improve bone healing. More recently, PRP in an injectable form has been used for the management of common muscle, tendon, and cartilage injuries. As predicted by the 2008 IOC consensus document on the molecular mechanisms in connective tissue and skeletal muscle injury and healing, there is significant anecdotal evidence that the use of PRP for treating musculoskeletal injuries has increased in recent times. Currently, PRP is not considered as a drug or a therapeutic substance, and therefore it does not have the usual regulatory requirements that would generally be needed for a substance used in regular clinical practice.

To discuss the use of PRP in a clinical setting, and the need for further research, the IOC assembled an expert group in May 2010 to critically review the current state of PRP treatment among athletes, aiming to provide recommendations for clinicians, athletes, and individual sports governing bodies. The purpose of this consensus paper is furthermore to review the evidence for the clinical effectiveness of PRP, its ergogenic potential and safety, and attempt to reconcile any possible disparity between its increasing popularity and the underlying science supporting its use.

After an introduction into the basic science of PRP (i), the group considered the following issues regarding PRP use in clinical practice; (ii) the role of PRP in muscle injuries; (iii) the role of PRP in tendon injuries; (iv) the role of PRP in cartilage injuries and the healing of other tissues; (v) suggested techniques for the application of PRP and post-injection recommendations; (vi) potential adverse effects of PRP use; (vii) developing a RCT on PRP; (viii) PRP and Anti-Doping regulations; and (ix) summary and recommendations.

(i) Basic science of PRP

In broad terms, PRP may be defined as a volume of the plasma fraction of autologous blood having a platelet concentration above baseline, and is therefore a concentrated source of autologous platelets. Platelets contain a number of growth factors that play an important role in the healing of injured tissue. PRP is prepared from a volume of autologous blood using extra-corporeal blood processing techniques such as blood cell savers/separators, table-top devices (centrifuges) and filtration methods. This volume may contain variable concentrations of red and white cells depending on the specific preparation technique that is used.

Not only can PRP be prepared in a variety of methods, but it can be administered in various forms; this diversity is reflected by the number of terms used to describe the product (Table 1). These variations will inevitably influence the composition and potential effectiveness of the biologically active material.

Table 1: Names of production devices and products

Technology summary	Device name	Name of product	Increase of platelet number per mL above baseline	Platelet recovery (%)	Prepared product content
Floating Buoy or shelf	Biomet GPS™	PCP	3.2 x	70	Buffy coat product: concentrated Platelets, WBC fractions and minimal amount of RBC
	Harvest® SmartPrep2 BMAC™ Depuy Symphony II	PRP	4.6 x 4.0 x 4.0 x	72	
Cell Saver Based Systems	Electa, Haemonetics, CATS, BRAT	PRP	4-6 x	75	Platelet concentrate only
Computer Aided System	Sorin Angel	PRP	4.3 x	70	Buffy coat product: concentrated Platelets, WBC fractions and minimal amount of RBC
	Arteriocyte Medical (Magellan™)	PRP	5.1 x	76	
Standard Centrifugation	AutoloGel System Smart PReP	PRP	1-2 x	78	Platelet in plasma suspension with minimum white cells and low concentration of Platelets
	Cascade PRFM Fibrinet system	PRFM	1-2 x	78	Platelet rich fibrin membrane
	Choukroun's PRF	PRF	1-2 x	70	Leukocyte and Platelet rich fibrin
Direct Siphoning	GenesisCS	PRP	6 x	68	concentrates of platelets, leukocytes through siphoning device
Direct Aspiration	Secquire Arthrex ACP	PRP ACP	1.6 x	31	Manual aspiration of platelet and plasma after centrifuging
Platelet Separation	Vivostat	PRF FS	6 x	65	Platelet Rich Fibrin Fibrin Sealant without Platelet
Platelet Filtration	Caption	PC	4.3 x	-	Concentrated platelets without plasma

PRP=platelet-rich plasma, PRGF=plasma-rich in growth factors, PRFM=platelet-rich fibrin matrix, PRF=platelet-rich fibrin, FS=fibrin sealant, PC=platelet concentrate, ACP=autologous concentrated plasma, PCP=platelet concentrated plasma

Allogenic fibrin glue was originally described in 1970, and is formed by polymerizing fibrinogen with thrombin and calcium. The first reference in the scientific literature to the use of PRP in clinical practice dates back to 1987, when PRP was used as an autologous transfusion component after open heart surgery to prevent the need for a homologous blood product transfusion. In 1990, an autologous fibrin gel (fibrin sealant or fibrin glue) was introduced; a biomaterial with hemostatic and adhesive properties. In 1999, the first autologous PRP prepared from a small quantity of blood was described.

Despite limited scientific support, musculoskeletal practitioners began using PRP for the management of cartilage problems as early as 2003. The use of PRP in many fields of medical practice has recently expanded rapidly, with many articles being published.

This results in part from its relative ease of use, relatively low cost, and a strong commercial industry investment, with the yet unsubstantiated promise that it may prove to be highly effective. In particular, in athletes with sporting injuries, especially in elite athletes where there is a relative urgency to facilitate a rapid return to competition, the use of PRP has expanded rapidly.

Platelets are cytoplasmic fragments of megakaryocytes that are formed in the bone marrow. They are the smallest of the blood components, with irregular shape and a diameter of 2-3 μm. They lack nuclei, but contain organelles and structures such as mitochondria, microtubules, and three forms of granules (alpha, delta, and lambda). The alpha (α) granules, bound by a membrane, are formed during megakaryocytes maturation and are about 200 to 500 nm in diameter. There are approximately 50 to 80 granules per formed platelet. They contain more than 30 bioactive proteins, many of which play a role in haemostasis or tissue healing. However, the entire and exact function of these proteins remains to be elucidated. These proteins are accumulated in α granules, and platelets contain distinct subpopulations of α granules that undergo differential release during activation, a potentially important point in understanding how PRP is activated and acts. Platelets contain, synthesize and release large amounts of biologically active proteins that promote tissue regeneration. Researchers have identified more than 1100 types of proteins inside platelets or on their surface. The most commonly studied platelet proteins include platelet-derived growth factor (PDGF), transforming growth factor (TGF-β), platelet-derived epidermal growth factor (PDEGF), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), fibroblastic growth factor (FGF), epidermal growth factor (EGF) and cytokines including proteins such as platelet factor 4 (PF4) and CD40L. Chemokines and newly synthesized metabolites are also released (Tables 2 and 3).

Table 2. Growth factor release and their possible roles

Growth factor	Effect
PDGF	• Angiogenesis, macrophage activation • Fibroblasts: proliferation, chemotaxis, collagen synthesis • Enhances the proliferation of bone cells
TGF-β	• Fibroblasts proliferation • Synthesis of type I collagen and fibronectin • Induce deposition of bone matrix, inhibits bone resorption
PDEGF	• Stimulates epidermal regeneration • Promotes wound healing by stimulating the proliferation of • Keratinocytes and dermal fibroblasts • Enhances the production and effects of other growth factors
VEGF	• Vascularization by stimulating vascular endothelial cells
IGF-1	• Chemotactic for fibroblasts and stimulates protein synthesis. • Enhances bone formation
PF-4	• Stimulate the initial influx of neutrophils into wounds. • A chemoattractant for fibroblasts
EGF	• Cellular proliferation and differentiation

Table 3. Growth factor receptors expression in musculoskeletal tissues (Ljungqvist 2008)

Growth factor	Muscle	Tendon/ligament	Cartilage	Bone
GH	+	+	+	+
IGF-1	++	+	+	+
MGF	+++	+	?	?
β-FGF	+	±	+	+
PDGF	-	±	-	±
VEGF	+	±	-	-
TGF-β	±	±	+	+
BMP	+	-	+	-

Abbreviations: B-FGF=basis fibroblast growth factor, BMP=bone morphogenic protein, GH=growth hormone, IGF-1=insulin-like growth factor-1, MGF=mechano growth factor, PDGF=platelet-derived growth factor, TGF-β=transforming growth factor-β, VEGF=vasucular endothelial growth factor

The basic premise of PRP use in clinical practice is to facilitate the application of autologous plasma and platelet-derived proteins, in addition to developing at the desired location a fibrin scaffold that can act as a temporary matrix for cell growth and differentiation to assist repair in the injured tissue.

PRP can be prepared in a laboratory, an operating theatre or an appropriate room in the outpatient clinic from blood collected in the immediate pre-therapeutic period. A sterile technique is followed when blood withdrawing, preparing and applying PRP. PRP can be applied percutaneously or during an open surgical procedure as fluid injections, gel, releasate serum or mixed with other biological active materials such as bone and ligament grafts. During open procedures, PRP is activated to form a gelatinous mass to facilitate ease of application. During closed procedures, more applicable to sporting injuries such as soft tissue muscle and tendon injuries, PRP is injected by a syringe in a fluid form. It is recommended that the injections are administered under ultrasound guidance, assuring the exact location of the product placements.

Platelets begin to actively secrete these proteins within 10 minutes of clotting, and more than 95% of the pre-synthesised growth factors are secreted within one hour. After the initial burst of growth factors, the platelets synthesize and secrete additional growth factors for the remaining several days of their life span.

When using anticoagulated PRP, activation is critical, as clotting results in the release of growth factors from the α-granules (degranulation) of the platelets. PRP may be activated immediately before application. Alternatively, activation can occur *in vivo*, i.e. with or after the injection in the tissue of interest. There is no consensus on the timing of PRP activation, or even whether activation is necessary at all. Furthermore, there is currently no consensus on whether the PRP is better activated *in vitro* and placed *in vivo,* or whether we allow the local environment (*in vivo*) to activate. Originally, bovine thrombin was used as an activating agent, but the rare and major risk of coagulopathy from antibody formation has restricted the routine use of bovine thrombin. Calcium chloride and autologous prepared thrombin offer an alternative pre-infiltration, *in vitro* activation means. Soluble type 1 collagen is equally effective as bovine thrombin in activating PRP. By relying on this pathway of activation of PRP by soluble type 1 collagen, PRP can be injected inactivated and thus be activated by the presence of type 1 collagen *in vivo* in the tissue, the same principle followed when PRP is used at time of surgery.

In vitro, the application of PRP enhances gene expression of the extracellular matrix proteins, collagen production, and tenocyte proliferation. Studies demonstrated the mitogenic activity of PRP, and also that stimulated tenocytes synthesize important growth factors such as VEGF and HGF, suggesting a beneficial effect for the management of tendon injuries by inducing cell proliferation and promoting the synthesis of angiogenic factors during the healing process. Animal studies have confirmed the usefulness of platelet concentrate in acute tendon injury, but this benefit of PRP is negated if the tendon is immobilised ,and hence no mechanical stimuli are applied to the tendon during the critical healing period.

Many platelet derived growth factors are also involved in the homeostasis of articular cartilage. These growth factors have been studied *in vitro* and *in vivo* in animal models, and demonstrate some benefit for their potential in assisting cartilage repair, although the evidence of their efficacy in humans is still lacking. The growth factors described in most of the studies include the transforming growth factor-beta super-family (TGF-β), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF) and fibroblast growth factor (FGF). Basic science studies have also documented the important role of growth factors in ligament and meniscus homeostasis and repair. For example, PDGF, TGF-β1 and βFGF are actively involved during the early stage of medial collateral ligament (MCL) and anterior cruciate ligament (ACL) healing, and several growth factors are also effective for meniscal regeneration.

In human tenocyte culture studies, PRP, but also Platelet Poor Plasma (PPP), stimulates cell proliferation and total collagen production. PRP, but not PPP, slightly increases the expression of matrix-degrading enzymes and endogenous growth factors. This demonstrates the complex nature of PRP with more *in vitro* and *in vivo* studies being required to delineate the clinical practicality of such findings.

In addition to healing ability, PRP may also contain antibacterial effects that could demonstrate clinical benefits. PRP or platelet-leukocyte rich plasma (PLRP) prepared by two-step centrifugation of whole blood contains high concentrations of platelets and leukocytes. Both platelets and leukocytes play an important role in antimicrobial defense by performing opsonophagocytosis, chemotaxis, and oxidative microbicidal activity. Furthermore, platelets and leukocytes can release a variety of small cationic peptides (antibacterial peptides) that, upon contact with pathogens, exert bactericidal activity via a non-oxidative mechanism. Another potential advantage is that *in vitro* and *in vivo* data have shown that these peptides possess potent microbicidal activities with minor cytoxicity for relevant mammalian cells. Thus, PRP may act in cooperation with host immune defence system to defend invasion of pathogens.

At present, there are no published applications of the antibacterial effect of PRP in sports medicine. However, in a study evaluating the effect of PRP on the postoperative wound healing process in patients receiving total knee prosthesis, 5% of patients not treated with PRP developed a superficial wound infection compared to none in the PRP group. PRP eliminated superficial and deep wound infections in a study on the use of PRP in cardiac surgery. *In vitro*, PRP gel displays antibacterial activity toward several bacterial strains, especially, methicillin sensitive and resistant *Staphylococcus aureus*. The antibacterial effects of PRP are transient, lasting for only 2-6 hours.

In summary, the antimicrobial effect of PRP and its use in clinical practice is, as its role in healing and repairing cells and tissue, yet to be fully elucidated. However, there could be a future use for PRP in both the prophylaxis of infection, in particular for surgical wounds, and as adjuvant to normal treatment regimes.

(ii) The role of PRP in muscle injuries

Muscle strain and contusion injuries are common in sports, and result in time loss from training and competition. In many sports, particularly the football codes, muscle injuries are the single largest cause of time loss from injury. However, despite advances in rehabilitation programs, re-injury rates for muscle injury remain high. Historically, the management of muscle injuries has involved the use of various stretching and strengthening regimes underpinned by a graduated return to activity and subsequent return to sporting competition. These management strategies lack sound scientific support.

The rapid return to functional activity and minimization of recurrence is the goal of any management intervention. In the past there has been little direct intervention. However, to facilitate an earlier return to sporting competition and with less risk of injury recurrence, invasive techniques using various substances are currently being considered for use. These include traumeel (a homeopathic anti-inflammatory), actovegin (protein-free extract obtained from filtered calf blood), growth factors such as IGF-1 and PRP. None of these proposed interventions, however, have any evidence base for their use in the treatment of muscle injuries. While the use of recombinant growth factors for muscle injuries has a strong theoretical and scientific basis, cost, side effects and prohibition by WADA contra-indicate their use in athletes. While acknowledging that the mode of delivery of growth factors (bolus versus sustained release) may significantly impact upon the clinical outcome in injured muscle tissue, the recognized physiological benefits of recombinant growth factors include the enhancement of muscle regeneration and minimization of scarring.

By contrast, while anecdotally being widely used in elite sport, the use of PRP for acute muscle injuries has little scientific support with very few studies in either animals or athletes.

In one study, 100 μL of PRP were repeatedly injected into the rat tibialis anterior muscle, which had been injured by super-imposing a maximal isometric contraction onto either a single lengthening (large strain) or a series of multiple lengthening contractions (small strain). This resulted in a functional improvement in large strain injury rats at day 3, and small strain injury rats at days 7 and 14 when compared to the rats that had a similar injury but with no PRP injected. Furthermore, evidence of elevated myogenesis was observed in the PRP treated group, but only in the small muscle strain injury model. Notwithstanding the observed outcome variability depending on the injury model utilized, and the unknown transferability of rat data to humans, this early research provides some support for the use of PRP in promoting muscle injury regeneration.

While not strictly PRP, another study investigated the potential of autologous growth factors to enhance recovery from muscle strain injury using autologous conditioned serum (ACS). By injecting 5 mL of autologous ACS, they compared the return to play time of 18 professional athletes with muscle strain injuries treated with ACS, with 11 athletes treated with traumeel and actovegin. While the authors report a significant reduction in return to play time for the treated group (16 versus 22 days), the large number of methodological concerns, including choice of control, lack of randomization, lack of blinding and potential bias of the MRI, limit its interpretation. These two studies are the only studies present in the published scientific literature demonstrating the paucity of evidence for use of PRP in muscle strain injury.

There are also two case reports utilizing PRP for treating muscle strain injuries. One described the use of serial PRP injections in a 35 year old professional body builder with an ultrasound confirmed adductor longus muscle injury. While the authors suggest that the recovery of this athlete was assisted by the PRP injections, the data presented provides only limited evidence for this. In the second case report, a single dose of injected PRP resulted in the rapid resolution, both clinically and at MRI, of a grade II semimembranosus muscle strain injury. This case also shows growth factor levels within the PRP consistent with previous reports, with the athlete experiencing no adverse effects from the procedure at 12 month follow up.

In summary, at present there is little scientific support for the use of PRP for the management of muscle strain injuries. This provides challenges for clinicians hoping to utilize this technology to treat this common sporting injury. Optimal timing, dose, volume, frequency, content and post injection rehabilitation techniques require future clarification in order to provide any coherent guidelines and future research should address these areas. However, as basic science supports the use of specific growth factors in muscle regeneration with minimization of muscle scarring, further investigation of the utility of PRP injection is warranted.

(iii) The role of PRP in tendon injuries

Chronic painful tendon disorders are common invalidating conditions in athletes, who can also suffer from acute and chronic, partial and complete, tendon tears. Tendinopathic lesions can occur along the entire course of the tendon (osteotendinous junction, main body of the tendon, musculotendinous junction). The surrounding tissues such as the tenosynovium and the peritendon can be affected alone or in combination with the main body of the tendon. Tendinopathy is characterized by swelling, pain and inability to perform at full capacity.

Despite the morbidity associated with tendon problems in athletes and an abundance of therapeutic options, management is far from scientifically based, and many of the therapeutic options in common use lack scientific support. Although tendon biopsies show an absence of inflammatory cell infiltration, anti-inflammatory agents (non-steroidal anti-inflammatory drugs and corticosteroids) are commonly used, but their efficacy and effectiveness is dubious. In most instances, the rate of success using anti-inflammatory agents, defined as improvement of symptoms and return to sport, is in the region of 65%, and the time to return to sport ranges from several weeks to several months.

PRP is one treatment that is a considered option for management of chronic tendon injuries in athletes, with a positive effect of PRP on tendon healing having been established in several animal studies. In one of these studies, PRP was percutaneously injected into the transected rat achilles tendon.

This increased tendon callus strength and stiffness by about 30% after one week, and mechanical testing indicated an improvement in maturation of the tendon callus when compared to controls. Another study showed that locally injected PRP in the rat patella tendon increased the activation of circulation-derived cells and the immunoreactivity for types I and III collagen at the early stages of tendon healing. Finally, the osteoinductive effect of PRP on tendon-to-bone healing was evaluated on a sheep infraspinatus repair model using MRI scan and histology. This study demonstrated an increased formation of new bone and fibrocartilage at the healing site.

Most of the scientific publications involving the use of PRP on human tendons are case studies, with the majority of them being of poor methodological quality (Table 4). Studies on Achilles tendons, patellar tendons, wrist extensors, and supraspinatus tendons have been published. At the moment, only few level I studies (randomized controlled trials) have been published or are in press. One of these studies demonstrated a positive effect on human wrist extensor tendons following the injection of PRP, whereas the other study performed on achilles tendinopathy did not demonstrate any significant benefit from the injection of PRP. There is limited evidence that PRP exerts a beneficial effect in surgical repair achilles tendon, with earlier recovery from the procedure. In the rotator cuff, the evidence is contrasting. Two investigations suggest that injected PRP is beneficial in patients with chronic patellar tendinopathy.

It is difficult to formulate indications for the use of PRP on tendon injuries in a clinical setting based on the available scientific evidence. In a recent review investigating the use of autologous blood products, including PRP, in the management of tendinopathy, only three studies on PRP had adequate methodology. All these three studies considered to have adequate methodology did not demonstrate any significant benefit from the injection of PRP into injured tendon.

In summary, there is a lack of well designed studies to support the use of PRP in clinical settings in the management of tendon injuries. More research on basic science and the clinical application of PRP needs to be undertaken before there is any comprehensive recommendation for PRP administration in injured human tendons. For each individual athlete and circumstance a risk/benefit analysis should be performed before embarking on this as yet scientifically unproven therapeutic modality.

Table 4: Studies on platelet-rich plasma and tendinopathy

Reference	Level of evidence	Tendon	Patients (n)	Follow-up	Outcome	Complications
Perbooms et al.	Prospective randomized study (Level I)	Elbow extensor or flexor tendon	100	52 weeks	DASH score improved in both groups, but sign. much more in the PRP group	No
De Vos et al.	Prospective randomized study (Level I)	Achilles tendon	54	24 weeks	Mean VISA-A score improved in both groups, however, no sign. group differences	No
Randelli et al.	Prospective randomized study (Level I)	Rotator cuff tendon	55	104 weeks	Sign. better external rotation strength, and higher SST, UCLA, Constant scores 3 mo after surgery, but no group differences after 2 yrs (only for sub-groups)	No
Castricini et al.	Prospective randomized study (Level I)	To be completed				
Mishra & Pavelko	Prospective cohort study (Level II)	Elbow extensor or flexor tendon	20	25.6 months (12-38 months)	Reduction of visual analog pain score (93% of treated patients)	No
Filardo et al.	Prospective cohort study (Level III)	Patellar tendon	31	6 months	Sign. improvements in Tegner score, EQ VAS score and pain level	No
Gawedal et al.	Case-control study (Level III)	Achilles tendon	14	18 months	AOFAS scale improved from 55 to 96 points VISA-A scale improved from 24 to 96 points	No
Sánchez et al.	Case-control study (Level III)	Achilles tendon	12	32-50 months	Earlier regain of RO, and less time to start running and training	In the control group (wounds)
Kon et al.	Cohort study (Level IV)	Patellar tendon	20	6 months	Improvements in Tegner, EQ VAS and SF 36 scores	No

VAS: visual analogue scale; SF-36: Short Form (36) Health Survey; EQ-5D: EuroQol-5D; VISA-A: Victorian Institute of Sport Assessment-Achilles

(iv) The role of PRP in cartilage injuries and the healing of other tissues

Cartilage, ligament, meniscal and labral injuries are common in athletes. Treatment options vary from traditional conservative management, to minimally invasive techniques, for example corticosteroid injections, to surgery. Sports medicine physicians are faced with the additional challenge of high expectations regarding the resolution of these difficult athletic injuries in an accelerated fashion.

PRP injection has been proposed as a novel treatment modality for the management of articular cartilage injuries of the knee, hip and ankle. Even though clinical evidence is lacking some basic research supports the use of PRP derived growth factors to improve tissue healing. As articular cartilage injuries are such a large cause of athlete morbidity, and morbidity in the wider general community, any procedure or method that may assist in the reduction of morbidity in these athletes would be most welcome. Hence, this has produced an increased interest in PRP application for injured joints. The most common reported method of clinical application consists of multiple intra-articular injections of PRP.

There are few published clinical studies on the use of PRP in cartilage pathology. In a pilot study of 100 patients with osteoarthritis of the knee receiving intra-articular PRP injections, favourable results with pain reduction and improved function were reported. Potential side effects of the injections were also monitored. Only minor adverse events, such as a mild pain reaction and effusion after the injections, have been reported. Patients were followed up at 2, 6, 12 and 24 months. Statistically significant improvement was observed in all the variables evaluated. However these positive beneficial effects of pain reduction and improved function were reduced at the 12 and 24 month follow up with a median duration of the beneficial effect of nine months.

In another study, a larger and longer beneficial effect in pain reduction and improved function after PRP injection into affected knees was documented in young males with a low BMI and a low degree of cartilage degeneration. Other patients in this study demonstrated less durable results.

The intra-articular injection approach for the management of degenerative joint disease has also been compared with another treatment commonly used in clinical practice. An observational retrospective cohort study in patients with knee osteoarthritis that compared PRP injections with hyaluronan injections demonstrated better pain control and an improvement in physical function in the intraarticular PRP group. Philippon et al. have published two papers on the use of PRP in the hip joint. However, no long-term follow-up is available.

Several growth factors may improve meniscal regeneration with the regenerative effect of PRP on meniscal cells having been documented both *in vitro* and *in vivo*, but there is a lack of clinical studies to prove its efficacy in human applications. One study has explored the role of PRP to augment meniscal repair and reported favourable outcomes, though scientific evidence for the clinical efficacy of this approach is limited to this single study, and any clinical use in this context has been limited.

Some preliminary findings reported results with the use of PRP to augment ACL reconstruction. PRP was used with hamstring double bundle ACL reconstruction aiming to accelerate tendon-to-bone integration in the femoral tunnel, and therefore allowan earlier and safer return to sport. MRI performed three months after surgery failed to demonstrate an acceleration of PRP on tendon-to-bone integration. Other investigations using PRP on ACL reconstructions have demonstrated theoretical benefits on the use of PRP. One study showed no significant effects of the platelet concentrate on the osteoligamentous interface or tunnel widening evolution. However, the graft maturation as evaluated by MRI signal intensity was enhanced. Another recent study demonstrated a 48% shortening of the time required to achieve a complete homogeneous graft signal, measured by MRI, when PRP was added.

The available clinical studies on PRP as a treatment option for articular injuries to the ankle, knee and hip are listed in Table 5. These reports on the use of PRP through intra-articular injections suggest a good potential in favouring pain reduction and improved function, but the methodology of these studies is questionable. The best procedure and proper application modalities still need to be defined. The procedures may vary widely among different groups not only for the type of platelet concentrate used, but also for many other aspects, such as number and frequency of injections, activation methods, storage modalities and associated treatments. At present, it is also not known how applicable the results of PRP being used for treating degenerative articular injuries in non-athletes would be for the active athletic population.

Table 5. Studies on platelet-rich plasma and intra-articular lesions.

Reference	Number	Study design	Inclusion criteria	Intervention	Control group	Primary outcome measures	Follow-up (months)	Outcome intervention group (% improvement)	Outcome control group (% improvement)
Orrego et al.	108	RCT (Level I)	ACL tear	PRP clotted around the graft and ACL reconstruction with bone plug	ACL reconstruction without PRP	MRI	3.6	Graft signal intensity 6 m: 100% mature with PRP, 93% mature with PRP + BP	Graft signal intensity 6 m: 78% mature with control, 89% mature with control + BP
Radice et al.	50	Case control trial (Level III)	ACL tear	PRP in a synthetic gelatin sutured on the ACL graft	ACL reconstruction without PRP	MRI	6	Homogeneity: 1.1 (0-4)	Homogeneity: 3.3 (0-4)
Sánchez et al.	60	Case control trial (Level III)	Knee OA	3 PRP injections	HA injections	WOMAC score	5 weeks	Pain subscale success: 34%	Pain subscale success: 10%
Silva et al.	40	Case control trial (Level III)	ACL tear	PRP in femoral tunnel PRP in femoral tunnel and intraarticular at 2-4 weeks PRP activated with thrombin in femoral tunnel	ACL reconstruction without PRP	MRI	3	NA	NA
Kon et al.	100	Case series (Level IV)	Knee OA and cartilage lesions	3 PRP injections	No control group	IKDC subj. (0-100) EQ-VAS score (0-100)	12	Mean IKDC score: 40.5 to 62.5 (34%) Mean EQ-VAS score: 50.3 to 69.5 (39%)	-

(v) Suggested techniques for the application of PRP and post-injection recommendations

It is difficult to give guidelines on the application of PRP using scientific evidence as there is not enough research comparing the different techniques. The following represents the majority viewpoint of the consensus committee on the current best practice administration of PRP.

Following appropriate clinical examination, imaging will assist in establishing the exact location and extent of the injury. As PRP is considered to best act when placed at the site of injured tissue, we recommend to use, if possible, ultrasound guidance to verify accurate needle placement. With respect to tendon administration, there is no agreement on whether the needle should be placed inside the tendon or in the surrounding tendon sheath. In the presence of exudates around the tendon, we suggest that this is evacuated before PRP is injected. If PRP is administered at arthroscopy, we suggest that the injection be performed after emptying the joint of arthroscopic fluid. In the case of open surgery, application of PRP can be undertaken using one of the gel and semi-solid forms. At all times and in all situations, the preparation and administration of PRP should be performed under strict asepsis. Disagreement exists on the use of concomitant NSAIDs before the PRP treatment and during the first two weeks following its application. Although there are published data on the role of NSAIDs and the healing of various tissue such as bone, tendon and muscle, there are no data on concomitant use with PRP. Controversy also exists regarding the concomitant use of local anesthesia for the application of PRP: with no available evidence, it is difficult to give a reasonable recommendation on whether using local anaesthetic will be detrimental to the final clinical outcome.

There is no general agreement on post injection treatment. Most studies have allowed exercises after 2-5 days. Patients should follow general recommendations after an injection with rest, ice and limb elevation for 48 hours. Depending on the site of treatment and extent and duration of the condition, patients could follow an accelerated rehabilitation protocols under appropriate supervision.

(vi) Potential adverse effects of PRP use

Oral and maxillofacial surgery is the medical field where the pioneering use of PRP was initiated. Based on long-term clinical experience in this field and thousands of patients being treated, the use of PRP is safe. In musculoskeletal tissues, although no long-term clinical studies with PRP exist, a large number of patients have been treated worldwide. Recently, Wang-Saugusa et al. reported that no adverse effects were observed when plasma rich in growth factors was infiltrated in more than 800 patients, many of which suffered from knee osteoarthritis.

As theoretically PRP is an autologous preparation, immunogenic reactions or disease transmission should be prevented. As discussed above, the use of bovine thrombin for activation hypersensitivity may be a concern and is therefore avoided in modern preparation techniques. Indeed, development of antibodies against clotting factors V and IX leading to life-threatening coagulopathies have been reported.

To date, there is not compelling evidence of systemic effect of local PRP injection. Furthermore, there are no scientific reports suggesting potential cause-effect relationships between growth factors present in PRP and carcinogenesis. Some potential arguments for these considerations include the limited need of PRP injections in clinics (as PRP is not chronically administered) and the short *in vivo* half-lives and local bioavailability of growth factors produced by PRP.

(vii) Developing a RCT on PRP

In general most available clinical studies on PRP lack scientific stringency, making it difficult for the clinicians to assess the efficacy of using this new treatment modality. Much of what is known about the basic function of PRP and the effect on healing tendons, ligament, muscle and cartilage has been obtained from animal studies. Given the paucity of existing studies, the clinical applicability and safety of PRP needs to be proven in humans for all forms of tissue pathology.

The production of scientific evidence may be pursued using different study designs. Case series, cohort studies and non-randomised trials provide some insight, but provide limited compelling evidence. Randomised controlled trials (RCTs) provide the most compelling evidence whether a given intervention is effective and safe. Finally, the strongest evidence will be provided when sufficient data are available from different RCTs on the same topic and analysed using meta-analytical methods. The best study to investigate the efficacy and safety of PRP in musculoskeletal injury would therefore be a double blind, placebo controlled RCT. In designing a RCT, the following elements are of major importance:

Clear inclusion and exclusion criteria. Particular attention should be given to any confounding variables that may affect healing response including age, gender, past treatment, concomitant medical conditions, lifestyle factors such as smoking, and use of medication.

Study population. The study population should be as homogenous as possible. This can be difficult when considering the demands for an early and effective return to competition for high level (elite) athletes. The natural history of the condition under study should be taken into account, and appropriate patient selection effected accordingly

Clear diagnosis of the injury. The diagnosis of the injury should be based on standard clinical assessment, and must be confirmed using suitable imaging techniques.

Production of PRP. It should be clear, which type of PRP product is used and how it has been prepared, validated and tested (Table 1).

Delivery of PRP. It is considered critical that PRP is administered in the correct location. Therefore, any study should ensure that PRP is injected into the injured area. The amount injected and the number of injections must be clearly defined. Ideally the platelet concentration should be determined, together with the content of growth factors.

Definition of outcome measures and end points. A robust study design would require well defined outcome measures and end-points with follow-up measurements for at least two years. This is often poorly done in studies using athletes, where return to sport measure is often the only included outcome criteria. Nearly all athletes, particularly professional athletes, will attempt to return to sport irrespective of their underlying condition. Several rating scales and outcome measures can be used according to the body part and tissue studied.

Standardized post-treatment protocol. A standardized post-treatment protocol should be used in both treatment and control groups and the adherence to it assessed at equal intervals. This protocol should be consistent with current best practice guidelines for that particular condition.

Follow-up. The flow of the study participant should be carefully documented using the CONSORT 2010 flow chart. The period of appropriate follow-up should be assessed according to the treated tissue.

Documentation of adverse events. All adverse events should be documented for the participants during the period of follow-up for several years.

Alternative to an RCT. The consensus group acknowledges that research in this field could also benefit from studies other than RCT's, such as prospective cohort studies. However, the consensus group cautions from basing therapeutic decisions uniquely on the lower level of evidence produced by such studies. Multi-centre trials may be required to reach the large number of patients required to achieve a meaningful statistical analysis. Randomisation of centres in a cluster trial could offer a logistically acceptable solution for variation in practice between centres, but the intrinsic lack of equipoise in the different centres should be explicitly acknowledged, accounted for, and built in the statistical model.

(viii) PRP and Anti-Doping regulations

WADA publishes a list of prohibited substances and methods every year. According to the World Anti-Doping Code, a substance or method is considered for the list when two out of three criteria are fulfilled: (i) potential for performance enhancement, (ii) risks to health, and (iii) violates the spirit of sport.

In 2010, PRP was specifically mentioned in the prohibited list for the first time. Intramuscular PRP injections were prohibited. All other routes of administration, such as intra-articular, intra or peritendinous were permitted, and required only a declaration of use. Note that specific purified or recombinant growth factors (e.g. IGF-1, VEGF, PDGF) are explicitly prohibited elsewhere in the list. Growth factors are permitted only when part of platelet derived preparations from the centrifugation of autologous whole blood.

There was concern by the WADA List Expert Group that growth factors contained in PRP may stimulate muscle satellite cells and increase muscular size and strength (beyond normal healing).

However, the different PRP formulations and treatment methodologies, as they exist now, have not been found to increase muscle growth beyond return to a normal physiological state. There are some animal studies that show faster muscle regeneration and recovery to full function following experimentally induced injury, but no enhancement of performance beyond normal. There is suggestion, but no compelling evidence, of systemic effects. The risk of adverse reactions (fibrosis, infection, carcinogenesis) are theoretical, and have not been documented clinically. The use of PRP injections for therapeutic purposes only does not violate the spirit of sport.

The prohibition for intramuscular injections of PRP has been deleted in the 2011 Prohibited List. PRP is now permitted by all routes of administration. WADA will continue to review PRP use as new medical and scientific information becomes available.

(ix) Summary and recommendations

There is a limited amount of basic science research on the influence of PRP on the inflammation and repair of connective tissue and skeletal muscle. There is an even greater paucity of well conducted clinical studies on the use of PRP to manage sport injuries. For clinicians, the generalizability of basic science must be tempered by clinical studies that inherently contain factors controlled for in basic science experiments. For these reasons, the design of robust clinical studies is essential for conclusions to be assigned sufficient validity to be used in clinical practice.

Although PRP has been in clinical use for decades, some basic science issues still require further investigation. Several techniques are available to prepare PRP; however, there is no evidence of standardization of preparation (in terms, for example, of length and speed of centrifugation) and use of PRP. In addition, different methods of preparation may produce different platelet concentrations such as storing the PRP for differing lengths of time before use, using different anticoagulants and variable degrees of other cells such as red and white cells in the PRP preparation. It is therefore possible that each preparation method may lead to a different product with different biology and potential uses.

As stated, all these variables may produce PRPs in which the amount and type of growth factors are different. Therefore, a classification system for different PRPs should be developed and should be used to define the PRPs used by different research and treatment groups. For clinical applications, based on different clinical conditions, the best time to inject PRP must be determined according to the different tissues and body districts. The kinetics of cytokine release from various PRPs with/without other biomaterials needs further investigation, as this may ultimately determine the best time for injection for a given PRP formulation. Furthermore, the tissue specific effects of PRP should be compared, as the underlying cellular and molecular processes for a particular tissue healing may be markedly quite different. For instance, muscle and bone healing need vascularization. However, a high degree of vascularization may not be required for tendon and articular cartilage injuries. In fact, it is plausible that the effect of PRP on a given tissue is influenced by the microenvironment within that tissue and therefore PRP activation may not be required prior its use. Lastly, the optimal use of PRP for regenerative medicine is still under investigation. Although application of the PRP may enhance mesenchymal stem cell proliferation and migration, exposure of cells to PRP may also limit differentiation of those cells into the appropriate cell lineages.

The question arises in this consensus statement on whether we as clinicians should use a treatment with very little scientific evidence supporting its clinical efficacy and with limited evidence supporting its safety. Medical ethics is anchored by the concepts of beneficence (doing good) and non-malficence (do no harm). Medical ethics includes the concept of patient autonomy (self-determination). Western medicine tends to hold to the principle that patients can themselves determine their treatment even if beneficence or non-malficence is not proved. For the doctor, non-malficence is the principal determinant of medical practice. While limited, current evidence suggests the use of PRP to be safe, and therefore the non-malficence principal is probably upheld, however there are few if any studies that document adverse or serious adverse events and there are no studies at all looking at long term effects.

As there is little scientific evidence that PRP injections are of clinical benefit, beneficence is at this time not proven. Current medical ethics generally allows clinicians to make an individual choice to prescribe treatments that have not shown beneficence as long as the treatment is non-malficent. With respect to PRP its increasing popularity appears to have outreached in some respects the principle of medical ethics and the usual conservatism that new treatments are taken up by the clinicians. Part of the answer to this would be that PRP is presently marketed and widely perceived as a natural healing method with the implications of minimal malficence.

The role of PRP in tissue healing and regeneration may open a new area in regenerative medicine, but there remains a large amount of work toward the understanding the mechanism of action of PRP in the regeneration and repair process of a given tissue. Firm recommendations on the effectiveness of PRP in the clinical setting to support the healing processes of muscle, tendon, ligament and cartilage injuries cannot be given. Results of studies on PRP are difficult to interpret as the methodological quality of published investigations varies substantially. More attention should be paid to methodological quality when designing, performing and reporting clinical trials.

The final recommendation of this consensus group would be to proceed with caution in the use of PRP in athletic sporting injuries. We believe more work on the basic science needs to be undertaken and greater rigour should be implemented in developing robust clinical trials to demonstrate the efficacy or otherwise of PRP.

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