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Growth Factor Delivery Methods in the Management of Sports Injuries: The State of Play

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Abstract

In recent years there have been rapid developments in the use of growth factors for accelerated healing of injury. Growth factors have been used in Maxillo-facial and Plastic Surgery with success and the technology is now being developed for Orthopaedics and Sports Medicine applications. Growth factors mediate the biological processes necessary for repair of soft tissues such has muscle, tendon and ligament following acute traumatic, or overuse injury, and animal studies have demonstrated clear benefits in terms of accelerated healing. There are various ways of delivering higher doses of growth factors to injured tissue, but each has in common, a reliance on release of growth factors from blood platelets. Platelets contain growth factors in their α-granules (IGF-1, bFGF, PDGF, EGF, VEGF, TGF-β_1) and these are released upon injection at the site of an injury. Three commonly utilised techniques are known as Platelet-rich plasma, autologous blood injections, and autologous conditioned serum. Each of these techniques have been studied clinically in humans to a very limited degree so far, but results are promising in terms of earlier return to play following muscle and particularly tendon injury. The use of growth factors in Sports Medicine is restricted under the terms of the WADA anti-doping code, particularly because of concerns regarding the IGF-1 content of such preparations, and the potential for abuse as performance-enhancing agents. We review the basic science and clinical trials related to the technology, and discuss the use of such agents in relation to the WADA code.

Introduction

Both tendinopathy and muscle strain injury are common sporting injuries with limited treatment options available. Until recently, rest, physical therapy and Non-Steroidal Anti-inflammatory medication (NSAIDs) have been the mainstay of therapy[1]. However these techniques[2,3] may offer little beyond the body's own healing processes, and in fact it is possible that NSAIDs may impair the healing process[4]. The use of novel treatment techniques which utilise the body's own growth factors, promise to provide a further therapeutic option to improve the quality and speed of recovery from injury.

It has long been recognised that growth factors are critical in wound healing[5], but controlled delivery of growth factors has been a limitation to their clinical application. In recent years, a number of methods have been developed allowing the utilisation of the bodies own growth factors, including systems which concentrate platelets, commonly referred to as "Platelet Rich Plasma" (PRP) preparations. The technique of deriving PRP was developed in the mid 1990's, for the discipline of maxillofacial surgery. Marx utilised the bodies own blood to concentrate growth factors, for use in Dental and Craniofacial Surgery[6]. Its appeal has spread to Plastic [7, 8] and Orthopaedic[9] applications and is now commonly used in North America[7], Spain[10] and Germany[9]. Its clinical utility has only recently been recognised in the UK[11].

For those physicians working with elite athletes and potentially having the most to gain from their use, the challenge of utilising GF technology is both exciting and challenging, in a sporting world where any mention of GF use is considered cheating.

This review assesses the current and potential use for GF and Platelet preparations in sports medicine and considers its position relative to the World Anti-Doping Agency Code.

Basic Biology of Growth Factors

Although this review primarily focuses on the therapeutic use of Platelet-Rich Plasma (PRP), a brief overview of the subject of growth factors is required to place the technology in context.

Growth factors are a heterogeneous group of proteins (peptides) secreted by many different body tissues including connective tissue cells (eg. fibroblasts – Fibroblast Growth Factor), haematopoietic stem cells (G-CSF – Granulocyte Colony Stimulating Factor), white cells (interleukins, cytokines), platelets (Platelet Derived Growth Factor, Vascular Endothelial Growth Factor, Transforming Growth Factor Beta-1, Epidermal Growth Factor and basic Fibroblast Growth Factor) and solid organs such as the Liver (Insulin-like Growth Factor-1). They have short biological half-life with quick systemic lavage leading to rapid disappearance of these substances from the circulation[12]. Subsequently their effects are mostly confined to the site of delivery[13].

Those Growth Factors found in Platelets are stored within a cytoplasmic organelle called the α-granule[15]. Platelets are the first cells to arrive at the site of an injury and because of their capacity to release growth factors, they play a critical role in mediating healing of the injured tissue. This has led to the use of platelets as a delivery tool for growth factors.

Growth factors and soft-tissue healing

Literature on the role of growth factors in tissue regeneration is abundant, and it is not the purpose of this review to examine the literature comprehensively with respect to animal studies or the use of isolated growth factors, rather to place the technology of PRP within context.

IGF-1 has been used in isolation by a number of investigators. Animal studies have suggested a role for IGF-1 in both the acceleration and enhancement of healing of tendon and muscle injuries [12,18]

Menetrey et al studied the use of FGF in healing muscle, alongside IGF-1, demonstrating that it can also increase the number of regenerating myofibres and functional recovery compared to control, though to a lesser extent than IGF-1[12]. Efthimiadou found that bFGF also increased angiogenesis in healing rat gastrocnemius muscle[21].

It is thought that PDGF may play a significant role in the early stages of healing where it may induce synthesis of other growth factors such as IGF-1[5]. Hildebrand et al applied PDGF on ruptured rabbit medial collateral ligament[19]. Biomechanical evaluation was performed at six weeks with improvement in the parameters of ultimate load to failure, energy absorbed to failure and ultimate elongation values of 1.6-2.4 that of controls. Further study in Rat MCL demonstrated a 73% improvement in healed ligament strength against controls at only 12 days[20].

Platelet Rich Plasma

Platelet-Rich Plasma is the therapeutic outcome of a technique involving the centrifugation of an autologous sample of human whole blood, which allows the extraction of that part of the plasma which contains a high concentration of Platelets.

The methodology developed by Marx[22], requires a sample of blood to be obtained with the addition on an anticoagulant, such as anticoagulant citrate dextrose A, in order to prevent platelet activation before therapeutic use. The sample is spun twice, firstly to separate the red blood cells from the plasma, and a second spin to concentrate the platelets in the plasma. This second spin results in the formation of two layers within the plasma – a platelet-poor component(PPP), and a platelet-rich component (buffy layer) – the so called 'Platelet-Rich Plasma'(PRP). The platelets are activated at the time of injection with the addition of Calcium (Ca^{2+}) and Thrombin.

The resulting Platelet-Rich Plasma has been found to contain up to 4-8 times the concentration of Platelets found in whole blood [6,7] (see table one). Technology is still evolving and, as such, the process of platelet concentration appears to result in a variable increase in α-granule derived growth factors [6,7]. (see tables 1 & 2).

While the techniques for the isolation and differentiation of Growth Factors from PRP continue to develop, it is recognised that the PRP contain the following growth factors[23]:

Platelet α-granule-derived:-

- PDGF (Platelet-derived Growth Factor)
- VEGF (Vascular Endothelial Growth Factor)
- TGF-β_1 (Transforming Growth Factor Beta-1)
- EGF (Epidermal Growth Factor)

- bFGF (basic Fibroblast Growth Factor)
- IGF-1 (Insulin-like Growth Factor-1)

Plasma Derived:-

- HGF (Hepatocyte Growth Factor)
- IGF-1 (Insulin-like Growth Factor-1)

Excluding HGF and IGF-1, the above factors are locally acting paracrine factors with few or unknown systemic actions[23]. By contrast, IGF-1 has several sources. It is released systemically from the Liver, under the control of pituitary Growth Hormone (GH) and from skeletal muscle following exercise[24,56], as well as being present in, and secreted from platelet α-granules at sites of tissue injury[23]. While PRP does contain some IGF-1, the proportions derived from plasma versus platelets remains unclear. It is likely that Platelets may release trivial amounts of IGF-1[8], however most of the IGF-1 present in PRP will be derived from the original plasma.[6,8,9,25,26].

Table 1: Absolute Growth Factor concentrations in PRP

PRP contents & normal values where known ( )	**Sanchez**[27]	**Eppley**[8]	**Anitua** [25]	**Marx**[22]
Platelet Count (150-400 x10^9L^{-1})	634	1600	460	1086
α-granule factors				
EGF (129)[8] (pg/ml)	481.5	470	442.5	-
VEGF (155)[8] (pg/ml)	383	955	297.5	-
TGF-β_1 (35)[8] (ng/ml)	74.99	120	37.83	170
PDGF (3.3)[8] (ng/ml)	35.62	17	13.33	133
bFGF	trace[9]	-	-	-
Plasmatic factors				
IGF-1 (ng/ml)	94.53	No ↑	115.71	No ↑
HGF(pg/ml)	593.87	-	435	-

PRP extract is injected directly into the damaged tissue, the aim being to enhance the wound healing through delivery of growth factors and theoretical optimisation of the healing environment[10]. Because it is an autologous sample the risk of allergy or the introduction of exogenous infection is considered negligible[6,13]. Once delivered the Platelets begin active secretion of Growth Factors within 10 minutes, and more than 95% of the presynthesized GF are released within an hour[22]. Platelets are viable for 7 days and will continue to release GF into the tissue during this time[22]. While Marx has suggested that a PRP preparation must contain at least 4-5 times the concentration of platelets compared to plasma in order to be effective[22], clinical efficacy of PRP has been demonstrated by other groups[8,27] with less concentrated preparations.

A theoretical advantage of PRP over the use of purified individual GF is that PRP contains several different GF, present in physiological proportions. Consequently a natural balance of proliferative and inhibitory effect, would be expected, rather than the potentially unbalanced effects that may ensue when using purified isolated GF. Since the injected platelets are viable for a further 7 days in the tissue and continue to release GF for this period, more than one injection is unnecessary[22].

Table 2: Biological roles and relative increase (multiplication factor) from baseline of growth factors derived from PRP and ACS technique compared to concentrations in whole blood (ABI)

	Source	Role	PRP	ACS
Platelets	Blood	Initial control of haemorrhage, release GF at injury site	3-8[6,7,8]	N/A (Serum contains no platelets)
PDGF	Platelets	stimulates cell replication, angiogenesis, mitogen for fibroblasts[15]	5-29[9,23]	No difference[28,29]
VEGF	Platelets	Angiogenesis[16]	6-52.7[8,9]	No data
TGF-β_1	Platelets	key regulator in balance between fibrosis and myocyte regeneration[4,41]	3.5-27[8,9,23]	1.3[28,29]
FGF	Platelets	stimulates proliferation of myoblasts, angiogenesis[1,8,12]	'detected'[9]	7.5[28,29]
EGF	Platelets	Proliferation of mesenchymal & epithelial cells, potentiation of other GF's[14]	3[8]	No data
HGF	Plasma	Angiogenesis, mitogen for endothelial cells[27], anti-fibrotic[10]	No increase from baseline[25]	1.3[28]
IGF-1	Plasma/ Liver	Stimulates myoblasts & fibroblasts, mediator in growth & repair of skeletal muscle[17,41]	No increase from baseline[8,9,25,26]	No difference[28]

Clinical use and Efficacy of PRP

Within the field of musculoskeletal medicine, there is only limited clinical research to support the use of any means of GF delivery methods[7,12,28,30,31] . Those limited clinical trials of tendon injury, in which these methods have been utilised tend to lack robustness, and have yet to be reproduced (see table 3). Lateral & Medial epicondylitis, Patella Tendinopathy and Achilles Tendinopathy have all been investigated to varying extents in animals and humans[7,27-31,37,43] PRP technology studies of muscle injury are minimal[32].

Animal studies are numerous, though extrapolation of data to humans is of questionable validity. An injection of platelet concentrate into surgically injured Achilles tendons in rats led to a 30% increase in tensile strength at one week in a single study[33].

Carda et al looked at surgically induced muscle injury in Sheep, demonstrating accelerated healing in PRP treated animals[32]. Lefaucheur et al examined mouse muscle injury with antibodies to neutralise bFGF, IGF-1 & TGF-β_1. The result was attenuation of the healing response, demonstrating that removal of these factors leads to poorer healing.

Human Studies

The application of PRP to ruptured Achilles tendon has been described in humans in a case report[35]. Sanchez et al applied PRP to the ruptured Achilles tendons of a Professional Basketballer and Professional Footballer, in conjunction with operative repair. He reported return to full match fitness in 14 weeks. In a further

report this same group[27] described a case series of 6 athletes undergoing open suture repair following complete Achilles tendon rupture, and compared the outcome with a comparable group who received the same operation with the incorporation of an injection of PRP to the wounded ends when sutured together. Results showed that PRP treated patients recovered their ROM sooner, had no wound complications, took less time to run and resume training. Cross sectional area of the treated tendons increased less compared to non-treated tendons[27].

Mishra et al[7] investigated PRP in elbow epicondylar pain also, utilising a series of 15 patients in a partially randomised trial, with chronic lesions (mean 15 months) who had failed conservative therapy, and a control group of 5 patients. At four weeks post-injection, PRP-treated patients reported a mean of 46% improvement in visual analogue pain scores compared with 17% in controls. At 8 weeks, they reported a 60% improvement in pain scores compared with 16% reduction in the controls, at which point 3/5 controls had dropped out of the study to seek alternative treatment. At 6 months pain scores were reduced 81% in the treatment group. At final follow-up (2 years) PRP-treated patients reported 93% improvement in pain, and 94% return to sport and work.

Human studies (Muscle)

Sanchez et al also published a Case Study of 20 professional athletes with small muscle tears in which PRP was injected under USS-guidance, reporting functional recovery up to twice as quickly as expected[35]. Significantly, this study did not appear to result in any excessive fibrosis, which may have been suspected from the involvement of TGF-B_1.

Autologous Blood Injection

Autologous Blood injection (ABI) refers to the re-injection, at an injury site, of a few millilitres of blood taken from the patient. The injection will contain some platelets cabable of releasing growth factors, but in much lower levels than that seen with the PRP technique. In a Rabbit study looking at Patella Tendons utilising ABI, normal tendons injected with ABI were found to have normal histology and a 15% increase in tensile strength compared with controls at 12 weeks[37]. The purpose of this study was to demonstrate the safety of ABI.

In humans the most extensively investigated pathologies are medial & lateral epicondylitis. Connell et al[30,38]used Ultrasound-guided ABI in 2 series of 20 and 35 patients with medial & lateral epicondylitis. They reported reduction in pain scores of 60% at 2 months, and 100% at 6 months. This same group have also recently evaluated ABI + Physiotherapy in Patella Tendinosis in a series of 47 knees. 44 patients returned to play at a mean of 14.8 months[39].

Autologous Conditioned Serum

Autologous Conditioned Serum (ACS), involves 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 yield of GF than PRP[28,29,40] since the method was originally described[40] for the production of inflammatory cytokines (IL-4) rather than GF. This technique has been investigated in Muscle Strain injury and shown to be effective[28,29]. Studies in rats have suggested the process of muscle healing is often incomplete due to the formation of scar tissue (fibrosis), at sites where

muscle satellite cells need to rebuild injured sarcomeres[28,29]. Two studies used Autologous Conditioned Serum, firstly in rats, and secondly in humans to look at the effects on histological and clinical outcomes of injecting ACS into injured muscle[28,29] (see table three). In ACS-treated Rat muscle injury there was 84% increased satellite cell activation, 27% increased regenerating myofibres and increased angiogenesis versus controls. In ACS-treated human muscle strain injury there was complete versus partial regression of subjectively assessed MRI findings in ACS treated patients, and return to sport of mean 16.6 days versus 22.3 in controls.

Table 3: Summary of Studies using Growth Factor application methods in animal and human trials of tendon, ligament and muscle healing

Technique	Species	Tissue-type	Study Details	Results	Type
Autologous Blood Injections (ABI)	Animal	Tendon Ligament	Taylor 2002[37] – Rabbit – normal Patella Tendon	No harmful effects	Crossover
	Human	**Tendon Ligament**	**1)Edwards 2003[31] – Lateral Epicondylitis 2) Connell 2006[30] – Medial Epicondylitis 3)Connell 2006[30] – Lateral Epicondylitis**	1)79% patients complete pain relief 2&3) No pain at 6 months	**Cohort**
Autologous Conditioned Serum (ACS)	Animal	Muscle	Wright-Carpenter 2004[28] – Mice Gastrocnemius	Increased satellite cells & myofibres	Controlled Trial
	Human	**Muscle**	**Wright-Carpenter 2004[29] – Human Skeletal Muscle**	Improved recovery 22.3 v 16.6 days	**Controlled Trial**
Platelet-Rich Plasma (PRP)	Animal	Tendon Ligament	Aspenberg 2004[33] – Rat Achilles tendon rupture	30% improved strength at 1 week	Cohort
		Muscle	Carda 2005[32] – Skeletal Muscle tears	Improved healing at 6 days	Cohort
	Human	**Tendon Ligament**	**1)Mishra 2006[7] – Elbow tendinopathy 2)Sanchez 2005[35] – Achilles tendon rupture 3)Sanchez 2007[27] – Achilles tendon rupture**	**1) 60% ↓VAS at 8/52 v 16%↓ control 2&3) full recovery 14 weeks v 21**	**1)Controlled Trial 2)Case Report 3)non-randomised Trial**
		Muscle	**Sanchez 2005[36]**	**Full recovery in ½ time v controls**	**Case series**
Suramin	Animal	Muscle	Chan 2005[43] – Mice Gastrocnemius	↓scar tissue ↑tetanic strength	Controlled Trial
Relaxin	Animal	Muscle	Negishi 2006[45] – Mice Skeletal Muscle	↓fibrosis ↑myofibre regeneration	Crossover

Potential risks of using GF in sports medicine

There is the potential for both local and systemic adverse effects of Growth Factor delivery methods:-

Potential Local Complications

A potential local complication of growth factor administration is induction of excessive fibrosis in the healing tissue.
Muscle Healing takes place in 4 overlapping stages[41,43,44], being:-

- Degeneration[41]
- Inflammation (first few days)[41]
- Regeneration (beginning day 5, peaking at day 14)[41]
- Fibrosis (beginning in 2nd week) which may become an overly aggressive healing response in extensively injured muscles[42-44].

Fibrosis is problematic in Muscle Healing since complete muscle regeneration cannot occur in the presence of fibrosis[42,44]. A key regulator of this process is TGF-β_1, which appears to regulate the balance between regeneration and fibrosis[43]. It is possible that use of multiple GF's in muscle injury may result in increased fibrosis and impair longterm outcomes.
Until recently the use of NSAIDs has been promoted in muscle injury. Wei-Shen[4,44] however has demonstrated that NSAIDs may impair muscle healing and promote fibrosis by increasing expression of TGF-β_1 and reducing expression of Prostaglandin E_2 . PGE_2 plays a role in the proliferation and differentiation of muscle satellite cells. Thus NSAIDs may impair muscle healing by delaying muscle regeneration and increasing scar tissue formation.
In order to address this problem, a number of substances have been tested including Decorin, Relaxin[45],Matrix Metalloproteinases[46] and Suramin[43] in the hope that these may provide therapeutic options to limit fibrosis.

Suramin, a polysulphonated naphthylurea, is an antiparasitic and antitumor drug which acts as an inhibitor of TGF-β_1 by competitively binding to the Growth Factors receptor. It has been shown to significantly reduce fibrotic tissue and increase the number of regenerating myofibres in mice when injected on Day 14 post injury[43]. Furthermore there was increased Fast-Twitch and Tetanic strength compared to control.
Relaxin, an ovarian-derived hormone structurally related to IGF[45], plays a role in pregnancy, softening the symphysis pubis and cervix in preparation for Labour. It also has effects on collagen production and degradation[45]. Relaxin has also been used to prevent muscle fibrosis after injury with promising results[45].

Potential Systemic Complications & effects

Infection

Since PRP is an autologous preparation the risk of introducing foreign material is effectively eliminated, although the entire procedure must be carried out in sterile conditions. The use of autologous blood products in this manner reduces the risk of transmissible infection and allergic reaction. Earlier techniques relied upon the

use of topical bovine thrombin, containing contaminants like bovine Factor Va as a platelet activation source[22]. This resulted in antibodies to Factors V and VI, with potentially life threatening coagulopathies resulting[13]. This is no longer utilised in commercially available techniques in the UK.

Carcinogenesis

Growth Factors act on cell surface receptors, do not enter the cell, and do not cause DNA mutation. There is no plausible mechanism by which GF result in neoplastic development, and there have been no reports of this in the literature[6,22]

Effect on Serum Growth Factor levels

Recent research by Banfi's group in Italy[47] looked at the potential systemic effects of locally administered PRP. This group found that a locally administered injection of PRP (4 patella tendons, 1 elbow) led to a fall in the Serum Concentration of Epidermal Growth Factor (EGF). There was no statistically significant difference in the concentration of VEGF, measured at 30mins, 3hrs and 24hrs post-injection wheras other GF were not measured. A limitation of this study unfortunately was its small size (n = 5), but the implication is that locally administered PRP will impact on systemic levels of GF, but in a negative manner.

The use of GF methods and conflict with the WADA code

In the United Kingdom, the use of autologous blood products containing growth factors entered the public arena when a Premiership Football Club Sports Physician made enquires to the National anti-doping organisation (UK Sport) and WADA regarding the legality of their use in sport[50]. The question asked forced WADA to consider their position on both the use of autologous blood injections and any autologous product which contains growth factors.

The response from WADA was quite clear, that the use of either of these techniques is prohibited under the terms of the Prohibited List[51](see figure 1). The use of ABI as described above was considered prohibited under section M1[48] while the use of any autologous product which contains GF was prohibited under Section S2. This section specifically mentions Growth Hormone (GH), Insulin-like Growth Factor-1 (IGF-1), and Mechano-Growth factor (MGF) as prohibited (see figure one).

Insulin-like Growth Factor-1 content of PRP:- therapy versus doping

Insulin-like growth factor-1 (IGF-1) is a 7.5kDa polypeptide, structurally similar to Insulin[49]. It induces proliferation, differentiation and hypertrophy of multiple cell lines, in particular skeletal muscle, and has an additional role of facilitating Glucose entry into skeletal muscle cells [24, 49].

IGF-1 is secreted as the result of a hypothalamic-pituitary-liver axis. The Hypothalamus secretes Growth Hormone-releasing hormone (GHRH), which stimulates the Pituitary to release Growth Hormone (GH), which in turn stimulates the Liver to release IGF-1[24]. Like most endocrine systems, the system is controlled by negative feedback, thus in normal individuals, exogenous administration of IGF-1 will

lead to suppression of the axis. Whereas GH secretion is pulsatile, with greatly varying levels in a 24hour period, serum IGF-1 levels are relatively stable within a 24hour period meaning a serum IGF-1 level is now the favoured test for Acromegaly or Growth Hormone Deficiency[52].

IGF-1 circulates in the serum 99% bound to a carrier protein Insulin-like Growth Factor Binding Protein-3 (IGFBP-3). Only 1% of serum IGF-1 is 'free' IGF-1 (fIGF-1), and it is the free portion which is believed to exert the biological effects, upon binding to the IGF-1 receptor (IGF-1R)[52]. IGF-1 has a serum half-life of 10 minutes (t½ 10mins) when unbound to IGFBP-3[53], and it is in this unbound form that IGF-1 is administered within PRP. In contrast, the IGF-1/IGFBP-3 complex has a much longer half-life of 16 hours (t½ 16hrs)[53].

IGF-1 has at least three Isoforms, namely:- IGF-1Ea, IGF-1Eb and IGF-1Ec. IGF-1Ea is the circulating form of IGF-1 released from the Liver, whereas IGF-1Ec, also known as Mechano-growth factor (MGF) is the tissue isoform released from skeletal muscle cells, and is believed to exert exclusively autocrine/paracrine actions[24].
The different isoforms have slightly different biological actions. IGF-1Ea is known to stimulate terminal differentiation of muscle cells into myotubes, and promote stem-cell mediated muscle regeneration, whereas MGF is damage sensitive, controls local tissue repair, and is more potent than IGF-1Ea at causing hypertrophy[24]. MGF is rapidly degraded in the serum[24].

These varying biological actions of IGF-1 isoforms are important since IGF-1 derived from PRP (IGF-1Ea) which is used for therapeutic purposes may not have the same performance enhancing implications as skeletal muscle derived IGF-1Ec (MGF).

Serum IGF-1 levels vary greatly between individuals, and are dependent on genetic influences and nutritional status, however a typical value of 300ng/ml (range 94-506) is seen in 17-20 year old adults and 250ng/ml (range 117-358) in 21-30 year olds[55]. In order to achieve such physiological levels, Children with Laron syndrome, a rare form of GH resistance typified by very low levels of natural IGF-1, are given exogenous IGF-1 in doses of 160mcg (micrograms) per day for many months[54,55]. Contrast this with a typical dose of a single locally administered PRP injection in the treatment of elbow extensor tendinopathy – 3mls of PRP containing ~ 100ng/ml of IGF-1 (total dose 300ng)[7] and there is a demonstrable 5 x 10^2 fold difference in even a single dose. It is also important to mention that exercise has some effect on circulating levels of IGF-1. Berg et al[56] studied changes in serum IGF-1 in relation to acute bouts of exercise. This group demonstrated a 27% increase in serum IGF-1 following 10mins of moderate exercise in healthy adults, corresponding to changes of 10-28mcg/l. This was likely to be IGF-1 released from skeletal muscle. The implication of this being that it would be difficult to differentiate changes in serum IGF-1 as a result of exercise, from changes caused by exogenous administration.

Thus there appear to be several compelling reasons to believe it would be unlikely that PRP would be a potent ergogenic aid:

- The unbound IGF-1 has too short a half-life to be able to exert systemic effects (10 minutes versus 16 hours).

- The isoform IGF-1Ea found in PRP is not the isoform principally responsible for skeletal muscle hypertrophy (IGF-1Ec/MGF).
- The doses of IGF-1 in PRP are sub-therapeutic in terms of producing systemic anabolic actions by a factor of 500 (300 nanograms versus 160 micrograms).

A recent IOC Medical Commission Consensus Statement on the use of Growth Factor technologies in therapy appears to welcome further research in the field "to ensure these therapies are optimised" and, "to ensure athlete/patient safety". We would welcome such assertions also, though the statement by the IOC somewhat contradicts the WADA Code which prohibits all use of Growth Factors therapies in elite sport[57].

Notwithstanding these concerns expressed by WADA, it is possible to apply to a WADA approved Anti-Doping Organisation for a Therapeutic Use Exemption to utilise these techniques for specific clinical indications, in elite athletes. Given the obvious difficulties associated with detection of these techniques and the bureaucratic delays the TUE process entails, it is unclear whether this approach has been widely utilised. Indeed, the only research known to have been conducted on professional athletes makes no mention of any anti-doping concerns[47]. The authors would strongly support the use of this approach in order for WADA to develop awareness of the current clinical utility of these techniques.

Figure 1: **Selected Sections of the 2006 WADA Prohibited List (WADA 2007)**

S2 Hormones and Related Substances

The following substances, including other substances with a similar chemical structure or similar biological effect(s), and their releasing factors, are prohibited:

1. **Erythropoetin**
2. **Growth Hormone (GH), Insulin-like Growth Factors (eg. IGF-1), Mechano Growth Factors (MGFs)**
3. **Gonadotrophins**
4. **Insulins**
5. **Corticotrophins**

- **M1 Enhancement of Oxygen Transfer**
  - **The following are prohibited:**
    a. **Blood doping, including the use of autologous, homologous or heterologous blood or red blood cell products of any origin.**

Conclusion:

Medical technology continues to advance at a furious pace. The use of Growth Factors promises to herald a new era of accelerated healing of injured tissues, and is already commonplace in many fields of medicine. The technology is still in its infancy with respect to soft tissue injuries, and the precise mechanisms of action, and

optimum therapeutics need to be developed. The use of Platelet-rich plasma promises to become a powerful therapeutic modality for use in muscle, tendon and ligament injury in the future, but at present its use is considered a doping violation under the WADA code, so research and treatment is restricted to non-elite sportspersons. In the future an ironic dichotomy may exist whereby the general public will be able to benefit from state of the art medical technology utilising growth factors, but elite athletes will be excluded because of doping restrictions. The World anti-doping agency and International Olympic committee must work with scientists to allow athletes to benefit from the best medicine available in a both a safe and fair environment.

What is already known on this topic

- Growth factors mediate tissue repair following injury
- Various techniques have been developed to deliver increased concentrations of growth factors to sites of injury, including Autologous Blood Injections and Platelet-Rich Plasma
- Robust data of clinical efficacy is lacking
- The use of growth factors is prohibited by the WADA Anti-Doping Code

What this study adds

- Growth factor technologies have the potential to accelerate healing in soft tissue injury
- The debate of therapeutic use versus doping needs to be opened in relation to the WADA Code

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