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Research article

Does single intramuscular application of autologous conditioned plasma influence systemic circulating growth factors?

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Abstract

Platelet-rich plasma (PRP) has been employed to treat sports injuries to possibly accelerate healing and regeneration. This method offers some potential, especially for athletes. Growth factors are generally prohibited by the World Anti Doping Agency with exception to PRP which may induce adverse effects. The aim of this study was to evaluate any systemic increase of growth factors such as Insulin Like Growth Factor-1, Endothelial Growth Factors, Platelet-Derived Growth Factors, Fibroblast Growth Factors, Vascular-Endothelial Growth Factor and Transforming Growth Factors after local intramuscular administration of PRP in young, healthy male subjects keeping in mind adverse treatment effects. Enriched plasma from centrifuged blood samples was injected into the gluteus muscle. Venous blood was collected and serum prepared before as well as 0.5, 3 and 24 hours after PRP administration. Growth factors were analyzed using ELISA test kits. No significant systemic increase of growth factor levels was found after PRP injection except TGF-ß2. For that reason the PRP method may be applied for muscle injury treatment in elite athletes although further studies are necessary to clarify the response to the unspecific increased TGF-ß2 blood levels, which could increase the risk for local fibrosis.

Key words: Autologous Conditioned Plasma, blood levels of growth factors, doping, platelet-rich plasma.

Introduction

Platelet-rich plasma (PRP) preparations are known to contain a series of concentrated cytokines that may be valuable to augment healing of a wide range of tissues (Marx, 2004; Sánchez et al., 2003) such as muscle injuries, osteoarthritis and chronic tendinopathies (Baltzer et al., 2009; Banfi et.al.,2006; Creaney and Hamilton, 2008).

Studies in animals have shown possible benefits of this therapeutic PRP application (Baltzer et al., 2009; Banfi et al., 2006; Mishra and Pavelko, 2006; Sánchez et al., 2009a; 2009b) and some prospective randomized controlled studies have shown positive effects e.g. in augmenting rotator cuff repairs (Castricini et al., 2011) or for the treatment of lateral epicondylitis (Peerbooms et al., 2010).

Despite its positive effects, concerns have been raised particularly regarding undesirable side effects such as fibrosis or infection (Engebretsen et al., 2010; LeRoith and Roberts, 2003; Sampson, et al., 2008; Wright-Carpenter et al., 2004). This method may be particularly interesting for elite athletes as there is enormous revenue generating potential connected with most famous sports and pressing demands are placed on the treating physician expecting them to facilitate a rapid return to competition.

PRP method and its application

PRP can be defined as plasma containing a concentration of platelets that is above the concentration found in whole blood (Marx, 2004). Platelets contain a number of proteins, cytokines, and other bioactive factors that initiate and regulate basic aspects of wound healing. Platelet-rich plasma, with a platelet concentration of at least 1 Mio platelets/µL, is very likely associated with the enhancement of healing. Platelet-rich plasma contains up to 4 times the concentration of platelets found in whole blood depending on the preparation. (Table 1)

The basic cytokines identified in platelets include the transforming growth factor–β (TGF- β), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), fibroblast growth factor (FGF), epidermal growth factor, vascular endothelial growth factor (VEGF), and endothelial cell growth factor. Endocrine factors including growth hormones and circulating mature insulin-like growth factors (IGF-1) have an effect on many tissues in the human body. These cytokines mainly play important roles in cell proliferation, chemotaxis, cell differentiation, and angiogenesis (Table 2).

TGF-ß is found in at least five isoforms, (TGF-ß1-5), TGF-ß1 is the prevalent form, being almost ubiquitously present. TGF-ß1 is active during inflammation, influences the regulation of cellular migration and proliferation and stimulates cell replication and fibronectin binding interactions. It is also strongly involved in collagen synthesis and promotes the production of the extracellular matrix (Table 2) (Anitua et al., 2005).

TGF-ß is also expressed by regenerating muscle tissue following trauma, suggesting that it may play a role in muscle regeneration. This may occur as a consequence of its effect on the reconstruction of the basement membrane and the extracellular matrix surrounding the damaged myofibres and the activated satellite cells. However, an excessive deposition of extracellular matrix leads to fibrosis (Sampson et al., 2008). It has been demonstrated that measures that can alter the effect of TGF-ß1 on its receptors may affect the fibrotic process (Anitua et al., 2009; Chan et al., 2005; Kjaer and Bayer, 2011). TGF-ß1-5 is all involved in this process, although the specific nature of the isoforms is not yet clear. TGF-ß has been studied extensively in ocular disease. TGF-ß1, -ß2, and -ß3 appear to have similar actions in vivo and all TGF-ß

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Table 1. Common Platelet-rich Therapy Preparation Systems*

System	Volume Of Blood (mL)	Centrifuge Time/Speed	Final PRP Volume (mL)	Final Platelet Concentration (compared with average)	Activator	Level of Growth Factors (compared with average)
Autologous Conditioned Plasma (Arthrex, Naples, FL)†	9	5 min/1,500 rpm	3-5	2-3x	None	PDGF (25x) EGF (5x) VEGF (11x) TGF-β1 (4x) IGF-1 (1x)
Cascade (Musculoskeletal Tissue Foundation, Edison, NJ)‡	9 or 18	First: 6 min/1,100g; Second: 15 min/ 1,450g	2 or 4	N/A	Calcium (forms a suturable clot for intraoperative use)	PDGF (N/A) EGF (5-10x) VEGF (5-10x) TGF-β1 (5-10x) IGF-1 (5-10x)
GPS III (Biomet, Warsaw, IN)§	27 or 54	15 min/1,900*g*	3 or 6	4-8x	Calcium chloride/ thrombin	PDGF (N/A) EGF (3.9x) VEGF (6.2x) TGF-β1 (3.6x) IGF-1 (1x)
SmartPReP (Harvest Technologies, Plymouth, MA)‖	20 or 60	14 min/1,000*g*	3 or 7	4.4-7.6x	Thrombin	PDGF (4.4×) EGF (4.4×) VEGF (4.4×) TGF-β1 (4.4×) IGF-1 (N/A)

* Information obtained from product manufacturers (platelet and growth factor concentration obtained from unpublished company data for all products listed except for Biomet GPS III [Eppley et al.])
† Arthrex: https://www.arthrex.com/innovations/index.cfm?adid=28&CFID=2168033&CFTOKEN=63754575
‡ Musculoskeletal Tissue Foundation: http://platelettherapy.com/
§ Biomet: http://www.biomet.com/biologics/information/pdf/BBI0003.0.pdf
‖ Harvest Technologies: http://www.harvesttech.com/products/smartprepmain.html
EGF = epidermal growth factor, IGF-1 = insulin-like growth factor-1, N/A = not available, PDGF = platelet-derived growth factor, PRP = platelet-rich plasma, TGF-β1 = transforming growth factor-β1, VEGF = vascular endothelial growth factor

isoforms are suggested to be potent modulators which stimulate the conjunctival scarring response (Cordeiro et al., 2000; Cordeiro et al., 1999). These studies indicate that TGF-ß2 may naturally modify the antiscarring effects of antimetabolites in glaucoma filtration surgery (Cordeiro et al., 1999; 2000).

Despite the possible beneficial effects of PRP, several concerns have been raised about undesireable side effects (Marx, 2004; Creaney and Hamilton, 2008). IGF-1 requires some special attention because of its potential doping effects (Tentori and Graziani, 2007). Up until now there has been a suspicion, but no compelling evidence, of systemic effects resulting from locally administered injections of PRP, yet very few studies have addressed this

Table 2. Summary of the effects of growth factors.

Growth factors	Function	References
TGF-ß1	Cellular migration and proliferation; cell replication, collagen synthesis production of extracellular matrix reconstruction of basement membrane of damaged myofibres and satellite cells, Scar tissue formation such as in adult wounds	Molloy, 2003 Husmann, 1996 Kovacevic, 2011
TGF- ß2	Increase of collagen production Scarless wound healing such as in fetal wounds	Klein, 2002 Pryce, 2009
TGF- ß3	Reduction of scar tissue formation after healing like in fetal wounds more favorable ratio of Collagen 1 to Collagen 3 ratio	Kovacevic, 2011
VEGF	Angiogenesis, tendon cell proliferation, type 1 collagen synthesis, muscle fibre reconstitution, angiogenesis in muscle	Anitua, 2005; Arsic, 2004; Bachl, 2009; Engebretsen, 2010
PDGF	Mesenchymal stem cell replication, ostoid production, endothelial cell replication, collagen synthesis, collagen and protein synthesis. Synthesis of other factors (e.g IGF-1) resulting in fibroblast proliferation and differentiation, collagen deposition, and angiogenesis	Hsu, 2004 Everts P, 2006 Foster 2009
FGF	Stimulator of angiogenesis and regulator of cellular migration and proliferation. Influencing angiogenesis and satellite cell numbers	Molloy, 2003; Wright Carpenter, 2004; Bachl N, 2009
IGF-1c (MGF)	Autocrine/paracrine, more potent than IGF-1Ea at causing hypertrophy	Philippou, 2007
IGF-1a	Stimulates terminal differentiation of muscle cells into myotubes and promote stem cell-mediated muscle regeneration	Philippou, 2007
EGF	Proliferation of fibroblasts and epithelial cells. Synthesis and turn over of proteins of the extracellular matrix, including fibronectin, collagens, laminin, and glycosaminoglycans. Strong chemoattractant for fibroblasts and epithelial cells	Borrione, 2010

issue (Banfi et al., 2006; Borselli et al., 2010).

We hypothesized that an intramuscular PRP application should increase relevant growth factors systemically, which are related to possible adverse side effects for local tissue repair.

The aim of this study is to investigate possible systemic effects of PRP applied intramuscularly on various serum growth factor levels in healthy subjects to rule out potential risks for adverse local tissue repair.

Methods

Ten 23 ± 1.5 year old, healthy, athletic male subjects (VO_{2max}: 52.0 ± 11.1 $ml.kg^{-1}.min^{-1}$; body mass: 78.7 ± 9.3 kg, height 1.84 ± 0.08 m) were studied. Written informed consent was obtained from the subjects. The study was approved by the local ethics committee (No.: 21-160ex 09/10). We used a PRP system called ACP manufactured by Arthrex®. The Autologous Conditioned Plasma (ACP) system is designed to extract platelet concentrate solution from a patient's own peripheral blood. The system has a specially designed and patented double syringe and eliminates a second centrifugation step, making it easy to use.

Prior to taking blood, 1ml of ACD-A (Anticoagulant Citrate Dextrose Solution, NoClot 400™, Cytosol Laboratories, INC) was withdrawn into the outer syringe of an ACP Doublesyringe system (by Arthrex®). Then 9 ml of venous blood was withdrawn with a butterfly cannula from the cubital vein. Blood was spun at 1500 rpm for 5 minutes (Hettich Rotofix 32A) to separate plasma from erythrocytes and leukocytes. After separation the plasma was transferred into the smaller syringe. 2.5 ml of the autologous conditioned plasma (ACP) was then injected into the right gluteus maximus of each subject. This application was performed within a clinical setting while conforming to proscribed standards.

Venous blood samples were drawn and serum was prepared before ACP administration after 30 minutes, 3 hours and 24 hours respectively, to determine IGF-1, PDGF-AB, PDGF-BB, TGF-ß1, TGF-ß2, VEGF, EGF and FGF levels. Samples were stored at -80 °C until further processing. Subjects were requested to abstain from any strenuous physical activity before the first blood draw and throughout the observation period.

All parameters were measured in serum using the R&D Quantikine ELISA testkits (Biomedica, Vienna, Austria) for human IGF-1, PDGF-AB, PDGF-BB, TGF-ß1, TGF-ß2, VEGF, EGF and FGF following the manufacturer´s instructions. In brief, samples were thawed and adequately diluted. Standards and samples were added to microplates precoated with a specific monoclonal antibody. After washing, bound growth factors were detected by a specific polyclonal antibody linked with horseradish peroxidase. After washing, substrate hydrogen peroxide and a colour reagent tetramethylbenzidin were added. Absorption was then measured at 450 nm after incubation. Quantitation was performed using the calibration curve obtained by adhering to proscribed standards. Each sample and standard was measured in duplicate.

Statistical analyses

Measures are reported as means (±SD). Comparisons between pre- and postbioactive factor levels were performed by means of repeated measures ANOVA. A p-value < 0.05 was considered to be significant. The required sample size of 10 subjects was calculated a-priori by G*Power analysis using an assumed large effect size of 0.4 (Cohen, 1988), and α-level of 0.05 and a power of 0.8 to simulate a meaningful elevation of the main variable above mean values (Faul et al., 2007).

Results

No systemic increase of the growth factors IGF-1, PDGF-AB, PDGF-BB, FGF, VEGF, EGF-1 and TGF-ß1 was found (Figure 1 A-G), but TGF-ß2 significantly increased 3 and 24 hours after administration (Figure 1H). The increase was found in all subjects and the mean TGF-ß2 after 24 hours was three times the value compared to resting conditions (Figure 1H). IGF-1 was found at the lower limit of age related norms (Brabant et al., 2003) and the application of ACP did not influence the mean IGF-1 values after 30 minutes, 3 and 24 hours as presented previously (Figure 1 A)(Schippinger et al., 2011).

Discussion

Several studies have suggested that PRP may be advantageous in sports medicine, but up until now, the majority of human studies that support this hypothesis are either small case series or level 4 and 5 studies, which demonstrate the efficacy of PRP/ACP in treating tendinopathies (Foster et al., 2009; Mishra and Pavelko, 2006; Peerbooms et al., 2010; Sánchez et al., 2009a; 2009b). In a preliminary analysis, intramuscular administration of PRP - in our study ACP - in young, healthy, athletic subjects had no effect on circulating IGF-1 values (Schippinger et al., 2011). Additionally, the growth factors PDGF-AB, PDGF-BB, TGF-ß1, VEGF, EGF and FGF showed no significant systemic increase after a single intramuscular ACP administration (Figure 1A-G). However, we cannot rule out a possible effect due to the small sample size tested and not using a control group with a sham application. TGF-ß2, a nonspecific growth factor involved in several growth processes in healing and wound repair (Borrione et al., 2010; Borselli et al., 2010; Cordeiro et al., 1999; Mc Pherron and Lee, 1997; Philippou et al., 2007), showed a significant increase over time (Figure 1 H).

Some researchers have raised concerns that PRP derivatives could induce a fibrotic healing response in local muscle tissues (Chan et al., 2005; Smith et al., 2007). This theoretical deleterious side effect of PRP is based on the local elevation of TGF-ß levels after injection into muscle tissue. Basic science studies have demonstrated that platelet granules can release TGF-ß when stimulated. TGF–ß has also been shown to stimulate fibrosis in in-vitro muscle tissue studies. It was hypothesized that fibrotic healing following muscular injury can lead to an increased incidence of re-injury (Chan et al., 2005). Creany and Hamilton (2008) mentioned potential local complications of using growth factors such

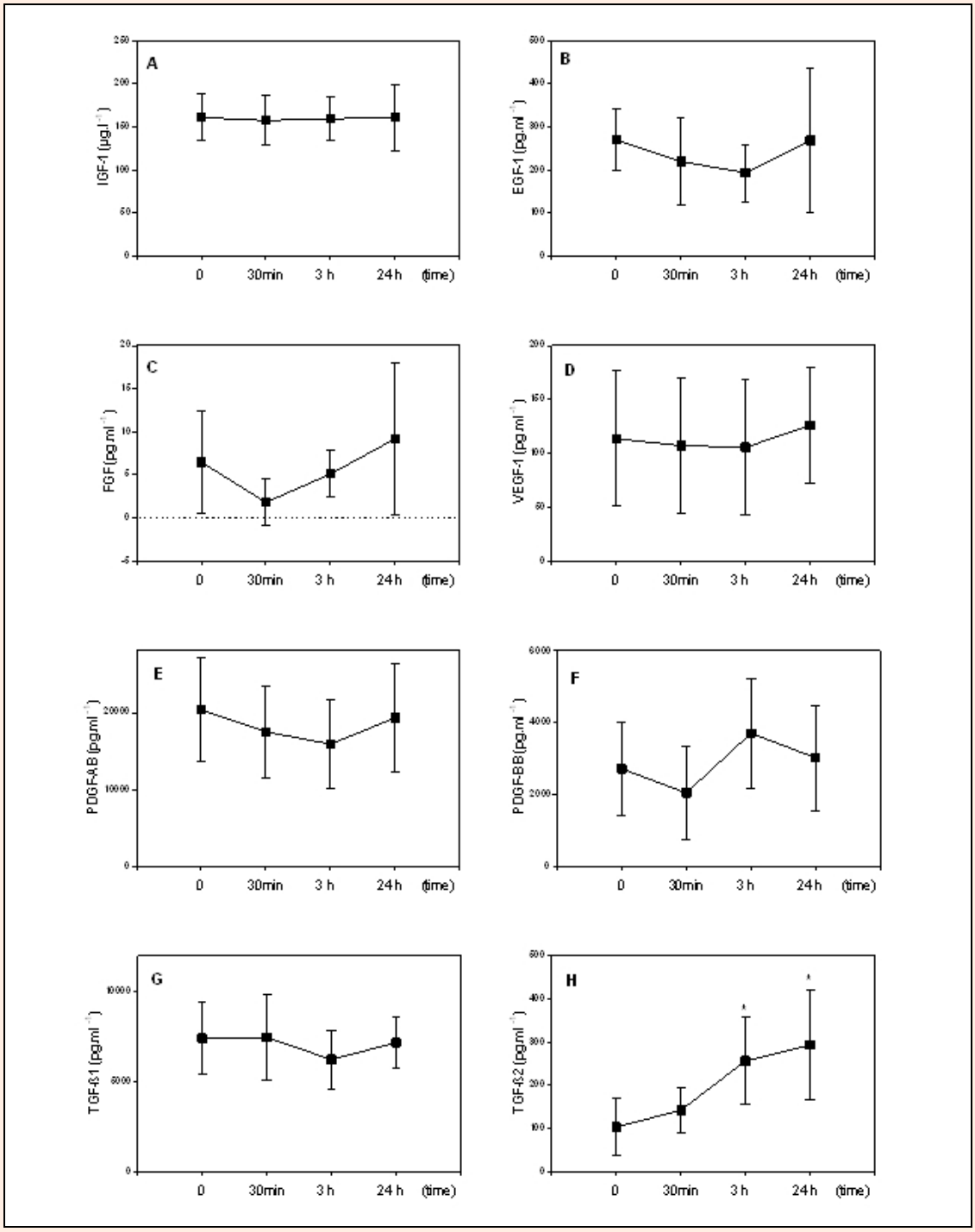

Figure 1. Blood levels of IGF-1, PDGF-AB, PDGF-BB, TGF-ß1, TGF-ß2, VEGF, EGF and FGF before, 30 minutes, 3 hours and 24 hours after administration of ACP

as excessive fibrosis in the healing muscle. They argue that complete muscle regeneration cannot occur in the presence of fibrosis. A key regulator noticed was TGF-ß1 which has been suggested to regulate the balance between regeneration and fibrosis. In our study TGF-ß1 did not change significantly on a systemic level (Figure1G) but a local effect cannot be ruled out. The role of TGF-ß2 in local tissue repair, significantly elevated in our study has to be ruled out in additional studies.

McLennan and Koishi (2002) described various effects of TGF-ß concluding that TGF-β2 regulates the fusion of myoblasts to myotubes and motoneuron survival.

TGF-ß has been studied extensively in ocular disease. TGF-ß1, -ß2, and -ß3 appear to have similar actions in vivo and all TGF-ß isoforms are suggested to be potent modulators which stimulate the conjunctival scarring response (Cordeiro et al., 1999; 2000). These studies indicate that TGF-ß2 may naturally modify the antiscarring effects of antimetabolites in glaucoma filtration sur-

gery (Cordeiro et al., 1999; 2000).

Limits of the study are a low number of subjects and that a non control sham application was performed. It might be possible that the injection itself may induce local effects on TGF-ß which may also be seen at the systemic level.

Conclusion

From our results we can conclude that a single intramuscular administration of ACP, a PRP preparation by Arthrex® does not significantly increase main systemic growth factor levels, except for the unspecific transforming growth factor TGF-ß2. For this reason, the PRP method e.g. intended for the treatment of muscle injuries may be applied for injury treatment, although further randomized controlled studies are necessary to clarify the local response of the unspecific increased TGF-ß2 levels in the blood circulation which may possibly increase the risk of fibrosis.

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Key points

- Muscle injury
- Autologous conditioned plasma
- Systemic circulating growth factors
- Doping

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