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Intra-Muscular Platelet Rich Plasma Increases Platelet Derived Growth Factor and Regenerates Exercise-Induced Muscle Damage

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ABSTRACT

Platelets rich plasma (PRP) is reported to facilitate muscle regeneration both in vitro and animal studies. The aim of the study was to evaluate the effect of intramuscular PRP on growth factors and the regeneration of exercise induced muscle damage (EIMD).Volunteers were assigned to a control (n=6) or PRP (n=6), and performed exhaustive exercise with one repetition maximum (1RM-80%) maximal voluntary contraction of the non-dominant elbow. The arms were treated with saline or PRP post-24h exercise and blood samples were obtained in the morning to establish a baseline value and also 1-4 days post-exercise. The baseline levels of serum insulin-like growth factor 1(IGF-1), insulin-like growth factor-binding protein 3 (IGFBP-3), vascular endothelial growth factor (VEGF) were different whilst growth hormone (GH) and platelet-derived growth factor (PDGF-BB) levels were similar in both groups. However, 24 h following exercise increased levels of IGF-1, GH and IGFBP-3 in control were observed. PRP up-regulated PDGF-BB and VEDF, it also inhibited GH, IGF-1 and IGFBP-3 levels post-exercise.

Introduction

Strenuous physical exercise induces muscle fibre damage and initiates a non-specific inflammatory response which in turn can lead to an increase in a wide spectrum of inflammatory mediators and growth factors. For example, platelet derived growth factor (PDGF), transforming growth factor-ß (TGF-ß) and vascular endothelial growth factor (VEGF) [1], insulin-like growth factor I (IGF-I) [2] and also IGF-1 binding protein 3 (IGFBP-3) [3] are all released following strenuous exercise. The most central angiogenic factor in skeletal muscle capillary growth is VEGF and during muscle contraction it is increased in the muscle interstitium, and acts on VEGF receptors in the capillary endothelium, and thereby stimulates angiogenic processes [2]. IGF- I is an anabolic growth factor and is involved in initiating the sequence of events involved in muscle repair and remodelling [4] and is considered a biomarker of health, fitness, and training status [5]. The protective and regenerative effects exerted by IGF-1 are most likely related to the potentiated action of neurogenesis (i.e., progenitor cell proliferation and new neurons, increased oligodendrocytes, and blood vessels in the dentate gyrus of the hippocampus) [6].Thus, IGF-I is considered a central therapeutic target for enhancing muscle function in aging and disease, and for accelerating repair following acute muscle damage [7].

PRP is rich in growth factors and other cytokines and its use in the treatment of tissue regeneration is supported by *in vitro* and animal studies which suggest a positive influence on the migration and proliferation of a number of cell types [8,9]. Platelet-rich plasma (PRP) provides many growth factors and is a relatively simple low cost solution, which can be used in a minimally invasive manner. Its use can lead to higher than physiological levels of growth factors in blood. The growth factors such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor-beta 1 (TGFb1), insulin-like growth factor (IGF-I), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and hepatocyte growth factor (HGF) present in granules are also up-regulated during tissue healing. In addition, a few studies suggest that PRP administration may improve recovery from tendon and muscle injuries [10, 11]. Due to these reasons the World Anti-Doping Agency (WADA) is considering whether PRP may be classified as a doping agent because it contains growth factors. However, WADA lifted the ban on PRP in 2011 in recognition of the lack of evidence to support a systemic performance-enhancing effect and to allow further research in this field. To our knowledge, few studies have been published on the systemic effects of locally administered PRP. In one study a decreased serum concentration of epidermal growth factor was observed and no statistically significant difference in the concentration of vascular endothelial growth factor (VEGF) up to 24 hours post-PRP was evident [12]. In contrast, it has been reported that serum IGF-1, VEGF, and BFGF levels were significantly elevated after PRP administration, supporting a possible ergogenic effect of PRP [13]. The product of IGFBP-3, IGF-1, hGH is an indirect marker of doping and is also significantly increased after PRP administration. Furthermore, we previously reported that post-exercise PRP administration improves inflammation by reversing the increase in the iron levels without displaying any myotoxicity and may have a role to play in the recovery of

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exercise-induced muscle damage [14]. As a continuation of our investigation, we hypothesized that intramuscular PRP administration may improve muscle damage by exerting a beneficial effect on delayed onset muscle soreness (DOMS) by modulated growth factors. The objective of the present study was to investigate whether intramuscular PRP injection can provide an effective recovery strategy and regeneration for attenuating DOMS and muscle damage induced by high-intensity muscle exercise in humans.

Method

Participants

Twelve moderately active male volunteers participated in this randomized double-blind placebo-controlled trial to verify the effects of the intramuscular PRP administration on hematologic and growth factors on muscle recovery after an eccentric/concentric exercise. Subjects were randomly divided into two groups: PRP (n=6, mean age 23±3 year, body weight 94 ± 6.9 kg, height 183.6 ± 3.2 cm) and control (n=6, mean age 22±2 year, body weight 86 ± 7.8 kg, height 177.6 ± 8.7 cm), and they had not been involved in any regular weight-training program and had no history of injury to the arm, shoulder, and elbow region. The nature and the risks of the experimental procedures were explained to the subjects, and signed informed consent to participate in the study was obtained. Before the test session, participants were examined and checked by the use of routine blood analysis by a medically qualified practioner. Ethical approval was obtained from The University Medical Faculty Ethics Committee (2013/14) and each participant gave written informed consent prior to the study.

Muscle damage exercise protocol

For the exercise-induced muscle damage test, subjects were seated on a bench with their arm positioned in front of their body and resting on a padded support, such that their shoulder was secured at a flexion angle of 0.79 rad (45^0) and their forearm was maintained in the supinated position throughout the exercise. Subjects were repeatedly weight-loaded upon dumbbell lowering to achieve an 80% of maximum voluntary contraction (MVC), 2-min rest between the sets of elbow extension from the flexed position at 90^0 to fully extended position slowly over 5 s, until exhaustion was experienced. The control group performed a mean average number of repetitions and number of set (47±6 and 13±3) respectively whilst the PRP group performed a mean average number of repetitions (44±3) and number of set (12±2) respectively.The subjects were also given verbal encouragement by the investigator to maintain constant speed throughout the procedure. The volunteers were instructed to continue with their normal activities and to abstain from any strenuous exercise at least 2 weeks prior to the commencement of the study. Moreover, they were asked to continue with their usual food intake, not to change the amount or frequency of dietary meat and not to use any dietary supplements, anti-inflammatory drugs, or anything else that could affect muscle soreness and damage until the end of the study.

Platelet-rich plasma and placebo

Each participant was assigned to either receive a control group (saline) injection or PRP group, injection in the non-dominant arms with post-24 h DOMS exercise based on computerized randomization. PRP preparation was obtained from 8 mL of peripheral blood which was drawn from the dominant arm and the samples were centrifuged for 9 min at 3500 revolutions per minute (H-19F, RegenCentrigel, Regen ACR-C; Regen Lab, Switzerland) according to manufacturers recommendation. Subsequently, 4 mL of PRP was injected using a 20-gauge needle into the pain full region of the non-dominant arm under sterile aseptic conditions. This kit produces 4 mL of PRP from 8 mL citrated blood. Therefore final platelet concentration was approximately 2 fold over whole blood platelet concentration. Platelet recovery is reported to be >95% and a leukocyte recovery of 58%. Venous blood samples were collected pre-, and 4 days post-exercise, and analyzed for GH, IGF-1, IGFBP-3, PDGF-BB,VEGF.

Biochemical analysis

Serum was separated by centrifuging at 825 g for 10 min and stored at -80°C for analyses of GH, IGF-1, IGFBP-3, PDGF-BB and VEGF. Serum level of these parameters was determined by enzyme-linked immuno-sorbent assay (ELISA) using commercially available kits (Shanghai Yehua Biotechnology Company,) on a diagnostic instrument (Thermo Scientific – Varioskan Flash Multimode Reader, Finland).

Statistical analysis

All calculations were performed using SPSS software (SPSS Inc., Chicago, IL, USA). The values of serum GH, IGF-1, IGFBP-3, PDGF-BB and VEGF were presented as raw values as area under the curve (AUC) during the experimental period. The AUC was calculated as the sum of four or five trapezoid areas separated by each supplement time point Two-way mixed model analyses of variance (2groups X 5 times) with repeated measures. Differences in continuous variables between groups were assessed using independent *t* test and between multiple points within the same group and were analyzed using Student's paired t test. Data is expressed as means ± SE and the level of significance was set at $p < 0.05$.

Results

There was no significant difference in body weight, height, age and exercise performance between the PRP and CONTROL group. The baseline values for plasma IGF-1, IGFBP-3, VEGF were different between the CONTROL and the PRP administered group ($p < 0.05$, Figure 2, 3, 4) whereas GH and PDGF-BB baseline values were similar in both groups (Figure 1 and 4).

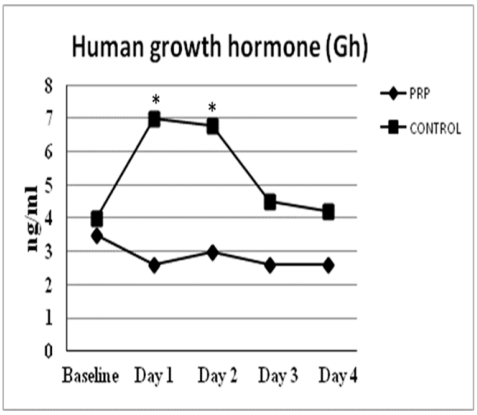

Figure 1. Human growth hormone (Gh) levels were analyzed at baseline and on days 1, 2 , 3, and 4 post-exercise induced muscle damage (Mean). *$p < 0.05$ compared with baseline analyzed by repeated measures by ANOVA. No significant differences between CONTROL and PRP , analyzed by independent-samples *t* test $p > 0.05$

However, 24 h post-exercise a significant increase in the level of the IGFBP-3 on the third day (p=0.006, Figure 3) was observed during the recovery period when compared to the baseline values in the control group. GH levels on the second and third day (p=0.01, p= 0.02, respectively, Figure 1), were also significantly increased and a similar pattern was observed for IGF-1 levels between day 1-4 (p=0.021, p=0.01, p=0.001, p=0.001, respectively) during the recovery period when compared to baseline values in the control group (Figure 2).

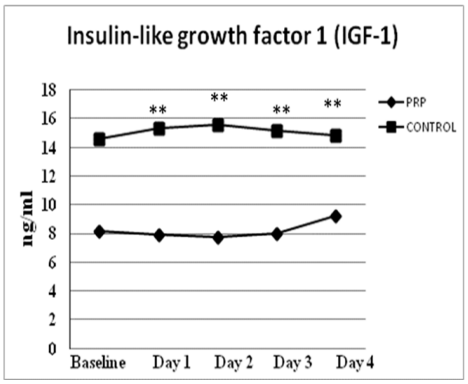

Figure 2. Insulin-like growth factor 1 (IGF-1) levels were analyzed at baseline and on days 1, 2 , 3, and 4 post-exercise induced muscle damage (Mean). **$p < 0.001$ analyzed by repeated measures by ANOVA. No significant differences between CONTROL and PRP , analyzed by independent-samples *t* test $p > 0.05$

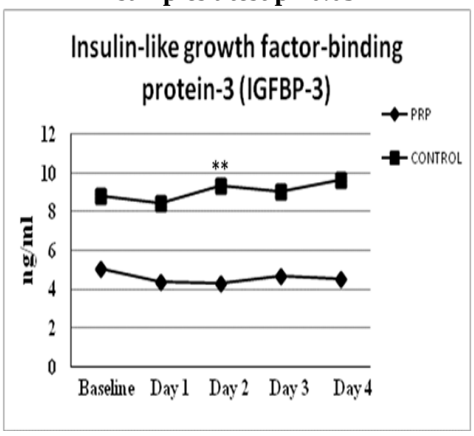

Figure 3. Insulin-like growth factor-binding-3 (IGFBP-3) levels were analyzed at baseline and on days 1, 2 , 3, and 4 post-exercise induced muscle damage (Mean). **$p < 0.001$ analyzed by repeated measures by ANOVA. No significant differences between CONTROL and PRP , analyzed by independent-samples *t* test $p > 0.05$

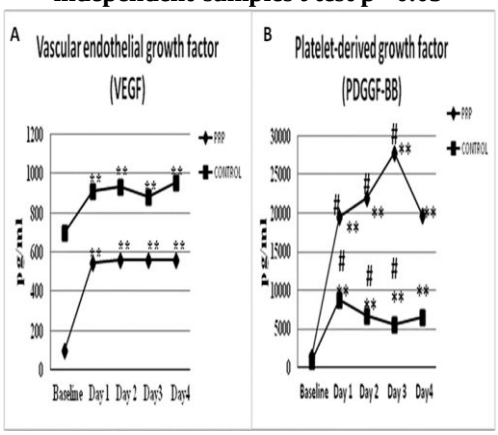

Figure 4. Vascular endothelial growth factor (VEGF) and Platelet-derived growth factor (PDGGF-BB) levels were analyzed at baseline and on days 1, 2 , 3, and 4 post-exercise induced muscle damage (Mean). **$p < 0.001$ analyzed by repeated measures by ANOVA. # $p < 0.05$, significant differences between CONTROL and PRP , analyzed by independent-samples *t* test

In contrast PRP administration inhibited the exercise induced increase in GH, IGF-1 and IGFBP-3 factors (Figures 1, 2, 3) Exercise up-regulated levels of VEGF and PDGGF-BB on day 1 to 4 post exercise in both groups (p=0.001, Figure 4). However, PRP administration resulted in a threefold increase in the levels of the PDGGF-BB and VEGF from day 1 to 4 post exercise (p=0.008, 0.03, 0.02, 0.001, respectively) when compared to the control group.

Discussion

In this paper we report the effect of a single dose of intra-muscular platelet rich plasma on growth factors in exercise-induced muscle damage in a pilot study involving six subjects. Acute exhaustive eccentric exercise up-regulated the plasma levels of GH, IGF-1, IGFBP-3, VEGF, PDGF-BB confirming exercise-induced muscle damage and regeneration. PRP administration resulted in improved VEGF and PDGF-BB and attenuated the plasma levels of GH, IGF-1, IGFBP-3 during the muscle recovery period. Inflammatory conditions have been essentially treated by the use of non-steroidal anti-inflammatory drugs (NSAIDs) although they are ineffective in reducing muscle pain and do not increase muscle performance during DOMS [15]. Also, provision of antioxidant supplementation can minimize damage to cellular structures caused by resistance training and help maintain muscular performance [16], however, there are a number of studies that have also reported no benefit of antioxidant supplementation on markers of antioxidant level or performance [17]. As an alternative to conventional treatments, platelet-rich therapy has been applied due to its potential in accelerating muscle healing and reducing a player's injury time. As far as we are aware, this study is the first to examine the effect of intramuscular PRP administration on DOMS and growth factors post exercise-induced muscle damage during the recovery period in healthy human volunteers. An acute exhaustive exercise increased the circulating levels of GH, IGF-1 and IGFBP-3 in the control group compared to the PRP group.

Importantly, our results showed that the acute exhaustive muscle exercise increased the plasma level of GH on the second and third day of the recovery period, although the baseline values were similar in both groups. Our findings on plasma GH response to acute exhaustive exercise are in agreement with previous reports [3, 18, 19] which also reported an increase in GH depending on several factors such as the volume and intensity and type of exercise. Additionally, the fitness level and the type of training also tend to influence the GH levels post-exercise responses [20, 21]. The serum IGFBP-3 levels tend to reflect the spontaneous endogenous GH secretion, and this binding protein is considered to be the most important of the carrier proteins for IGF-1, an important anabolic biomarker [22], which modulates the interaction with the receptors and accounts for 95% of the circulating IGF-1 [23].With respect to IGFBP-3 levels in this study, a significant interaction between exercise order and time was observed. Moreover, interval and the high-intensity exercise methods promote increases in IGFBP-3 levels [22]. Circulating IGF-1 somewhat increased in response to the acute resistance exercise protocol on day 1-4 post-exercise. This is in agreement with previous observations [24] which also reported that acute exhaustive resistance exercise results in increases in IGF-1 levels. Regardless of the mechanism involved in the increase in circulating IGF-1 in response to exercise, this observed increase may have a role to play in skeletal muscle regeneration and hypertrophy [25].

We also observed that intramuscular PRP administration inhibited the effect of exercise induced increase in GH, IGF-1, IGFBP-3 levels during the muscle recovery period. These results are novel and to the best of our knowledge, no data exists concerning the acute effect of intramuscular PRP administration on plasma GH, IGF-1, IGFBP-3 levels during recovery period in an acute exercise-induced muscle damage model. In general,

related studies have reported that PRP treatment has anti-inflammatory properties via its effects on the canonical nuclear factor κBsignalling pathway in multiple cell types including synoviocytes, macrophages and chondrocytes [26]. A few studies have reported the systemic response of several growth factors after a single PRP application [12, 13, 27, 28] which showed that hGH increased significantly within the first 24 hours of PRP treatment, and although IGF-1 and IGFBP-3 increased at both 24 and 48 hours, this increase was not statistically significant [13]. In contrast some studies have reported no significant systemic increases of IGF-1 level after a single dose intramuscular PRP injection [27, 28].

Our findings on increased VEGF and PDGF-BB post-exercise levels in muscle recovery period in both groups are in agreement with previous reports [29, 30, 31, 32] in which acute bout of physical exercise resulted in an increased serum level of VEGF 2 hours post-exercise [30] or after a marathon race [32]. The angiogenic growth factor VEGF is an important element in angiogenesis, and it is involved in the vascular remodeling that occurs in response to exercise and muscle contraction [29]. PDGF-BB is a mitogen for myoblasts and participates in the regeneration process in muscle development [33]. Consistent with our results, PDGF-BB protein levels were previously shown to be increased after acute bouts of maximal exercise (3-fold), but strength training did not alter this response [34]. It is known that PDGF-BB and VEGF levels are increased in response to exercise and have been implicated in muscle repair [35, 36, 37]. Other related studies have reported that the levels of the VEGF and PDGF-BB increase between 1-3 days post-PRP treatment [12, 13]. Additionally, our study demonstrated that intramuscular PRP injection improves VEGF and PDGF-BB levels during the muscle damage recovery period which was induced by acute exhaustive muscle exercise and it may have a role in repairing muscle damage. However, PRP administration attenuated the levels of GH, IGF-1 and IGFBP- in the post-exercise muscle recovery period and this finding was unexpected. These results are novel and to the best of our knowledge, no data exists concerning the acute effect of intramuscular PRP administration on plasma GH, IGF-1, IGFBP-3 levels during recovery period in an acute exercise-induced muscle damage model. One study has shown that antioxidant supplementation in men significantly lowers GH levels after hypertrophic resistance training compared to the placebo group [38]. One possible explanation is that GH, IGF-1 and IGFBP-3 levels appear to be influenced by the degree of skeletal muscular fatigue induced by exercise. Further research is needed to help determine this possibility and the potential role of intramuscular PRP injection on these growth factors.

In the present study results indicate that acute exhaustive exercise increases muscle damage markers, including plasma GH, IGF-1, IGFBP-3, VEGF and PDGF-BB indicate muscle damage. PRP administration improved the response of some of the growth factors by altering their levels and may have a role to play in the recovery and regeneration of exercise-induced muscle damage. Further studies are needed to define the potential effects of PRP on muscle growth factors during the recovery period of exercise-induced muscle damage. In the conclusion, this paper is novel in that for the first time we have shown that PRP administration can alter growth factors which are induced during excercise muscle damage. Hence, PRP may help in the recovery and regeneration of damaged muscles and this has implications for the management of injuries in elite athletes.

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