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ScienceDirect

Journal of Sport and Health Science 5 (2016) 109–114

www.jshs.org.cn

Original article

Single dose of intra-muscular platelet rich plasma reverses the increase in plasma iron levels in exercise-induced muscle damage: A pilot study

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Received 26 July 2014; revised 2 October 2014; accepted 17 November 2014
Available online 16 February 2015

Abstract

Background: Platelet rich plasma (PRP) therapy is widely used in enhancing the recovery of skeletal muscle from injury. However, the impact of intramuscular delivery of PRP on hematologic and biochemical responses has not been fully elucidated in exercise-induced muscle damage. The purpose of this investigation the effects of intramuscular delivery of PRP on hematologic and biochemical responses and recovery strategy muscle damage induced by high intensity muscle exercise (exercise-induced muscle damage, EIMD).

Methods: Moderately active male volunteers participated in this study and were assigned to a control group (control, $n = 6$) and PRP administration group (PRP, $n = 6$). The subjects performed exercise with a load of 80% one repetition maximum (1RM) maximal voluntary contraction of the elbow flexors until point of exhaustion of the non-dominant arm was reached. The arms were treated with saline or autologous PRP post-24 h EIMD. Venous blood samples were obtained in the morning to establish a baseline value and 1–4 days post-exercise and were analyzed for serum ferritin, iron, iron binding capacity (IBC), creatinine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

Results: The baseline levels of plasma iron, ferritin, IBC, CK, LDH, AST, and ALT were similar in both the control and PRP groups. However, 24-h following exercise a significant increase in these parameters was observed in both groups between 1 and 4 days during the recovery period. Interestingly, PRP administration decreased plasma iron levels compared to the control on the second day post-exercise. Plasma IBC increased in PRP group from Days 2 to 4 post-exercise compared to the control group whilst PRP administration had no effect on plasma ferritin, CK, AST, ALT, or LDH.

Conclusion: Acute exhaustive exercise increased muscle damage markers, including plasma iron, IBC, and ferritin levels, indicating muscle damage induced by exercise. PRP administration improves inflammation by reversing the increase in the iron levels post-exercise without displaying any myotoxicity and may have a role to play in the recovery of exercise-induced muscle damage.

Keywords: Exercise-induced muscle damage; Ferritin; Plasma iron; Platelet rich plasma

1. Introduction

Recently platelet rich plasma (PRP), an autologous derivative of whole blood containing a supraphysiological concentration of platelets, has gained increasing popularity in both the scientific literature and the wider media for its potential application in the treatment of traumatic musculoskeletal and sports-related injuries, cancer biology, and dermatology. In addition, it has been reported that PRP administration may improve recovery from tendon and muscle injuries.[1,2] Biologic healing utilizes the normal mechanisms for tissue repair and incorporates these at the site of injury. Blood components such as platelets migrate to the injury site and play an important role in tissue repair. Platelets contain various growth factors and cytokines that initiate and promote healing by stimulating cell migration, cell proliferation, angiogenesis, and matrix. Other important bioactive factors released from platelets include histamine and serotonin, and these platelet

Peer review under responsibility of Shanghai University of Sport.
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http://dx.doi.org/10.1016/j.jshs.2014.11.005

growth factors enhance DNA synthesis, chemotaxis, and angiogenesis, increase collagen deposition, and stimulate synthesis of extracellular matrix.[3]

It is well established that an unaccustomed and strenuous exercise in the trained and untrained individual can induce skeletal muscle damage;[4] this phenomenon is commonly known as "exercise-induced muscle damage" (EIMD) and is determined by the type, intensity, and duration of exercise.[5] Moreover, in sports, the eccentric/concentric type of exercise has been used as a specific training model for muscle strength improvement during training sessions. However, symptoms of EIMD include reduced muscular force, increased stiffness, swelling delayed onset muscle soreness (DOMS), and an increased blood activity of muscle proteins such as creatine kinase (CK > 1000 IU/L),[4] alanine transaminase (ALT),[6] aspartate transaminase (AST),[6] lactate dehydrogenase (LDH) activity,[7] and this may have a negative impact on performance.[4] Moreover, EIMD initiates an inflammatory response associated with secondary muscle damage and remodeling[8] sinceduring the acute phase, both neutrophils and phagocytic macrophages can release reactive oxygen and nitrogen species and remove debris by phagocytosis.[9] Moreover, recent studies have reported the levels of the iron-regulatory hormone hepcidin are also increased after exercise.[10–12] Hepcidin is a liver-produced peptide hormone, up-regulated in response to elevated iron levels and the inflammatory cytokine interleukin-6 (IL-6),[13,14] and an increase in hepcidin levels usually occurs as a homeostatic response to inflammatory stimuli namely the IL-6 or elevated iron levels.[13] Peeling et al.[11] reported that inflammation, hemolysis, serum iron, ferritin, and urinary hepcidin were elevated in the high intensity interval post-running session. As such, the post-exercise hepcidin response is likely to be homeostatic in nature, to help control and reduce the elevated levels of serum iron resulting from the exercise-induced hemolysis.[15]

Many studies have been published proposing various methods for treating DOMS, including cryotherapy, anti-inflammatory medication, stretching, hyperbaric oxygen, homeopathy, ultrasound, *L*-carnitine, rest, light exercise, and electromagnetic shields.[16–21] For example, non-steroidal anti-inflammatory drugs (NSAIDs) are routinely prescribed to alleviate EIMD-related symptoms and restore normal physical function of the muscle.[22] However, it has been reported that NSAIDs act by blocking Cyclooxygenase (COX) and thus they may have a detrimental effect on muscle regeneration and super-compensation.[20] Moreover, there is moderate to strong evidence that intramuscularly injected local anaesthetics and NSAIDs are myotoxic. The administration of PRP has also been reported to induce myotoxicity, however, the evidence is conflicting and further studies are required to confirm this as well as the possible myotoxic effects of corticosteroids.[23] Furthermore, clinical and histopathological studies have shown the potential myotoxicity of intramuscular injections in both animals and humans,[24,25] resulting in pain at the injection site and histopathological changes of inflammation, necrosis, and fibrosis. Besides histological changes, the local plasma CK concentration is the most commonly used valid marker for skeletal muscle myotoxicity.[26–28] There is conflicting evidence regarding the myotoxicity of intramuscular PRP injections. Two studies used an animal muscle injury model and reported increased signs of regeneration, less necrosis, and less granulomatous tissue in the muscles injected with PRP[29,30] andautologous conditioned serum (ACS),[31] than in control muscles on histological evaluation for up to 2 weeks. However, information regarding the myotoxicity of intramuscular PRP injection or the cross-talk between hematologic and biochemical response has not been reported in exercise-induced muscle damage. Therefore, we hypothesized that intramuscular PRP injection might improve inflammation and beneficial effect on DOMS and muscle damage induced by exercise without mytoxicity effects. The objective of the present study was to investigate whether the myotoxicity effects of the intramuscular PRP injection can provide an effective recovery strategy for attenuating DOMS and muscle damage induced by high-intensity muscle exercise in humans.

2. Methods

2.1. Study design

Twelve moderately active male volunteers participated in this randomized double-blind placebo-controlled trial to verify the effects of the intramuscular PRP injection on hematologic, biochemical response, and mytoxicity on muscle recovery after an eccentric/concentric exercise. Subjects were randomly placed into two groups: PRP (n = 6) and control (n = 6), 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 Balikesir University Medical Faculty Ethics Committee (2013/14) and each participant gave written informed consent prior to the study.

2.2. 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°) 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° to fully extended position slowly over 5 s, until exhaustion was experienced. The subjects were also given verbal encouragement by the investigator to maintain constant speed throughout the procedure. They were instructed to continue their normal activities and to abstain from any strenuous exercise at least 2 weeks before the experiment. Moreover, they were asked to continue their usual food intake, not to change the amount or frequency