Original Article

Effect of creatine monohydrate on time to volitional fatigue during an incremental speed running and blood parameters

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Abstract:

This study examined the effect of short-term creatine monohydrate on time to volitional fatigue during running and blood parameters. Using a random, double-blind design, eleven male subjects (age 20.23 ± 1.18 years, height 173.32 ± 4.55 cm, weight 67.05 ± 1.89 kg) participated in an incremental speed running test on treadmill following 5 days of creatine supplementation (CRE; 20 g/d followed by 5 g prior to trial) or control (CON trial). The subjects began the test with a standardized warm-up procedure of a 5-minute and 2 minutes stretching exercise for lower limbs. Each subject initially ran at 9 km/h on a treadmill. Every 2 minutes, the speed was increased by 1 km/h until the point of volitional fatigue. Creatine kinase, blood lactate, and blood glucose were measured after each trial. The results showed that the time to volitional fatigue was significantly longer in CRE than that in CON (15.08 ± 0.91 min; 11.21 ± 0.91 min, respectively) ($P < 0.05$). Levels of creatine kinase, blood lactate and glucose were significantly higher in CRE compared to CON. This suggests that the ergogenic effect of creatine monohydrate following 5 days of supplementation have a positive impact on endurance exercise.

Key words: creatine monohydrate, supplementation, blood parameters, endurance, exercise.

Introduction

Creatine (a-methyl-guanidinoacetic acid (Evangliou et al.,2009) or N-aminoiminomethyl- N-methylglycine (Alves et al.,2013)) which was discovered in 1982 by chevereul (James et al.,2002) is the most popular supplement used by athletes (Hoffman,2010;Gualano et al.,2008;Ferrauti and Remmert,2010;Paula et al.,2008; Rosene et al.,2009;Cornelissen et al.,2010;Webster et al.,2012;Taylor et al.,2011) especially following the summer olympic games in Barcelona-1992 (Rawson and Clarkson,2000). Creatine (Cr) is an amino acid derivative produced by the liver, kidneys, and pancreas (Tortora and Derickson,2009; James et al.,2002;Hoffman,2010;Andres et al.,2014). However, Cr formation begins in the kidneys (Hoffman,2010) through arginine and glycine (Dickinson et al.,2014 Hoffman,2010;Andres et al.,1999). This action catalyzed via arginine-glycine aminotransferase (AGAT) and this operation is Followed by hepatic methylation via guanidinoacetate methyltransferase (GAMT) (Dickinson et al.,2014;Paula et al.,2008;James et al.,2002). Cr then is transported free from the liver into blood stream to most body tissues via creatine transporter (Tarnopolsky et al.,2007;Dickinson et al.,2014) which is known as sodium-dependent neurotransmitter transporter (James et al., 2011;Andres et al.,1999).

The vital role of Cr in the cell is to provide for a high-energy phosphates especially during exercise (Tarnopolsky et al.,2007;Brudnak, 2004). Once inside the cells, a percentage of Cr is then phosphorylated to form phosphocreatine (PCr) by the creatine kinase (CK) (Dickinson. et al.,2014). PCr is phosphorylated form of Cr and serves as an energy source. CK catalyses the phosphorylation of adenosine diphosphate (ADP) to yield adenosine triphosphate (ATP) (James et al.,2002;Ferrauti and Remmert,2010). PCr resynthesis is an aerobic process (James et al.,2002;Rawson and Persky,2007) that takes roughly 3 to 6 minutes to complete (Rawson and Persky,2007), whereas ATP synthesis from PCr is an anaerobic process (James et al.,2002).

Cr supplementation is commonly used by athletes to increase Cr body content which result in increased PCr availability which in turn maintaining force of muscle. Approximately 50% of Cr body content is maintained by endogenous synthesis (Evangliou et al.,2009), and acquired from diet (approximately 1-5 g/d (Alves et al.,2013)) especially red meat, fish (Dickinson et al.,2014;Evangliou et al.,2009), milk products (Dickinson et al.,2014), and eggs (Tortora and Derickson, 2009). Red meat and fish contain 4 to 10 g/kg of Cr (Harris et al.,2002). About 90-95% of Cr is found in skeletal muscle (Paula et al.,2008;Evangliou et al.,2009;James et al.,2002), 40% as free Cr (Rossiter et al.,2007;Poula et al.,2008), and 60% as PCr (Andres et al.,1999;Rossiter et al.,2007;James et al.,2002;Paula et al, 2008). The remaining amounts of Cr (5%) is stored in brain, heart, testes (Paula et al.,2008;Evanglious et al.,2009;Hoffman,2010), kidneys (Evangliou et al.,2009;Paula et al.,2008), lungs and liver (Paula et al., 2008). The average plasma concentration of Cr is 50-100

micromoles per liter (Andres et al.,1999), and the average dry muscle concentration of Cr is 125 mmol. kg^{-1} (James et al.,2002;Ferrauti and Remmert,2010). However, vegetarians have a lower muscle total Cr content compared to nonvegetarians (Watt et al.,2004;Tarnoposky et al.,2007) Once Creatine concentrations in dry muscle reach 150-160 mmol. kg^{-1} , additional supplementations does not appear to be able to further increase (Hoffman,2010;James et al.,2002). After cessation of Cr intake, the Cr concentration return to a basal level for 28 days (Ferrauti and Remmert,2010;Hoffman,2010). Actually, the surplus of Cr is excreted in the urine by kidneys (Ferrauti and Remmert,2010) at a rate of 1 to 2 g/d (Jame et al.,2011). Approximately 1.6% of total Cr is degraded to creatinine (Crn) (Andres et al.,1999).

There are several types of supplementation including creatine monohydrate, Creatine pyrovate, creatine ethyl ester, tri-creatine citrate, and di-creatine citrate (Webster et al.,2012;Hoffman,2010). Creatine monohydrate is commonly used by athletes due to monohydrate is already absorbed in the gut (Harris et al.,2002). About 100% is absorbed when Cr is taken in the monohydrate form (Hoffman,2010). It is well documented that Cr monohydrate supplementation is an ergogenic resource (Harris et al.,2002;James et al.,2002;Rawson and Clarkson,2000;Ferrauti and Remmert,2010). The majority effects of Cr supplementation is increase of muscle strength and power (James et al.,2011;Harris et al.,2004 Sanchez-Gonzalez et al.,2011;Tylor et al.,2011), acts as antioxidant, stabilize of lipid membranes, maintain of mitochondrial function and ATP turnover (Dickinson et al.,2014), and alter hormones (Rawson and Clakson,2007). Sheikholeslami et al.(2011) reported that testosterone concentration was significantly higher in creatine trial compared to placebo after short-term Cr supplementation for 6 days in amature male swimmers.

During physical stress, decrease in ATP is prevented as PCr phosphorylates ADP to form ATP. Thus, athletes administrate Cr to increase availability of PCr. To achieve that, several strategies of Cr supplementation have been used in many investigation when exercise intensity maximal, repeated bouts, intermittent, or when exercise time is short. However, one of the original dosage of Cr is described that athlete should ingest 20-25 g/d ($0.3 \text{ g} \cdot \text{kg}^{-1}$ body mass (Hoffman ,2010)) for 5-7 days of loading phase (Tarnopolsky et al.,2007;Rawson and Clarkson,2000;Hoffman,2010;Ferrauti and Remmert,2010;Andres et al.,1999;James et al.,2002). This protocol is known as high-dose short-term Cr supplementation (Rawson and Clarkson,2000). To maintain the intramuscular Cr content, a maintenance phase of 2-5 g/d ($0.03\text{-}0.07 \text{ g} \cdot \text{kg}^{-1}$ body mass (Hoffman,2010;Ferrauti and Remmert,2010)) following the loading phase is good used (Hoffman,2010;Ferrauti and Remmert,2010).Athlete can administrates 3 g/d during 28 days but without a loading phase (Ferrauti and Remmert,2010;Rawson and Clarkson,2000). This course is known as low-dose long-term Cr supplementation (Rawson and Clarkson,2000). Intramuscular Cr levels may still elevated as long as the maintenance dose is taken (Hoffman,2010).

Besides the role in improvement of physical performance, Cr can penetrate the blood-brain barrier which in turn enhancing brain metabolism (Alves et al.,2013). McMorris et al. (2007) examined the effect of 5 g of Cr monohydrate per day for one week and placebo on cognition of elderlies. The main results of the previous study showed that Cr monohydrate aids cognition in the elderly. In addition, Cr supplementation might enhance physical activity in patient with heart failure (Webster et al.,2012;Cornelissen et al.,2010), and coronary artery disease (Cornelissen et al.,2010). Although some studies reported that long-term Cr supplementation is associated with muscle cramping (Oca et al.,2013), dehydration, and impair renal function (Oca et al.,2013;Neves et al.,2011;Tortora and Derickson,2009;Jounson and Mair,2006). However, Gualano et al.(2008) evaluated the effects of 10 g/d Cr supplementation for 3 months and placebo (dextrose) on renal function of healthy sedentary subject submitted to exercise. The results of the previous study indicated that Cr did not provoke renal function. Neves et al. (2011) concluded that 20 g/d Cr monohydrate for one week did not affect glomerular filtration rate in postmenopausal woman compared with placebo.

Studies focused on intermittent cycle sprint performance are more convincing with respect to ergogenic effect of Cr (Ferrauti and Remmert, 2003).. In addition, Cr supplementation might induce collagen proteolysis after sprint running (Tang et al.,2014). Studies examined the effect of Cr supplementation on endurance are less convincing. Lee et al. (2011) showed that 0.3 g/kg of Cr per day for 5 days followed by 6 mg/kg of caffeine (CRE+CAF trial) increased time to exhaustion during incremental maximum cycling test compared to creatine and placebo trials. Thus, the time to exhaustion in previous study did not significantly difference between creatine and placebo. However, in the study of Lee et al. (2011) the test was on the cycle. In our knowledge, no previous study examined the effect of Cr on time to volitional fatigue during incremental running on treadmill.

The primary purpose of this study was to determine the effect of short-term creatine monohydrate supplementation on time to volitional fatigue during an incremental speed running treadmill test. The secondary purpose was to investigate the effects of creatine monohydrate on biochemical parameters. We hypothesized that creatine monohydrate loading is suggesting to has an effect on treadmill to volitional fatigue.

Methods

Subject

Eleven males (age 20.23 ± 1.18 years, height 173.32 ± 4.55 cm, weight 67.05 ± 1.89 kg) studying at the department of physical education in the yarmouk university-Jordan were participated in this study. All of the

subjects provided written consent to the trials in the study which were approved by the Faculty's Health Research Ethics Committee. All of the subjects answered questions about health problems and use of any ergogenic aids. Results indicated that none of the subjects ingested any ergogenic aids. The subjects maintained regular physical activity which occurred routinely in the lectures, but were asked to abstain from intense exercise for 24 hours prior to visit to the laboratory. Each subject presented to the laboratory at 9:00 am after an overnight fast. After 30 minutes of the visit, 8 ml of blood sample was drawn from antecubital vein. This operation was to determine the baseline measures of blood parameters (Table.1)

Table 1. Baseline of blood parameters. Data are Mean $\pm$ SD

Variable	Value
Creatine kinase (U/L)	60.91 $\pm$ 10.32
Blood lactate (mmol.l)	1.75 $\pm$ 0.31
Blood glucose (mmol.l)	4.85 $\pm$ 0.55

Experimental design

A double-blind design was used in the study, which consisted of two trials (creatine (CRE) trial and control (CON) trial). After one hour of the first visit to the laboratory, each subject habituated to the treadmill device. During the second visit, an incremental treadmill performance test was set but without any ergogenic aids. After that, each subject ingested 250 ml only water for 5 days followed by 250 ml on the sixth day before commencement of the test. One week apart, each subject received Cr monohydrate for 5 days. On the sixth day (during the fourth visit) each subject administered 5 g Cr one hour before the trial. This separation method was to abstain the presence of Cr inside the subjects body during application of the CON trial.

Exercise procedure

After the subjects arrived at the laboratory. Each subject was administered 5g of Cr monohydrate (CRE trial) dissolved in 250 ml of warm water. After one hour, the subjects began the incremental speed running treadmill test (ISRTT) with a standardized warm-up procedure of a 5-minute on a treadmill at 8 km/h and 2 minutes stretching exercise for quadriceps, hamstring, and lower legs. Each subject initially ran at 9 km/h on a treadmill. Every 2 minutes, the speed was increased by 1km/h until the point of volitional fatigue. Blood samples (8ml) were collected from subject's antecubital vein two minutes after each trial. The blood tubes were contained ethylenediaminetetraacetic acid (EDTA) and centrifuged at 3000 rpm for 15 minutes. Analysis of serum creatine kinase was performed by (spectrophotometry/LKB Rack, Finland). (Integral 400 (Roche), Switzerland) was used to analysis the blood lactate and glucose.

Supplementation protocol

One week after the third visit to the laboratory the subject received 20 g of Cr monohydrate (4 x 5 g/d for five days followed by 5 g as a single dose before the CRE trial). Packages of supplements were coded so that neither the experimenters nor the participants were known of the contents. Cr monohydrate is odorless, tasteless, and white powder. The subjects were asked to intake their supplements preferably a long with meals (breakfast, lunch, afternoon, snack, and dinner). Each 5 g of Cr was dissolved in 250 ml of warm water. During the intake of packages of supplements, the subjects were asked to abstain from beverages or food containing ergogenic effect such as energy drink or fish meal/oil.

Statistical analysis

Data are presented as mean $\pm$ SD. Owing to study consisted of two trials for the same population, Paired sample t-test was used to determine possible differences between trials at the end of volitional fatigue. $P < 0.05$ was considered to be significant. SPSS version 16.0 was used for all analysis.

Results

Exercise time to volitional fatigue is shown in table 2. CRE trial achieved increases of 3.87 minutes during incremental speed running treadmill test (ISRTT) ($P < 0.05$) compared with CON. The time to volitional fatigue was significantly longer in CRE (15.08 $\pm$ 0.91) than that in CON (11.21 $\pm$ 0.91). Table.3 illustrates the blood parameters. At post-trial, serum CK was significantly increased in CRE (282 $\pm$ 16.88 U/L) compared to CON (230.09 $\pm$ 10.30 U/L) ($P < 0.05$) (table 3). Blood lactate in the CRE was significantly higher than that in CON (7.05 $\pm$ 0.96, mmol.l; 5.65 $\pm$ 0.64 mmol.l, respectively, $P < 0.05$) (table 3). Blood glucose was significantly higher in CRE (7.76 $\pm$ 0.80 mmol.l) compared to CON (6.02 $\pm$ 0.74 mmol.l) ($P < 0.05$) (table 3).

Table 2. Paired Samples t-test for the time to volitional fatigue in the tow trials after incremental speed running test

	Trial	Mean	SD
Time to Volitional Fatigue (min)	CRE	15.08	0.88
	CON	11.21	0.91

(*) Significantly different from CON ($P < 0.05$), (t) t-test, (df) degrees of freedom.

Table 3. Paired Samples t-test for blood parameters in the tow trials after incremental speed running test.

Variable	Trial	Mean	SD	t	Sig.
Creatine Kinase	CRE	282.00	16.88	24.982	.000*
	CON	230.09	10.30		
Blood Lactate	CRE	7.05	0.96	8.477	.000*
	CON	5.65	0.64		
Blood Glucose	CRE	7.76	0.80	17.321	.000*
	CON	6.02	0.74		

(*) Significantly different from CON ($P < 0.05$), (t) t-test, (df) degrees of freedom.

Discussion

We studied the effect of creatine monohydrate (20 g/d for 5 days followed by 5 g before commencement of trial) on time to volitional fatigue and some blood parameters. In our Knowledge, this study was the first to examine the effects of short-term Cr monohydrate supplementation on time to volitional fatigue during an incremental speed running test on treadmill. The result of the study showed that Cr monohydrate loading enhanced exercise performance and increased values of creatine kinase, blood lactate, and glucose.

The time of volitional fatigue during ISRT with CRE was greater than that achieved with CON (% increase). This result determined that short-term Cr loading (20 g/d for 5days) followed by 5 g Cr monohydrate could delay time to volitional fatigue during incremental speed running test on treadmill. This result can explained by the increment of intramuscular creatine during the loading phase (James et al.,2002;Ferrauti and Remmert,2003;Rawson and Persky,2007;Cornclissen et al.,2010) which supports rapid ATP resynthesis and allows for the continuation of muscular effort for a longer period of time (McKinnon et al.,2012). Muscle cycle contraction continues if ATP is available (Tortora and Derickson,2009). Many studies have reported that muscle Cr content increases 17-22 % and PCr 6-12 % during the loading phase (Rawson and Clarkson,2000) and body mass 0.6-1.9 kg (Ferrauti and Remmert,2010).

Additionally, an increase in time to volitional fatigue might be explained by a delay of PCr depletion (Oca et al.,2013) or a reduction of subject's feeling in muscle pain which causes exhaustion (Lee et al.,2011). Studies have reported that Cr supplementation is used to alleviate mental fatigue (Alves et al.,2013;McMorris et al.,2007), and to improve emotional state in elderly (Alves et al.,2013). Some studies related to Cr supplementation reported that the loading phase delays muscle fatigue (Andres et al.,1999;James et al.,2002). The result of the present study concur with Oliver et al. (2013). In their study, they demonstrated that ingestion of 5 g/d of Cr for 6 days increased total time to fatigue during incremental cycling exercise. Rawson et al. (2011) showed that ingestion of 2.3 g/d of Cr for 6 weeks enhanced resistance to fatigue during 5 sets of 30 concentric knee extensions at 180 degrees/s. Sheikholeslami et al. (2011) reported that short-term Cr supplementation for 6 days has decreased 50 m sprint time.

The significant increase in creatine kinase in CRE trial compared to CON is likely due to the long duration of running or depended of subjects on Cr/PCr system during the running. This result concur with kelle et al. (2013). They showed that 20 g/d of Cr monohydrate for 6 days did not prevent increase in CK level following a repeated bouts of resistance exercise (4 sets of bicep curls at 75 % 1-RM) to concentric failure. Biomarkers of muscle damage are influenced by duration of exercise (Magal et al.,2010). Prolonged endurance exercise induces increased CK level (Anugweje and Okano,2012). Nonweight-bearing exercises cause nominal increase in CK level whereas weight lifting and similar activities may result in an increase in CK levels of 10 to 20 times normal (Latham and Combell,2008).

There was a significant increase in blood lactate in CRE than in CON. This result can be explained by the longer time in running or decrease in blood lactate clearance (Lee et al.,2011). Actually, endurance exercise induces accumulation of lactate, especially at the end of race (Anugweje and Okank,2012). Thus, as the speed was increased 1km/h every 2 min in the present study, the accumulation of lactic acid in active muscles and then defused into blood could occur.

The present study showed significant increased blood glucose in CRE compared to CON. The explanation of this result is likely attributed to reduction in glucose uptake by active skeletal muscles (Lee et

al.,2011), to delayed start of the anaerobic glycolysis (James et al.,2002) which contributed to high blood glucose level, or to changes in glucose metabolism with Cr supplementation (Paula et al.,2008). This result disagree with study of lee et al. (2011). In their study, no significant difference was observed in blood glucose between CRE+PLA and BASE (control trial) after 0.3 g/d of Cr supplementation for 5 days. Also, study of Paula et al.(2008) was showed no significant differences in plasmatic glucose between Pre-supplementation and post-supplementation with decreased glucose level during submaximal cycloergometer test. Recently, Fu-Chun et al. (2014) showed that 12 g Cr monohydrate per day for 15 days induced a decrease of muscle glycogen after 60 min running. Actually, Cr supplementation could stimulate the secretion of insulin (Paula et al.,2008;Ferrautiand Remmert,2003) and increase of glucose receptors (GLUT-4) (Paula et al.,2008). Thus, the increment of insulin induces increase in creatine uptake by active muscle cells along with exercise induces increase of insulin sensitivity (Ferranti and Remmert,2003). However, muscle glycogen concentration was not measured in the present study and the mechanism of increased blood lactate and glucose with Cr supplementation need further study.

Conclusion

In summary, creatine monohydrate had effect on time to volitional fatigue during an incremental speed running test, in healthy students subjects relative to control. This suggests that supplementing creatine at a rate of 20 g/day for 5 days leading up to an incremental speed running protocol does increase the time to volitional fatigue. Thus, Cr monohydrate supplementation delayed volitional fatigue along with increased the concentration of creatine kinase and the levels of blood lactate and glucose.

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