

RESEARCH ARTICLE

## Creatine supplement affects cervical vestibular myogenic potentials in healthy volunteers

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### Abstract

**Background and Aim:** Creatine is an energy-supplying protein in neuromuscular system with a protective role in relieving neurological symptoms. Since the enzymes and other mechanism involved in the conversion of creatine in the inner ear and vestibular nuclei are found in abundance, the aim of this study was to measure the effects of creatine on cervical vestibular evoked myogenic potentials (cVEMP) parameters.

**Methods:** In this double-blind study, 35 healthy males aged 20-25 were randomly divided into an interventional (given creatine monohydrate) and a placebo groups (given maltodextrin). Participants received 5 g of dissolved powders in 250 ml water 4 times/days for 5 consecutive days. Cervical myogenic potentials were recorded before and after intervention with 500 Hz tone burst in 95 dBnHL.

**Results:** In intervention group, cVEMP amplitudes increased from 41.86 to 55.71  $\mu$ V and p13 and n23 latencies decreased from 13.81 and 22.61 to 13.32 and 21.69 ms, respectively. Also thresholds decreased from 85.52 to

81.71dBnHL. All changes were statistically significant ( $p < 0.05$ ).

**Conclusion:** The improvement of VEMP parameters following consumption of creatine supplement is likely due to increased sensitivity of saccule and vestibulocolic reflex pathway in normal subjects and maybe beneficial to patients with vestibular disorders.

**Keywords:** Creatine supplement; vestibular evoked myogenic potentials; vestibulocolic reflex; vestibular system muscles

### Introduction

In recent years, consumption of creatine supplement has been increased by athletes, patients and even ordinary people [1]. Surveys indicate that 17-74% of athletes of various ages and sport disciplines use creatine [2]. Creatine is naturally generated in human's body from endogenous production and consumption via the diet [3]. After uptake, creatine is transported to muscles, brain, inner ear, eye and heart that have high energy demand via blood circulation [1,4]. Creatine is converted into phosphocreatine (PCr) through a process catalyzed by creatine kinase (CK). PCr donates a phosphate group to adenosine diphosphate (ADP) to produce adenosine triphosphate (ATP) during first seconds of increased energy demand

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[5].

Existence of creatine and CK enzyme has positive effects on brain, muscle and inner ear. Creatine can improve function of brain pathways [6,7]. The neurological abnormalities of patients with Creatine deficiency syndromes indicate that Cr/PCr is important for normal brain function and creatine kinase deficiency results in reduced learning, decreased habituation and reduced acoustic startle reflex responses [8]. Recent studies have shown neuroprotective effects of creatine in reduction of symptoms of neurologic disorders, including traumatic brain injury [6], cerebral ischemia [9], Alzheimer's disease [10], Huntington's disease [11], Charcot-Marie-Tooth disease [12], and Parkinson disease [13]. Moreover, creatine strengthens muscles in athletes [14], improves performance during resistance training [15] and decreases muscle relaxation time [16].

CK has been identified abundantly in inner ear structures including utricle, saccule, inner and outer hair cells, and Deiter's cells in cochlea and its deficiency causes elevated hearing thresholds and vestibular dysfunction in rats [17]. Since preserving normal function of the vestibular and cochlear system during conditions of oxidative stress depends on CK efficiency [18] and creatinotherapy decreases neurologic symptoms, we examined consumption of creatine supplements effects on improvement of detection and transmission of vestibular sensory information. Among vestibular tests we selected cervical vestibular evoked myogenic potentials (cVEMPs). The cVEMP is an otolith-dependent reflex and thought to originate predominantly in the saccule [19,20]. This reflex tests mainly the integrity of saccule, the inferior vestibular nerve, medial vestibular nucleus and the sternocleidomastoid (SCM) muscle, an arc that consists of both neural and muscular components. We tried to investigate creatine consumption effects on cVEMPs parameters' outcome and to clarify possible protective role in creatine monohydrate consumers. Therefore, dietary supplement may be beneficial to patients with vestibular hypofunction.

## Methods

Thirty five untrained men (aged between 18-25 and BMI between 18-24 kg/m<sup>2</sup>) took part in this double-blind interventional study. All subjects had normal hearing sensitivity (20 dBHL, ANSI 1996) at the octave frequencies from 250 to 8000 Hz, negative history of middle ear pathology and no history of vestibular disorders, muscular, kidney or digestive disease. They gave written informed consent. The study was approved by the Human Research Ethics Committee of Tehran University of Medical Sciences.

Participants were randomly assigned to the creatine supplementation consumption (Cr.SC) group (n=19) and the maltodextrin consumption (placebo) group (n=16). The examiner and the subjects were unaware of the assignment.

The participants were asked to consume their daily dose (20 g creatine monohydrate for Cr.SC group and 20 g maltodextrin for placebo group) dissolved in 250 ml of warm water in 5 g doses at four equally spaced intervals throughout the day for 5 consecutive days. Also, they were asked not to consume products containing caffeine [21] and maintain their normal dietary intake and physical activity during the period of the study.

The cVEMPs were recorded with an auditory evoked potential system (Eclipse EP25, Denmark). Reference electrodes were placed on the upper one-third of the contracted SCM muscle, and the active electrode was placed on the upper sternum. Ground electrode was attached on the forehead. Before placing the electrodes, the skin was cleansed and scrubbed with an impedance lowering gel. Prior to each test run, impedance were measured from each electrode to ensure adequate electrode contact and symmetrical measures of impedance between sides. The responses were obtained from each side separately using 500 Hz tone bursts (rise/fall time=1 ms, plateau time=2 ms, repetition rate=5.1 Hz) in rarefaction polarity which were delivered unilaterally with an insert earphone. Each side was subject to runs of 200 tone bursts in the analysis, time for each response was 60 ms and the results were

averaged. The participants were seated in a comfortable chair and were instructed to rotate their head to the side contralateral to the stimulated ear to contract the SCM on the stimulated side. The muscle activity was amplified and bandpass-filtered (10-1250 Hz). The EMG activities were monitored during recording and subjects received a visual feedback in order to maintain muscle activities at a relatively constant level. The cVEMP responses were recorded for each subject at 95dBnHL and Ten-decibel decrements were used to determine thresholds. For each intensity level, response was repeated. Threshold was defined as the lowest intensity, which elicited cVEMP response.

The resultant response consisted of an initial negative peak (p13) and a subsequent positive peak (n23). The ipsilateral latency for p13 and n23 and the amplitude p13-n23 were analyzed after stimulation of the right and left sides. The amplitude p13-n23 and the p13 and n23 latency were calculated for each ear and compared between creatine supplementation consumption group and placebo group. To determine the relation of the amplitudes of both sides in Cr.SC and placebo groups, an asymmetry ratio (AR) was calculated using the following formula:  $AR\% = 100(AL - AR) / (AL + AR)$  and the accepted difference between amplitude was less than 34% [22].

cVEMPs were measured two times in each subjects. The first was on day 1 before creatine supplementation or maltodextrin consumption, and the second was on day 5 after consumption completion. On day 1 (before cVEMPs testing) and day 5 (after cVEMPs testing), 5ml blood sample was taken from each participant for measuring blood creatine.

Normality of p13 and n23 latencies, amplitudes and ARs were confirmed with Kolmogorov-Smirnov test before analysis. We compared cVEMP amplitudes, latencies and AR before and after consumption using paired t-tests. The cVEMP thresholds and blood creatine before and after consumption were compared using Mann-Whitney U test. All cases were considered significantly different when  $p < 0.05$ .

## Results

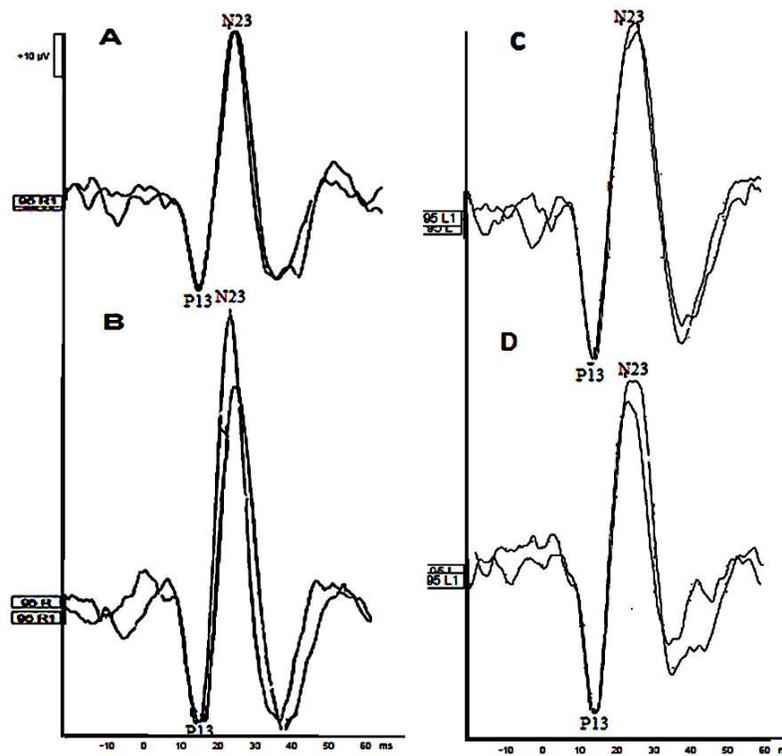
The cVEMPs recorded before and after consumption were present in all subjects. In Fig. 1, data recorded for two participants before and after creatine supplementation and maltodextrin supplementation are given as an example. The means and standard deviations for blood creatine, amplitudes, latencies, thresholds, and ARs before and after consumption are shown in Table 1. There was no significant difference between right and left ear in all of the parameters; therefore data from the right and left ears was averaged.

There were significant changes in the blood creatine, p13 and n23 latencies, amplitudes and threshold ( $p < 0.05$ ). No significant change was observed in the AR before and after creatine monohydrate consumption ( $p = 0.916$ ).

## Discussion

In this study we found that creatine monohydrate had significant effects on p13 latency, n23 latency, amplitude and threshold but could not significantly change AR.

The p13 and n23 latencies significantly increased after creatine supplementation. Intracellular creatine is responsible for rapid transphosphorylation and ATP-creatine transphosphorylase affects muscle relaxation time [23]. ATP has relaxing effect on muscle function and this mechanism is supported by two substances that normally occurring in tissues, PCr and inorganic pyrophosphate (PP) [24]. PCr is closely linked with muscle actin and actin is responsible for the absorption of nucleotide by the contractile elements [25] and this relationship increases muscle contraction and accelerate relaxation time in muscle fibers [26]. Similar to muscle fibers, nervous system uses PCr to supply its high and fluctuating energy demands [5]. Increasing ATP results in closure of ATP-sensitive  $K^+$  channels such as Kir6.1 and Kir6.2 which are found in the vestibular system [27]. Closure of channels leads to cell firing and accelerates action potentials propagation through lateral vestibulospinal tract (LVST) and medial vestibulospinal tract (MVST) to lower targets.



**Fig. 1. The cVEMPs recorded before (upper panel) and after (lower panel) consumption in creatine supplementation consumption group (A,B) and maltodextrine consumption (placebo) group (C,D).**

Amplitude significantly increased in Cr.SC group. In addition to the integrity of neural pathway from ganglion cell to accessory nerve, the amount of cVEMP amplitudes depend on muscle contraction. Bozler (1953) found that if PCr exists in contracting muscle although ATP has been washed out, muscle fibers are still able to contract well. PCr accelerates relaxation time of muscle even if concentrations of ATP are very low. Therefore, PCr is a strengthening factor and prepares a pool of energy for muscle tissue that boosts muscle contraction, albeit the amount of PCr effects in muscle fibers depends on the presence of bound nucleotide which acts as an energy transfer mechanism [26]. These effects of PCr can lead to an increase of amplitude in cVEMP test.

Creatine consumption causes ATP increase in vestibular hair cells, and first and second order neurons. Through mechanism mentioned above, increasing ATP leads to cell firing that in turn,

causes enhancement of the myogenic potentials since the magnitudes of the myogenic potential amplitudes depend on action potentials summation in vestibular nuclei. The final result would be improvement of performance and sensitivity of vestibular system [28]. Moreover, Shin et al. found that hair bundles are specialized for ATP delivery via creatine kinase. They found that creatine kinase was the next most abundant bundle protein in hearing and vestibular organs maintains high ATP levels in both systems, and eventually is necessary for high-sensitivity hearing and vestibule function [17]. After Inhibition of creatine kinase by dinitrofluorobenzene (DNFB), Shin et al. used tail-suspension and swim tests to evaluate vestibular function in knock-out mice. The results of this study showed malfunctioning of the vestibular system [17]. The above results show that increase of PCr can lead to enhancement of amplitude in cVEMP test and

**Table 1. Comparison of mean (standard deviation) of cVEMP parameters before and after consumption in two groups**

Parameters	Creatine supplementation consumption group (n=19)			Maltodextrin consumption (placebo) group (n=16)			p*
	before	after	p	before	after	p	
Blood creatine (mmol/kg dm)	1.00 (0.16)	1.27 (0.18)	0.000**	1.05 (0.17)	1.06 (0.16)	0.564**	0.000**
p13 latency (ms)	13.81 (0.6)	13.32 (0.7)	0.015***	13.98 (1.03)	14.18 (1.05)	0.110***	0.003***
n23 latency (ms)	22.61 (0.95)	21.69 (0.27)	0.000***	23.97 (1.56)	24.11 (1.70)	0.067***	0.000***
Amplitude (µv)	41.86 (23.03)	55.71 (32.81)	0.000***	51.51 (17.90)	48.55 (20.10)	0.102***	0.000***
Asymmetry ratio (%)	-0.47 (12.80)	-0.15 (9.32)	0.916***	2.31 (11.73)	1.36 (12.38)	0.150***	0.315***
Threshold (dB)	85.52 (6.50)	81.71 (5.33)	0.000**	83.90 (3.53)	84.16 (3.73)	0.317**	0.000**

\*Comparison of changes between groups

\*\* Mann-Whitney U

\*\*\* Paired t-test

reduction of threshold.

Asymmetrical ratio did not significantly change in Cr.SC group because blood uniformly distributed in the body and loading of creatine was equally distributed in cVEMP arc reflex.

### Conclusion

Creatine consumption leads to enhancement of cVEMP amplitudes and reduction of latencies and thresholds that means creatine supplements improves sensitivity of saccule and vestibule-cervical reflex pathway in normal male. We suggest dietary administration of creatine supplement may be beneficial to patients with vestibular weakness.

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