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Original Article

A SUPLEMENTAÇÃO DE CREATINA PROMOVE MUDANÇAS NA FUNÇÃO COGNITIVA EM PESSOAS COM DOENÇA ARTERIAL PERIFÉRICA? UM ENSAIO CLÍNICO RANDOMIZADO

DOES CREATINE SUPPLEMENTATION PROMOTE CHANGES IN COGNITIVE FUNCTION IN PEOPLE WITH PERIPHERAL ARTERIAL DISEASE? A RANDOMIZED CLINICAL TRIAL

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RESUMO

O objetivo do estudo foi verificar o efeito de oito semanas de suplementação de creatina na função cognitiva de pacientes com doença arterial periférica (DAP) sintomática. Os pacientes (n=29), de ambos os sexos, foram divididos de forma randomizada e duplo-cega em dois grupos, Placebo (PLA, n = 15) ou creatina monoidratada (Cr, n = 14). Todo o protocolo de suplementação durou oito semanas e incluiu uma fase de carregamento de 20g/dia durante uma semana, divididas em quatro doses diárias iguais, seguida por uma fase de manutenção de 5g/dia nas sete semanas subsequentes. Antes e após o período de suplementação, a função cognitiva foi avaliada usando o teste Stoop. Foram considerados o número de respostas corretas e o tempo de resposta (segundos). O Modelo de Equação de Estimativa Generalizada foi usado para comparações entre os grupos. O nível de significância foi P <0,05. Para o número de respostas corretas (PLA: pré 26 ± 5 vs. pós 26 ± 5; Cr: pré 24 ± 5 vs. pós 25 ± 5, p = 0.801) e o tempo de resposta (PLA: pré 4.9 ± 6.1 s vs. pós 4.9 ± 5.2 s; Cr: pré 2.7 ± 4.4 s vs. pós 1.2 ± 4.6 s, p = 0.820) não foram encontradas diferenças significativas. Oito semanas de suplementação de creatina parece não melhorar a função cognitiva de DAP sintomáticos.

Palavras-chave: Claudicação intermitente. Função cerebral. Ingestão de dieta.

ABSTRACT

The aim of the study was to verify the effect of eight weeks of creatine supplementation on cognitive function in patients with symptomatic peripheral arterial disease (PAD). The patients (n=29), of both sexes, were randomly divided in a double-blind manner into two groups: Placebo (PLA, n = 15) or creatine monohydrate (Cr, n = 14).. The entire supplementation protocol lasted eight weeks and included a loading phase of 20g/day for one week, divided into four equal daily doses, followed by a maintenance phase of 5g/day for the subsequent seven weeks. Before and after the supplementation period, cognitive function was assessed using the Stoop test. The number of correct answers and response time (seconds) were considered. The Generalized Estimation Equation Model was used for comparisons between groups. The level of significance was P <0.05. For the number of correct answers (PLA: pre 26 ± 5 vs. post 26 ± 5; Cr: pre 24 ± 5 vs. post 25 ± 5, p = 0.801) and response time (PLA: pre 4.9 ± 6.1 s vs. post 4.9 ± 5.2 s; Cr: pre 2.7 ± 4.4 s vs. post 1.2 ± 4.6 s, p = 0.820) no significant differences were found. Eight weeks of creatine supplementation does not appear to improve cognitive function in symptomatic PAD.

Keywords: Intermittent claudication. Brain function. Dietary intake.

Introduction

Peripheral arterial disease (PAD) affects 202 million people worldwide[1]. PAD increases the costs of public health services[2], leads to poor quality of life[3], reduced functional capacity[4], and is associated with a high rate of mortality from all causes and cardiovascular diseases[5].

PAD is a marker of dementia and cognitive impairment[6-7]. The evidence indicates that, when compared to individuals without the disease, patients with symptomatic PAD exhibit lower cognitive performance in domains such as non-verbal memory, executive function, concentration, manual dexterity, and perceptual-motor speed[8]. As there is an association between cognitive dysfunction and functional impairment in this population, these findings become clinically significant[9]. Nutritional strategies to minimize the impacts of cognitive impairment have been widely studied[10-13].

Recently, its use in cognitive function has been studied. Studies have demonstrated the potential benefits of creatine supplementation on cognitive function in young[10] elderly individuals[14-11], people with mild traumatic brain injuries[12], and depression[15]. While much of the creatine is produced in the kidneys, liver, and pancreas, it can also be endogenously synthesized in the brain. [16].

The brain, despite comprising only about 2% of the total body mass, is a complex and highly energy-demanding organ, consuming approximately 20% of the total energy while at rest [17]. Neurons need a continuous provision of adenosine triphosphate (ATP) for diverse cellular functions, such as maintaining ionic gradients, neurotransmitter release, and synaptic activity[18]. Due to its importance in ATP resynthesis, creatine has been investigated in situations of increased cognitive metabolic demand[11,19,20].

In patients with PAD, the use of creatine supplementation has been investigated in renal function[21] and in functional capacity and muscle oxygen saturation[22]. Creatine supplementation is safe for renal function, and the increase in plasma creatine content is effective, indicating that patients with PAD have good creatine absorption when administered exogenously[21]. In terms of functional capacity, creatine supplementation does not seem to promote an increase in walking distance, muscle strength, and balance, nor does it promote changes in oxygen saturation in the calf muscles of symptomatic PAD patients[22].

In fact, there is a need for studies that investigate the effects of Cr supplementation on the various health conditions of patients with PAD, especially symptomatic ones. The promising effects of creatine supplementation on cognition reinforce the use of Cr in patients with other clinical conditions, in addition to the elderly[11] or individuals with neurological diseases[12], and its use in patients with vascular diseases could be explored.

Given that symptomatic PAD patients present cognitive dysfunctions[23,24], creatine supplementation can be an efficient and alternative strategy to improve cognitive function in PAD patients[8,23]. Based on the hypothesis that creatine supplementation can enhance cognitive function, the present study aimed to investigate the effect of eight weeks of creatine supplementation on cognitive function in symptomatic PAD patients.

Methods

Experimental design

From December 2016 to October 2017, an 8-week randomized, double-blind, placebo-controlled clinical trial (NCT02993874) was conducted in São Paulo, Brazil. This study follows the CONSORT guidelines[25]. The patients were divided in a double-blind manner into two experimental groups: Placebo (PLA; n = 15) or creatine monohydrate (Cr; n = 14) supplementation. Sex and total walking distance were considered for randomization (1:1). Assessments were conducted before and after the supplementation period.

Participant recruitment and screening

The sample consisted of 29 symptomatic PAD patients of both sexes. The inclusion criteria required patients to: a) present symptoms of intermittent claudication during the six-minute walk test; b) have an ankle-brachial index (ABI) <0.90 in one or both lower limbs; and c) have a creatinine clearance <30 mL/min, indicating the absence of chronic renal failure. Patients with musculoskeletal disorders that could prevent participation and those with gastrointestinal adverse effects due to supplementation were excluded from the sample. The research was carried out in accordance with the guidelines of the Declaration of Helsinki, approved by the Ethics Committee of Hospital Israelita Albert Einstein, Brazil (process 62601416.7.0000.0071), and all participants were informed about the study procedures and signed a consent form.

Creatine supplementation protocol and blinding procedure

Patients received coded sachets with similar colors and textures, containing either placebo (PLA) (dextrose - Probiotica, São Paulo, Brazil) or creatine monohydrate (Cr) (Creapure, AlzChem Trostberg GmbH, Germany). The protocol was divided into two phases. In the first phase, referred to as the loading period, participants received 4 daily doses of 5g for one week, and they were instructed to ingest the sachets in the morning, at lunch, in the afternoon, and at night. In the second phase, called the maintenance period, participants ingested 5g daily for seven weeks, always after lunch[26-27]. The provided creatine monohydrate had a high degree of purity, according to the manufacturer's report. All blinding and supplement delivery procedures were conducted by a third party who was not directly involved in the study.

Preliminary assessment

Clinical characteristics were obtained during a vascular consultation. Body mass (kg) and height (m) were measured (Welmy, São Paulo, Brazil), and the body mass index (BMI) was calculated (BMI = body mass / height²). The ankle-brachial index (ABI) was determined by the ratio of ankle to brachial systolic blood pressure. Arm blood pressure was measured using the auscultation technique, while ankle blood pressure (in the dorsalis pedis artery or posterior tibial artery)[28] was measured using a Doppler Vascular device (Martec DV600, 7-10 MHz, height: 16 cm; width: 9 cm; depth: 4.5 cm, Ribeirão Preto, Brazil). An aneroid sphygmomanometer was utilized for both measurements, as previously described[5]. All measurements were performed by a trained and experienced assessor.

Assessment of cognitive function

The Stroop test[29] was administered individually using a computer, lasting approximately five minutes. The test was performed in an adequately lit room, in an environment free from noise, with a controlled temperature (23º to 25ºC) to prevent distractions and increase the participants' comfort level. At the start of the test, the participants were informed that they were going to be presented with a series of color stimuli (yellow, blue, green, red) and that the test would be composed of three phases; the first phase comprised selecting the presented color on a square on the computer screen, the second consisted of choosing the color written on the screen, and the third of selecting the color of the word presented on the screen. The participants were instructed in every phase to choose the alternatives as fast and as correctly as possible. The test was performed in the same order for all participants, starting with phase 1, followed by phases 2 and 3. For the selection of colors, the participants selected the key (<) for colors on the left and the key (>) for colors on the right. If no response was given in 4000 milliseconds or the response was incorrect, the score was considered incorrect.

Statistical analysis

Based on a previous study[30], with an effect size of 0.46, α = 0.05, and 80% power, the sample size required to detect a significant interaction was 28 patients (14 per group) using GPower 3.19 software. Normality of data was assessed using the Shapiro-Wilk test. Comparisons of sample characteristics were conducted using either independent samples t-test or Mann-Whitney U test, depending on data distribution. Categorical data were compared using the Chi-square test. Between-group comparisons at baseline were tested using the Mann-Whitney U test. Generalized Estimating Equations model was used to compare the number of correct responses and response time on the Stroop test between groups. All analyses were performed using SPSS (Statistical Package for Social Sciences), version 25. Statistical significance was defined as $P<0.05$.

Results

In the pre-supplementation period, both groups were homogeneous ($p>0.05$), as shown in Table 1, which presents the sample's characterization data at baseline.

Table 1. Characteristics of the groups at baseline.

	PLA (N=15)	Cr (N= 14)	P-Value
Women (%)[a]	54	46	0.56
Age (years)[a]	64 ± 8	64 ± 10	0.54
Weight (kg)[a]	77 ± 10	68 ± 17	0.18
Height (m)[a]	1.64 ± 0.09	1,60 ± 0.06	0.21
Body mass index (kg/m^2)[a]	28.7 ± 3.1	26.7 ± 6.5	0.43
Ankle-brachial index (mmHg)[a]	0.50 ± 0.13	0.51 ± 0.16	1.00
Initial claudication distance (m)	143 ± 84	143 ± 65	0.88
Total walking distance (m)[a]	371 ± 81	344 ± 82	0.65
Comorbidities (%)			
Hypertension[c]	86.7	78.6	0.67
Diabetes[c]	60.0	50.0	0.43
Dyslipidemia[c]	6.7	7.1	0.74
Current smoking[c]	78.6	78.6	0.68
Coronary artery disease[c]	46.7	28.6	0.26
Medications (%)			
Diuretics	46.7	35.7	0.41
ACE inhibitors	21.4	35.7	0.33
ARA II	46.7	35.7	0.41
BCC	35.7	28.6	0.50
Insulin	35.7	28.6	0.50

Statins	73.3	78.6	0.54
Vasodilators	7.1	14.3	0.50

Note: Data are presented as mean and standard deviation for numerical variables and frequency for categorical variables. [a]T-test for independent samples. [b]Mann-Whitney U test. [c]Chi-square test. PLA: placebo group. Cr: creatine group. ACE: Angiotensin-converting enzyme inhibitors. ARA II: Angiotensin II Receptor Blocker. BCC: Calcium Channel Blockers.
Source: authors.

Initially, 160 patients were interviewed for eligibility; of these, 118 did not meet the inclusion criteria. Thus, 32 patients started the study, with 17 allocated to the placebo group and 15 to the Cr group. Before the beginning of the protocol, one patient was excluded for not attending the evaluation (placebo). During the loading period, one patient receiving Cr was excluded due to gastric discomfort. During the maintenance supplementation period, one patient was excluded for presenting pleural perfusion (placebo group). Twenty-nine patients completed the study (PLA n = 15 and Cr n = 14) (Figure 1).

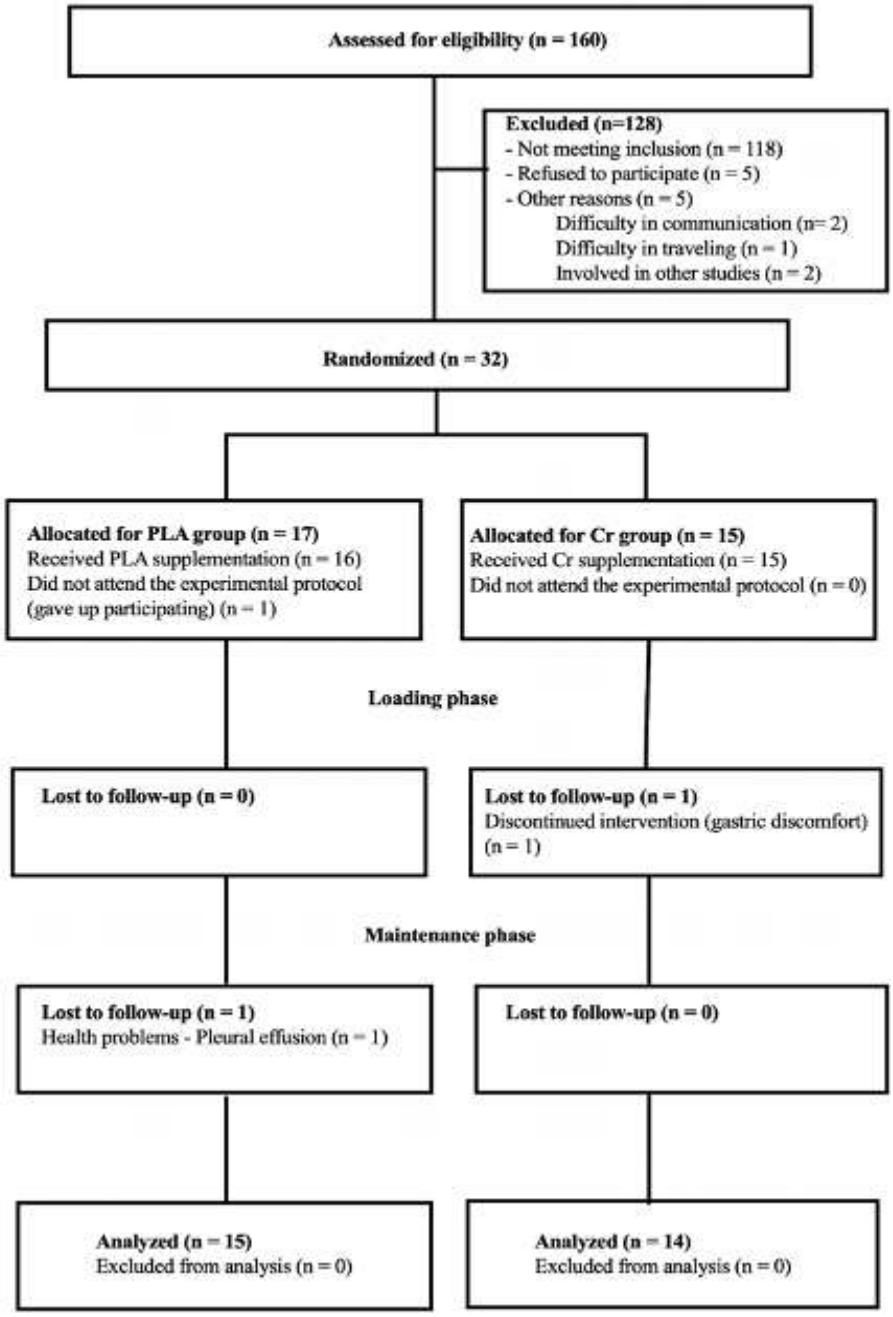

Figure 1. Study flow

No significant interactions were found in the number of correct answers (figure 2A) (PLA: pre 26 ± 5 vs. post 26 ± 5; Cr: pre 24 ± 5 vs. post 25 ± 5, time*intervention effect p = 0.801) or response time (PLA: pre 4.9 ± 6.1 s vs. post 4.9 ± 5.2 s; Cr: pre 2.7 ± 4.4 s vs. post 1.2 ± 4.6 s, time*intervention effect p = 0.820) (Figure 2B).

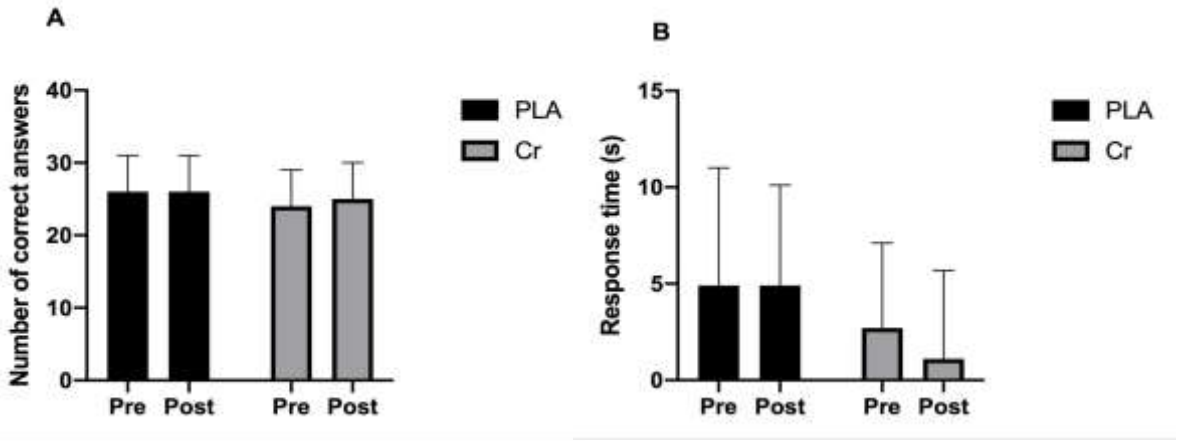

Figure 2. Cognitive function parameter data before (pre) and after (post) eight weeks of Cr supplementation (PLA, n = 15; Cr, n = 14)

Discussion

The main findings of the study were that an eight-week period of Cr supplementation did not affect cognitive function in patients with symptomatic PAD.

Studies that verified the effects of creatine supplementation on cognitive function are recent[30-31]. The first studies carried out with young individuals, without cognitive dysfunctions, apparently did not demonstrate potential effects of creatine supplementation on cognitive function[30]. However, over the years, creatine supplementation has become promising in improving cognitive function in some specific populations[32-33]. Morris et al[32] demonstrated that creatine supplementation had positive effects on mood and cognitive tasks, which required stress in the prefrontal cortex area of sleep-deprived subjects. Interestingly, similar results were demonstrated in elderly. McMorris et al[33], showed positive effects of creatine supplementation in random number generation, progressive number and spatial recording tasks, long-term memory tasks, except in reverse number recall. These data reinforced the need for future studies to be carried out in other populations.

In our study we sought to verify the effect of eight weeks of creatine supplementation in symptomatic PAD patients. Our findings did not demonstrate effects of supplementation on the number of correct answers and response time to the Stroop test. These indicators correspond to the selective attention and inhibitory control domains of the brain. Our findings corroborate clinical trials carried out in young adults[34] healthy elderly people[35]. In fact, there is controversy between the effects of creatine supplementation on cognition. A recent meta-analysis, which included only randomized controlled trials, demonstrated positive effects of creatine supplementation on cognition in healthy individuals[13], in which the magnitude of the effect was greater in older adults. However, the lack of sample homogeneity is a conflicting factor in the interpretation of these findings[13]. On the other hand, studies that investigated the effects of creatine supplementation in people with creatine deficiency in the body[36], demonstrated positive effects on cognition. Benton e Donohoe[36], supplemented 120 women (placebo, n = 60; creatine, n = 61) for 5 days (5g/day), and found that creatine supplementation did not influence measures of verbal influence and vigilance. However, in vegetarian women and those who did not consume meat, creatine supplementation resulted in an improvement in memory. Although not described in this study, all symptomatic PAD participants in the present study consumed

meat, with an average protein intake of 49.7g and 59.2g, placebo and creatine groups, respectively[21]. Indeed, increasing brain creatine content under conditions of creatine deficiency appears to be a relevant factor for the mechanism of action of exogenous creatine supplementation[12].

Apparently, the effects of creatine supplementation on cognition depend on the condition of each population being investigated. Turner et al[37], investigated the effect of creatine supplementation in young healthy individuals undergoing acute hypoxia. The findings identified that creatine supplementation increased cortical-motor excitability, by increasing the availability of energy in the brain system due to the increase in neural membrane potentials[38]. These findings are supported in patients with depression and bipolar state[39], in which long-term creatine supplementation (6 weeks of supplementation) was found to improve verbal influence in this population[39], creatine supplementation did not improve the parameters of inhibitory control and cerebral selective attention, corroborating the findings of our study. It is important to highlight that the brain creatine content in the left dorsolateral prefrontal cortex, left hippocampus and occipital lobe, brain areas responsible for memory and planning, appears to remain unchanged after creatine supplementation[40]. This mechanism suggests that exogenously administered creatine supplementation is not capable of crossing the blood-brain barrier in humans[11]. However, creatine supplementation appears to be effective in patients with stressful conditions or deficiencies in creatine transporters at brain levels[41]. In our study, we assumed that because PAD patients were symptomatic, they presented cognitive declines[23]. However, for creatine supplementation to have an effect on the brain, cognitive declines need to be severe[37].

Our study has some limitations. We did not measure the amount of brain creatine, only blood plasma creatine (PLA: pre 21.5 ± 38.9 μmol/l vs. post 30.7 ± 39.8 μmol/l; Cr: pre 32.1 ± 61.4 μmol/l vs. post 163.2 ± 42.65 μmol/l)[22]. Our protocol consisted of an eight-week supplementation period. Dechent et al.[42], in a study carried out with healthy young adults, after a protocol of creatine supplementation composed of 20g/day for 4 weeks, suggested that the brain could be resistant to exogenous creatine, requiring a protocol with long-term high supplementation doses. In our study, we used a 1-week loading period (20g/day, divided into 4 doses of 5g) followed by a 7-week maintenance period (5g, 1x daily), totaling 8 weeks. However, the duration of creatine supplementation does not seem to influence cognitive responses, even after 24 weeks of supplementation[35]. The sample was heterogeneous, composed of people with PAD associated with hypertension, diabetes, dyslipidemia, coronary artery disease and smokers. The age range and heterogeneity of the sample must also be considered, as these conditions impact cognitive function. Our findings are restricted to patients with symptomatic PAD, and further studies with other clinical populations are needed. Finally, it is suggested that future works combine creatine supplementation with resistance training to investigate cognitive function[(8)].

Conclusion

As a practical application, our findings suggest that eight weeks of creatine supplementation is not capable of altering cognitive function in the areas of selective attention and inhibitory control in the brain in symptomatic PAD patients, suggesting that the effects of supplementation are mainly dependent on the cognitive health condition of each population.

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