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Effects of creatine supplementation on exercise performance and muscular strength in amyotrophic lateral sclerosis: preliminary results

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Abstract

Creatine supplementation in humans has been reported to enhance power and strength both in normal subjects and in patients with various neuromuscular diseases. The purpose of this study was to examine the effects of supplementation on exercise performance and maximal voluntary isometric muscular contraction (MVIC) in Amyotrophic Lateral Sclerosis (ALS) patients.

We report the results obtained in 28 patients with probable/definite ALS. In each patient we acquired the dynamometric measurement of MVIC in 10 muscle groups of upper and lower limbs and a measure of fatigue by means of an high-intensity intermittent protocol in elbow flexors and knee extensors muscles. All patients completed the protocols at the baseline and after supplementation of 20 g per day for 7 days and after supplementation of 3 g per day for 3 and 6 months. MVIC increased after 7 days of supplementation in 20 patients (70%) in knee extensors and in 15 (53%) of them also in elbow flexors. A statistically significant difference between pre and post-treatment mean values of MVIC was found both in elbow flexors ($P < 0.05$) and knee extensors ($p < 0.04$). The analysis of the slopes of fatigue test showed a statistically significant improvement after 7 days of supplementation in 11 patients (39%) in elbow flexors and in 9 patients (32%) also in knee extensors muscles. During the 6-month follow-up period all the examined parameters showed a linear progressive decline.

In conclusion, our preliminary results have demonstrated that supplementation temporary increases maximal isometric power in ALS patients so it may be of potential benefit in situations such as high intensity activity and it can be proposed as a symptomatic treatment.

Keywords: Amyotrophic lateral sclerosis; Creatine supplementation; Fatigue; Strength

1. Introduction

Creatine supplementation in humans has been reported to elevate muscle total content [1,2] as well as enhance power and strength [3,4], decrease performance time [5] and increase muscle mass [3]. Because of these effects, it has been used as therapeutic agent in neuromuscular disease [6], in muscular dystrophies [7] and in mitochondrial cytopathies [8]. In all studies, supplementation increased the high intensity strength. Moreover, previous experimental studies [9] demonstrated that administration protected transgenic Amyotrophic Lateral Sclerosis (ALS) mice from increase in biochemical indices of oxidative damage.

The purpose of this study was to examine the effects of supplementation on exercise performance and maximal isometric muscular strength (MVIC) in ALS patients.

2. Patients

A total of 53 patients (28 M and 25 F) entered the study. The criteria for entry included: (1) clinical status consistent with probable/definite ALS; (2) Amyotropic Lateral Sclerosis-Functional Rating Scale (ALS-FRS) score ≥ 20; (3) Medical Research Council (MRC) score ≥

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3; (4) Forced Vital Capacity (FVC) ≥ 50%. Exclusion criteria included: (1) Age over 75 years; (2) Disease duration longer than 5 years; (3) Prior use of monohydrate or anabolic steroids.

3. Methods

3.1. Clinical and functional examination

This included a computation of the Norris score [10] and the ALS-FRS [11]. Bulbar function was also quantified on a scale from 3 (normal) to 0 (markedly impaired) for speech and from 4 (normal) to 0 (markedly impaired) for eating; the maximum bulbar score was 7. Body weight was also assessed.

3.2. Maximum isometric muscle strength

In each patient MVIC was evaluated by means of a dynamometric system made and standardized in our Institute according to the guidelines of the Tufts Quantitative Neuromuscular Evaluation [12]. The characteristics of the device and the standardization of the protocol had been previously described [13,14]. Dynamometric measurement of MCVI of 10 muscle groups of upper and lower limbs (shoulder, elbow, hip, knee flexors and extensors, ankle dorsiflexors and plantar flexors) and of the grip of both sides of the body was obtained in each patient. The mean values of upper and lower limbs were considered in the analysis.

3.3. Fatigue test

A high-intensity intermittent protocol was also chosen to test fatigue. All examinations were performed by two registered physical therapists handling the same equipment utilized for the dynamometric measurements of MVIC. Patients were asked to perform three consecutive maximal efforts of 4–5-s duration of elbow flexors and knee extensors muscles. The maximum force generated during each effort was recorded and the mean of the three trials was used as a measure of the MVIC. Then subjects were asked to perform 12 maximal efforts of 5-s duration separated by a 5-s interval (Fig. 1, left panel). A software programme acquired the analogue signal during each voluntary contraction and automatically computed the maximal peak of strength, the rise time and the area of the contraction peak. We computed for each session the slope of regression line fitting the values of the peaks obtained at each efforts (alfa-coefficient) in function of time. In order that each of the measurements be weighted approximately equally, the values of the peak force had been previously normalized and expressed as percentage of the mean of the three maximal peaks (Fig. 1, right panel). Subjects were tested by the same examiner twice on successive days to assess the learning effect. The test has been previously standardized in a group of 11 normal volunteered subjects.

3.4. Experimental design

Eligible patients were consecutively recruited from January 2000 to June 2000. All patients gave their informed

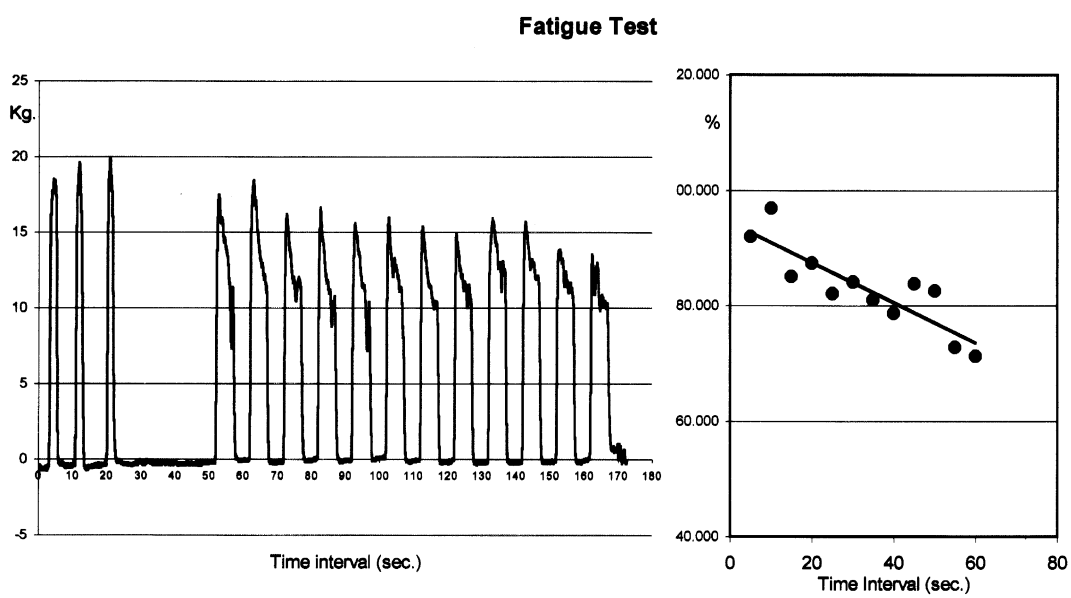

Fig. 1. Example of the fatigue test in a ALS patient. Left panel: the peaks of MVIC generated during each effort in knee extensors muscle are reported. In the first part of the trace the three consecutive maximal contractions are shown (the mean of the three trials was used as a measure of the MVIC) followed by the 12 maximal efforts of the fatigue test. The contractions of 5-s duration are separated by a 5-s interval. Right panel: the values of the peaks obtained at each effort, expressed as percentage of the mean of the three maximal peaks, are fitted in function of time and the regression line computed.

Table 1
Baseline characteristics of patients who entered in the analysis

Variable	
Number of patients	28
Sex	15 M and 13 F
Mean age	57.46 ± 12 (range: 27–75)
Clinical form of disease at onset (months)	18 S and 10 B
Mean duration of the disease (months)	22.5 ± 17 (range: 8–60)
Norris score	73.7 ± 13 (range: 45–96)
ALS-FRS score	29.3 ± 4.8 (range: 20–37)
FVC (%)	87.2 ± 24 (range: 50–120)

consent prior to their inclusion in the study. At day 1 patients underwent clinical examination, spirometric evaluation of the forced vital capacity (FVC) and dynamometric measure of MCVI. At day 2 the fatigue test was performed and at day 3 it was repeated to assess the learning effect. The second experiment was used as baseline pre-treatment evaluation. After baseline testing, patients began consuming 20 g monohydrate per day for 7 days. This dosage pattern of administration has been shown to increase muscle in normal subjects [1]. Fatigue test was assessed after 7 days of supplementation.

To examine the effects of long-term use patients progressively reduced the daily dose and continued to consume 3 g per day for 6 months; 2 or 3 g of supplement per day, in fact, has been found to maintain elevated muscle stores [2]. Patients were seen at the 3rd and 6th month of supplementation by means of clinical and functional examination, FVC and MVIC. Because this assessment is part of the routine monitoring of all ALS patients in our Institute, a group of 20 patients had also a 6-month period of observation before supplementation.

4. Statistical analysis

Data were analyzed using the paired *t*-test while an unpaired *t*-test was used to compare the mean values. Simple regression analysis was used to determine the rate of decline of MVIC during the fatigue test. Correlations with clinical variables were performed by means of Spearman rank correlation coefficient. Significance was accepted at $P < 0.05$.

5. Results

Four of the 53 patients enrolled were unable to perform the entire protocol, 5 patients were unable to complete the 6-month treatment period, 10 patients dropped out and 6 patients withdrew because of side effects, hence, 28 patients entered in the analysis. The baseline characteristics of these patients are reported in Table 1.

In the short term, diarrhea was the most common side effect of large doses of creatine ingestion (20 g per day) while 20% of subjects experienced increase of fasciculations and cramps. No deterioration in liver and renal functions was detected.

5.1. Maximum isometric muscle strength

After 7 days of 20 g per day supplementation we found an increase of MVIC in 20 patients (70%) in knee extensors and in 15 (53%) of them also in elbow flexors.

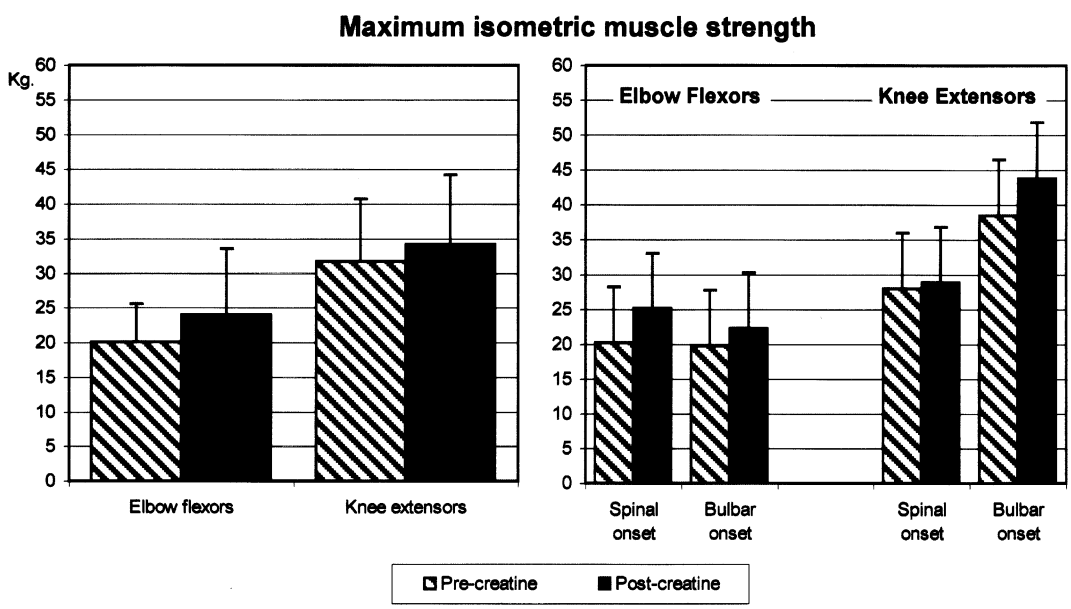

Fig. 2. Left panel: comparison of the mean values (±S.D.) of MVIC before and after 7 days 20-g supplementation both in elbow flexors and knee extensors muscles. Right panel: comparison of the mean values (±S.D.) of MVIC before and after 7 days of 20-g supplementation both in elbow flexors and knee extensors muscles of patients classified on the basis of the clinical form of the disease at onset.

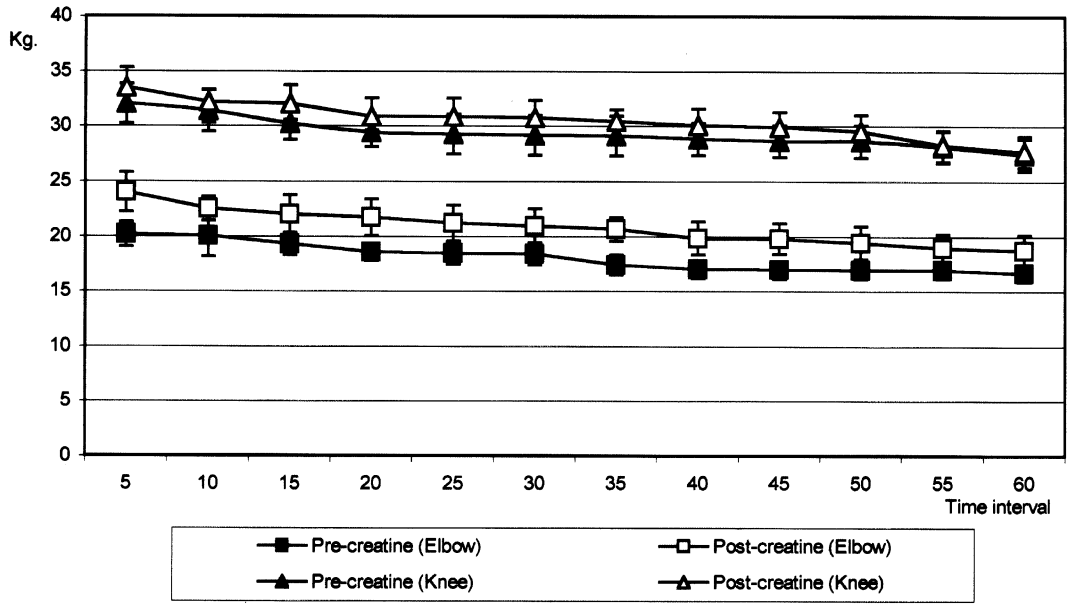

Fig. 3. Fatigue test. Values are means (±S.D. of the peaks obtained from the first to the twelfth effort of the fatigue test in all subjects, before and after 7 days of 20-g supplementation.

Comparing the pre-treatment and post-treatment values we found a statistically significant increase of MVIC both in elbow flexors ($P < 0.05$) and knee extensors ($p < 0.04$) (Fig. 2, left panel). No significant correlation was found between the degree of increase of MVIC after supplementation and the examined clinical and functional variables except the clinical form of the disease at onset. The difference between the pre-treatment and post-treatment MVIC of knee extensors muscles, in fact, was significantly higher ($P < 0.03$) in patients with bulbar onset of the disease than in patients with spinal onset (Fig. 2, right panel).

5.2. Fatigue

The analysis of the slopes of fatigue test, in each subject, showed a statistically significant difference of the alpha coefficient between the baseline and the post-treatment evaluation in 11 patients (39%) in elbow flexors and in 9 patients (32%) also in knee extensors muscles. This

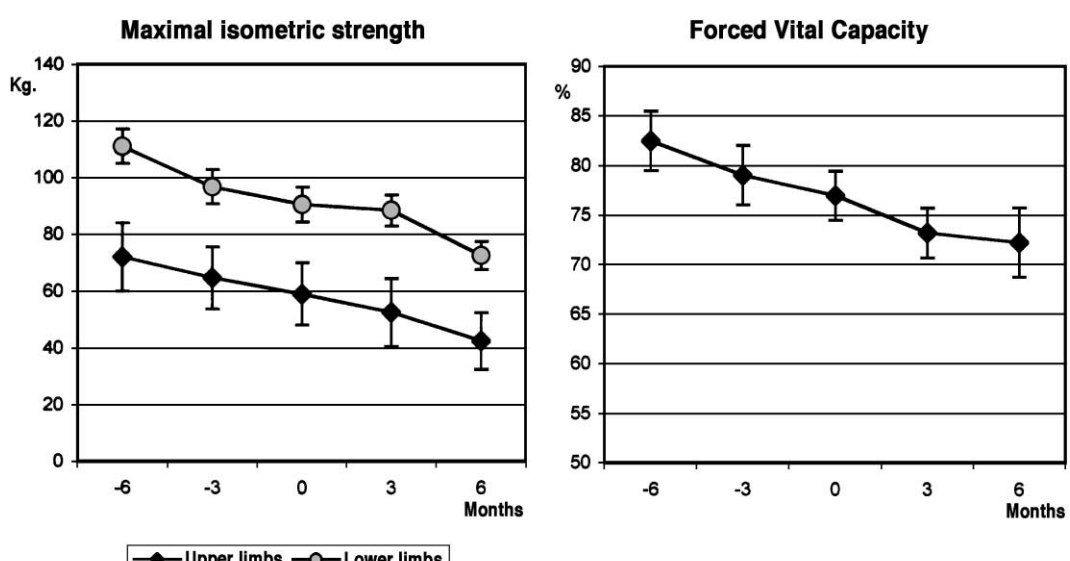

Fig. 4. Left panel: changes of the dynamometric measures of MVIC in the 6-month period of observation before supplementation and during the treatment period. Values are means (±S.D.). Right panel: changes of the FVC in the 6-month period of observation before supplementation and during the treatment period. Values are means (±S.D.).

difference was indicative of a lower rate of decline of maximal peak force from the first to the twelfth contraction of the fatigue test after supplementation.

Fig. 3 shows the average slopes computed by fitting the mean values of the peaks obtained from the first to the twelfth efforts in all subjects, before and after 1 week of supplementation. It is evident that the maximal peaks of each contraction were higher after supplementation both in elbow flexors and knee extensors muscles. The comparison between the averages slopes showed a statistically significant difference only in the elbow extensors muscle ($P < 0.04$), which was indicative of a lower rate of decline of maximal peak force from the first to the twelfth effort after supplementation.

No significant correlation was found between the alpha-coefficients of the regression lines and the clinical and functional variables of the disease.

5.3. Long-term follow-up

During the 6-month follow-up period all the examined parameters changed in a linear fashion as a function of time. Particularly, MVIC showed a linear progressive decline both in upper and lower limbs.

Fig. 4 (left panel) shows the results of the pre- and post-treatment dynamometric measures of MVIC obtained in the group of 20 patients with the 6-month period of observation before supplementation. The comparison of all averages slopes did not show any significant difference between the pre-treatment and treatment period both in upper and lower limbs. Even the FVC showed a linear progressive decline (Fig. 4, right panel) without any difference between the pre-treatment and treatment period.

A trend towards an increase of the Body Mass Index (BMI) was observed during the 6-month treatment period, however, the difference between pre- and post-treatment period was not statistically significant.

6. Discussion

Our data show that short-term monohydrate supplementation can temporary increase MVIC in ALS patients as previously reported in a variety of neuromuscular diseases [6,15]. As demonstrated by the studies performed in normal subjects [16], this effect is evident only in some subjects while others can be considered nonresponders. In our study responders and nonresponders were not different with regard to the clinical and functional characteristics of the disease. However, patients with bulbar onset showed a greater improvement of MCVI after supplementation than those with spinal onset. We can hypothesize that in bulbar patients the spinal muscles are affected later in the course of the disease, hence the phosphate flux in the muscles is preserved longer than in patients with spinal onset. Therefore, creatine supplementation in these patients can more easily enhance the muscular stores of phosphocreatine (P) which may result in increased muscle energy. Further studies in a larger population of patients, however, are needed to verify these results.

This study lacks placebo because is easily available in pharmacy at a low cost, hence patients were very reluctant to enter a placebo-controlled trial. However we think that the use of standardized dynamometric methods allowed us to obtain objective measures which are only slightly influenced by placebo effect. Supplementation was well tolerated and side effects were mild and comparable to those reported in normal subjects [17,18].

Supplementation seems also to influence fatigue but to a lesser extent than MCVI. A similar result has been obtained also in normal subjects [19] and it could be related to the limited effect or by increase in P only at the time of initiating the subsequent intense exercise. Our experimental protocol typically employed high-power output efforts separated by a fairly brief period of rest (5 s). This is the exercise condition where the transitional energy contribution from P is likely most significant. However, the short-term rest periods between bouts are probably insufficient to permit an enhanced recovery of the muscle P concentration, particularly in those individuals with a lower total concentrations due to muscle wasting.

A number of studies [3,20,21] indicate that long-term supplementation in normal subjects results in significant increases in strength and body mass. This effect was not evident in ALS patients. We observed, in fact, an increase of body weight in a small percentage of subjects but muscular strength showed a linear progressive decline during the 6-month follow-up as in the pre-treatment period. Moreover, supplementation did not influence forced vital capacity deterioration and functional abilities of patients. Recent experimental findings, however, have demonstrated that affords significant neuroprotective effects against oxidative insult [9], hence we think that its use as a neuroprotective agent in ALS patients must be verified in a larger number of patients in controlled trials.

In conclusion, our preliminary results have demonstrated that supplementation temporary increases high-intensity, isometric power in ALS patients so it may be of potential benefit in situations such as high-intensity activity (sport, manual task, physical therapy) and it can be proposed as a symptomatic treatment.

Acknowledgements

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