ALS and other motor neuron disorders 2002 3, 43–46
 ISSN 1466-0822

No effect of creatine on respiratory distress in amyotrophic lateral sclerosis

Vivian E Drory[1] and Ditza Gross[2]

[1]Department of Neurology and ALS Clinic;
[2]Respiratory Rehabilitation Unit and ALS Clinic,
Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel

Correspondence:
Vivian E Drory, MD
Dept. of Neurology
Tel-Aviv Sourasky Medical Center,
64239 Tel-Aviv, Israel
Tel/Fax: +972-3-6973689
E-mail: emgunit@tasmc.health.gov.il

Received 14 January 2002
Revised 2 April 2002
Accepted 7 April 2002

OBJECTIVE: To evaluate the effect of creatine supplementation on the respiratory function of patients with advanced amyotrophic lateral sclerosis (ALS).
METHODS: Five grams creatine daily were administered orally to 14 patients with definite advanced ALS. For comparison we used a group of 13 patients with a similar respiratory function. All patients performed pulmonary function testing including forced vital capacity (FVC), forced expiratory volume (FEV_1), peak expiratory flow rate (PEF) and maximum voluntary ventilation (MVV) – expressed as percent of the predicted value – at baseline and each month thereafter.
RESULTS: There was no significant difference in any measured variable between the treatment group and the control group at 1, 2, 3 and 4 months follow-up. Thereafter the high patient drop-out rate did not allow statistical evaluation.
CONCLUSION: The present study did not show any clinically significant, long-term effect of creatine on the function of respiratory muscles in ALS patients with respiratory distress. (ALS 2002; 3: 43–46)

Keywords: amyotrophic lateral sclerosis – motor neuron disease – creatine – respiratory function

Introduction

Creatine is a natural guanidine compound found in meat, which may increase muscle strength in healthy humans[1] and is often used as an energy-increasing nutritional supplement by athletes.[2] Orally ingested creatine is metabolized to phosphocreatine by creatine phosphokinase (CPK).[3] Phosphocreatine is an immediate energy source for muscle and thus can lead to improved exercise performance[4] and shortening of recovery time after exercise.[5]

A trial of creatine in patients with various neuromuscular disorders, not including amyotrophic lateral sclerosis (ALS), showed that within a treatment period of 11 days creatine significantly increased isometric and isokinetic muscle strength and attenuated muscle fatigue.[6] Other studies showed a mild positive effect of creatine on muscle strength in patients with mitochondrial myopathies[7] and muscular dystrophies,[8] when given for 11 days and 8 weeks respectively, although this effect was not confirmed in later published work.[9,10]

A pilot double blind study of creatine in patients with ALS showed that patients taking creatine had a more modest decline of muscle strength than those taking placebo and that this effect was maintained through the 9 months period of the study.[11] Another study showed that creatine temporarily improved muscle strength of patients with ALS.[12] The pharmacology of creatine and its potential role in the treatment of various neurological disorders have been reviewed.[13]

Transgenic mice with a mutation in the superoxide dismutase (SOD1) gene given creatine showed an improvement in their motor performance and extended survival. The effect of creatine in this study was not restricted to enhanced muscle function, but it seemed to protect motor neurons from oxidative stress.[14] Wobbler mice (an older animal model for motor neuron diseases) treated with high doses of creatine showed a slower deterioration of muscle strength and a reduced rate of degeneration of spinal motor neurons.[15] These observations constitute the main rationale for administering creatine to ALS patients, which has become a common practice in many ALS clinics, although the influence of creatine on human ALS is not yet proven.

Double-blind, placebo-controlled, long-term studies on the efficacy of creatine on human ALS are needed, but are difficult to perform, as creatine is readily available, off prescription.

Respiratory insufficiency due to weakness of intercostal and diaphragmatic muscles is the main cause of death in advanced ALS. Any treatment able to maintain the level of performance of respiratory muscles and postpone the need for mechanical ventilation would be valuable. Therefore,

Original Research

the aim of this study was to examine in an open design the influence of creatine administration on ALS patients with mild to moderate signs of respiratory insufficiency, and compare their outcome to that of historical controls.

Patients and methods

Fourteen patients with advanced sporadic ALS with clinical signs of respiratory insufficiency, followed up at our clinic during the years 2000–2001, formed the prospective study group. For comparison we used a group of 13 historical controls, followed up one year previously (before the first reports of creatine use in neuromuscular diseases), using the same evaluation protocol.

Patients in both groups were defined as probable or definite ALS by the revised El Escorial criteria,[16] had similar ages of disease onset and inclusion in the study, had a similar mean duration of disease, a similar proportion of bulbar onset forms and a similar degree of disability, as measured by the ALS functional rating scale (FRS)[17] and respiratory status. Clinical data of patients in both groups are summarized in Table 1.

Patients were included independently of their pulmonary function tests if they reported either spontaneous or exertional dyspnea or symptoms related to nocturnal hypoventilation, such as fragmentary sleep and daytime sleepiness. Two patients in each group had shortness of breath at rest. We excluded patients who needed invasive ventilation at the time of entering the study. Most bulbar onset patients need early invasive ventilation and therefore this study includes relatively few bulbar-onset patients. The patients continued all their previous medications throughout the period of the study. In all patients complete pulmonary function tests were performed at regular monthly intervals.

During the follow-up period most patients dropped out due to death, initiation of mechanical ventilation or severe motor deterioration, which made clinic visits impossible. At 4 months, only five patients in the treated group and four patients in the control group were evaluated. The longest follow-up period was 9 months, in one patient in the treated group, and 6 months in the control group.

Pulmonary function tests were performed using a Compact II spirometer (Vitalograph). We measured the following variables: forced vital capacity (FVC), forced expiratory volume (FEV_1), peak expiratory flow rate (PEF) and maximum voluntary ventilation (MVV) – all expressed as percentage of the predicted value for age, height, weight and gender.

Patients in the treatment group were administered creatine monohydrate, 5 g once daily, in a liophilized powder form.

Comparison between the two groups at baseline was performed using Wilcoxon's rank sum tests. Changes occurring with time in the various respiratory variables in each group were assessed by analysis of variance (ANOVA) with repeated measures.

Results

At baseline, the treatment and control groups were not statistically different in any of the measures of respiratory function examined. Over the following months all patients in both groups deteriorated. In the treated group we evaluated ten patients at 1 month, eight at 2 months, and five at 3 and 4 months. In the control group we evaluated ten patients at 1 month, six at 2 and 3 months and four at 4 months. Thereafter the small number of patients tested did not allow a meaningful comparison. Statistical analysis, performed 1, 2, 3 and 4 months after initiation of treatment, did not reveal any significant benefit of creatine over controls (Figure 1).

None of the patients complained of any side-effects. One patient reported a significant improvement in limb strength, although this could not be confirmed on neurological examination, and he deteriorated relatively rapidly.

	Treatment group n = 14	Control group n = 13
% males	57	54
Mean age at study (years)	61 ± 13	58 ± 14
Time from disease onset (months)	23 ± 11	25 ± 10
Number with bulbar onset	2	1
FRS	20.7 ± 7	22.5 ± 8
FVC (%)	44.7 ± 16	58.1 ± 23
FEV_1 (%)	46.8 ± 15	50.2 ± 25
PEF (%)	42.6 ± 17	45.3 ± 26
MVV (%)	38.2 ± 12	36.7 ± 27

Differences between the groups were not statistically significant.

FRS – functional rating scale; FVC – forced vital capacity; FEV_1 – forced expiratory volume; PEF – peak expiratory flow rate; MVV – maximal voluntary ventilation.

Table 1

Clinical data and respiratory function tests at baseline of patients in treated and control groups

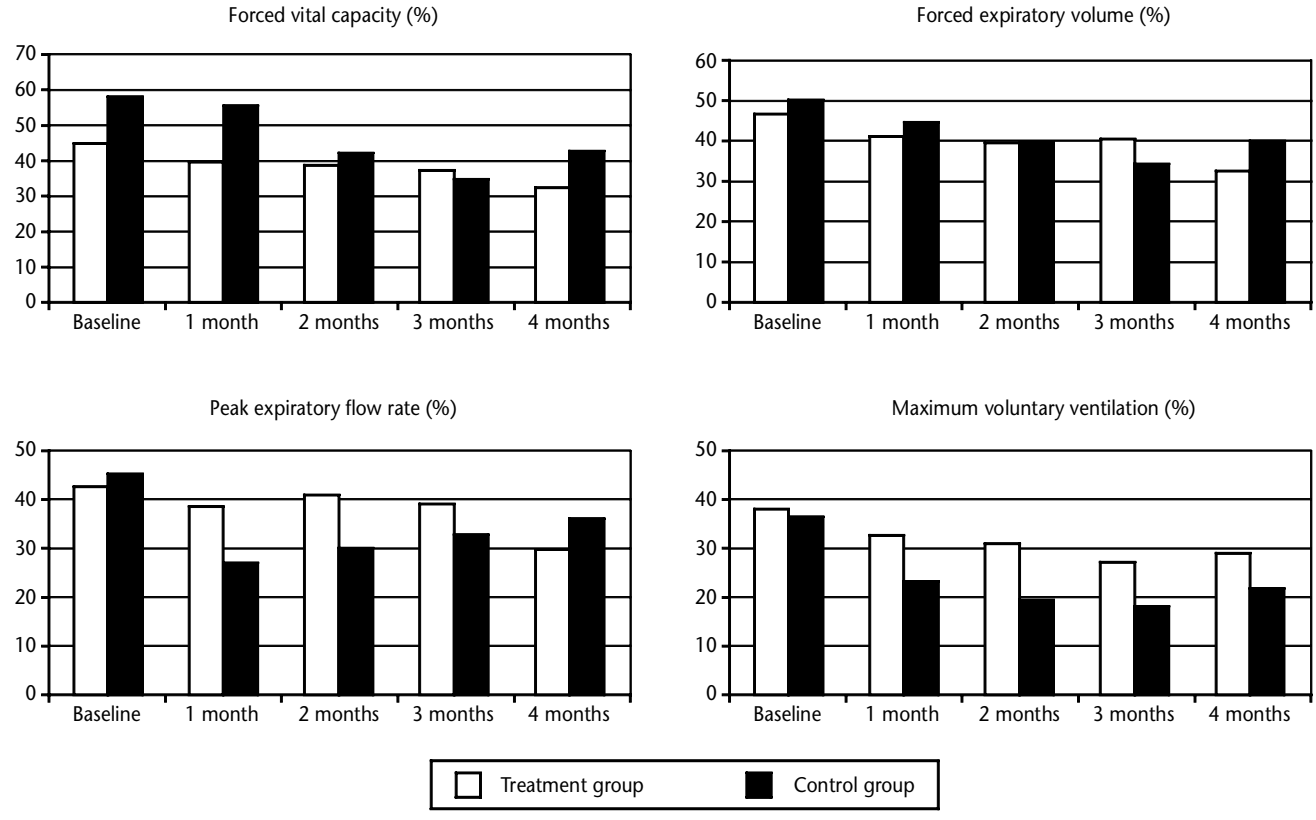

Figure 1
Parameters of respiratory function in patients treated / not treated with creatine. All measurements are expressed as percentage from the predicted value for age, gender, height and weight. The differences between the groups were not statistically significant.

Discussion

Creatine has been considered as a potential adjunct in the treatment of ALS, following preliminary observations about its efficacy in humans with ALS[6–8,11,12] and in transgenic mice with SOD1 mutations.[14] Two different modes of action of creatine are implied: a direct, non-specific action on the muscles, and a protective effect on motor neurons.

The present study was designed to evaluate the direct action of creatine on the respiratory muscles. We were not able to demonstrate any benefit from creatine on these muscles, although one patient reported a subjective improvement in his limb weakness. We emphasize that our study included relatively severely affected patients. It could therefore be argued that patients with milder disease would respond better to creatine than our severely affected patients. However, we do not think that the degree of severity of the disease is of major relevance in this study, as the mechanism of action of creatine is thought to influence the muscles directly, rather than the motor neurons. As muscle metabolism itself is not primarily abnormal in ALS, there is no reason to assume a markedly different response to the drug in patients with severe, as compared to mild, disease. Nonetheless, our results may not extrapolate to all patients with ALS. Two things which might make the interpretation of our results difficult are the small number of patients in each study arm and the high drop-out rate. These could result in our missing a small positive effect of creatine, and further studies, including more patients, are, of course, warranted.

It is possible to postulate that creatine could have a different influence on muscle fibers with different metabolism: limb muscles contain many type II fibers, with predominantly glycolytic metabolism and high energy requirements. Maximal voluntary isometric muscle testing, as was performed in other clinical studies of creatine,[6,7] particularly evaluates the function of this type of fiber. Conversely, most fibers of respiratory muscles are type I (oxidative), with low energy needs, and so possibly less influenced by creatine. Interestingly, this dichotomy was also observed in one other study,[8] in which creatine improved the muscle strength of patients with muscular dystrophies, but not the vital capacity.

Another question regarding the effect of creatine in improving strength is whether any induced benefit is durable. When given to athletes, the effect needs to last only a few hours; in the neuromuscular disorders trials[6–8] it was given for only 11 days to 8 weeks. But in order to regard the drug as effective in a disease such as ALS, it should maintain a positive influence over extended time periods. Tarnopolsky and Martin[6] followed patients taking creatine for over 6 months, but did not state whether an objective gain of strength was maintained. A report by

Rosenfeld et al[11] is the only one to date which shows a positive effect of creatine over months. Our study did not consider short-term effects, but looked at the possible long-term efficacy of the drug, but no effect could be demonstrated. A lack of efficacy of creatine on long-term treatment could be explained by the demonstrated down-regulation of creatine transporter proteins in skeletal muscle after prolonged creatine feeding.[18]

On the other hand, if the purpose of creatine treatment is not the improvement of muscle strength, but neuroprotection, as suggested by Klivenyi et al,[14] the clinical follow-up period should be much longer in order to see an effect. Our patient population was too small and in too poor a clinical condition to analyze any possible neuroprotective effect.

In conclusion, we did not find a sustained benefit of creatine on the respiratory muscle function of patients with advanced ALS.

References

1. Earnest CP, Snell PG, Rodriguez R, Almada AL, Mitchell TL. The effect of creatine monohydrate ingestion on anaerobic power indices, muscular strength and body composition. Acta Physiol Scand 2000; 153: 207–209.
2. Balsom PD, Soderlund K, Ekblom B. Creatine in humans with special reference to creatine supplementation. Sports Med 1994; 18: 268–280.
3. Greenhaff PL, Bodin K, Soderlund K, Hultman E. Effect of oral creatine supplementation on skeletal muscle phosphocreatine resynthesis. Am J Physiol 1994; 266: E725–E730.
4. Kreider RB, Ferreira M, Wilson M et al. Effects of creatine supplementation on body composition, strength, and sprint performance. Med Sci Sports Exerc 1998; 30: 73–82.
5. Hultman E, Soderlund K, Timmons JA, Cederblad G, Greenhaff PL. Muscle creatine loading in man. Am J Appl Physiol 1996; 81: 232–237.
6. Tarnopolsky M, Martin J. Creatine monohydrate increases strength in patients with neuromuscular disease. Neurology 1999; 52: 854–857.
7. Tarnopolsky MA, Roy BD, MacDonald JR. A randomized, controlled trial of creatine monohydrate in patients with mitochondrial cytopathies. Muscle Nerve 1997; 20: 1502–1509.
8. Walter MC, Lochmuller H, Reilich P, et al. Creatine monohydrate in muscular dystrophies: A double-blind placebo-controlled study. Neurology 2000; 54: 1848–1850.
9. Klopstock T, Querner V, Schmidt F et al. A placebo-controlled crossover trial of creatine in mitochondrial diseases. Neurology 2000; 55: 1748–1751.
10. Doherty TJ, Lougheed K, Markez J, Tarnopolsky MA. Creatine monohydrate does not increase strength in patients with hereditary neuropathy. Neurology 2001; 57: 559–560.
11. Rosenfeld J, Jackson CE, Smith J, King RM, Myers D, Wrench MM. A pilot trial of ultrapure creatine in amyotrophic lateral sclerosis. ALS 2001; 2 (Suppl 2): 20.
12. Mazzini L, Balzarini C, Colombo R et al. Effects of creatine supplementation on exercise performance and muscular strength in amyotrophic lateral sclerosis: preliminary results. J Neurol Sci 2001; 191: 139–144.
13. Tarnopolsky MA, Flint Beal M. Potential for creatine and other therapies targeting cellular energy dysfunction in neurological disorders. Ann Neurol 2001; 49: 561–574.
14. Klivenyi P, Ferrante RJ, Matthews RT et al. Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. Nat Med 1999; 5: 347–350.
15. Ikeda K, Iwasaki Y, Kinoshita M. Oral administration of creatine monohydrate retards progression of motor neuron disease in the wobbler mouse. ALS 2000; 1: 207–212.
16. Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. ALS 2000; 1: 293–299.
17. The ALS CNTF Treatment Study (ACTS) Phase I-II Study Group. The amyotrophic lateral sclerosis functional rating scale. Assessment of activities of daily living in patients with amyotrophic lateral sclerosis. Arch Neurol 1996; 53: 141–147.
18. Guerrero-Ontiveros ML, Wallimann T. Creatine supplementation in health and disease. Effects of chronic creatine ingestion in vivo: Down-regulation of the expression of creatine transporter isoforms in skeletal muscle. Mol Cell Biology 1998; 184: 427–437.