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ORIGINAL COMMUNICATION

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Creatine monohydrate in myotonic dystrophy

A double-blind, placebo-controlled clinical study

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Abstract We assessed safety and efficacy of creatine monohydrate (Cr) in myotonic dystrophy (DM1) in a double-blind, cross-over trial. Thirty-four patients with defined DM1 were randomized to receive Cr and placebo for eight weeks (10.6 g day 1–10, 5.3 g day 11–56) in one of 2 treatment sequences. There was no significant improvement using manual and quantitative muscle strength, daily-life activities, and patients' own global assessment comparing verum with placebo administration. Cr supplementation was well tolerated without clinically relevant side effects, but did not result in significant improvement of muscle strength or daily-life activities.

Key words myotonic dystrophy (MD) · creatine monohydrate · therapy · supplementation

Introduction

Myotonic dystrophy type 1 (DM1) is the most common inherited muscle disorder in adults. DM1 is a multi-system disease in which the most disabling feature is muscle wasting that begins in the distal limb and cranial muscles. The genetic basis for DM1 is an expanded CTG repeat in the DMPK gene on chromosome 19q13.3 [1]. The size of the expanded repeat, and the severity of the disease, tend to increase in successive generations. Clinical symptoms in DM1 are muscle wasting, myotonia, cataracts, heart block and neurobehavioral abnormalities. Up to now, curative therapy for DM1 is not available.

Creatine monohydrate (Cr) is a natural metabolite of the amino acids glycine, arginine and methionine and plays an important role in skeletal muscle energy metabolism. Cr therapy has resulted in increase of high-intensity strength in patients with different types of neuromuscular diseases such as mitochondrial cytopathies, neuropathic disorders, muscular dystrophies/congenital myopathies, inflammatory myopathies and miscellaneous conditions in a partly open, partly single-blinded trial [2]. In mitochondrial cytopathies, a consistent effect of Cr could not be demonstrated [3, 4]. In different types of muscular dystrophies and in McArdle disease, a mild beneficial effect of Cr supplementation was recently shown [5, 6]. The present study was designed to evaluate therapeutic efficacy and side effects of Cr in DM1 patients.

Methods

Study-Design

A 2-treatments – 2-periods crossover-design was used in this double-blind, placebo-controlled trial. Thirty-four patients, (mean age 44 ± 13 years) with clinically, electrophysiologically and genetically defined DM1 were included in the study and treated for the full study period. CTG repeat length varied between 0.3 and 4 kb (110–1300

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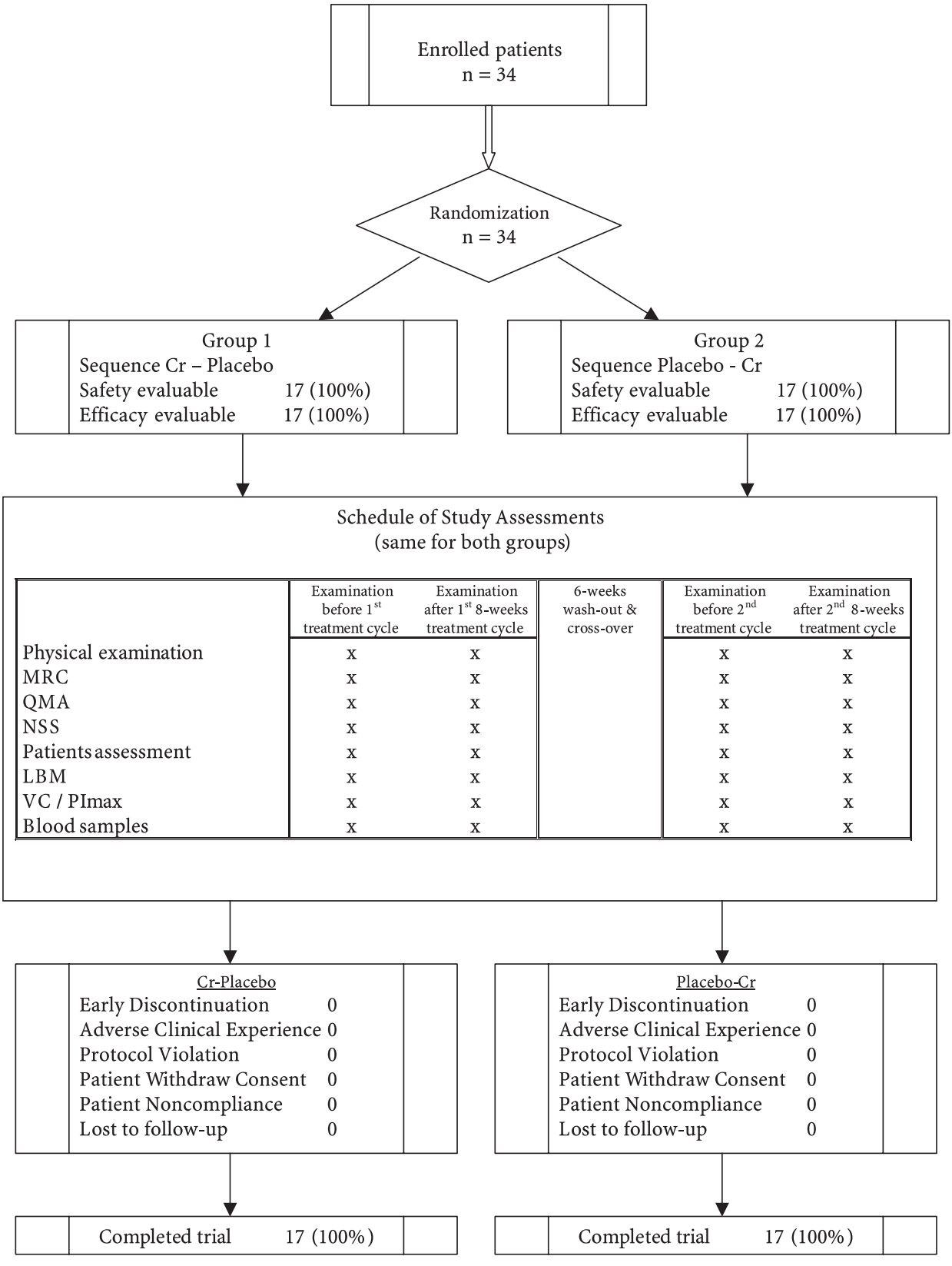

Fig. 1 Flow diagram of progress through the trial, including patient registration, randomization, timing of outcome measures, and patient disposition.

CTG repeats), medium repeat length was 1.6 ± 0.9 kb. Group 1 was randomized to receive verum (CREAPURE®, Degussa AG, Trostberg, Germany (10.6 g day 1–10, 5.3 g day 11–56)) first, group 2 started with placebo (microcrystalline cellulose). Treatment duration was 8 weeks per period, between the 2 crossover periods a wash-out period of 6 weeks was included. Seventeen patients (mean age 46 ± 16 years) were randomized to group 1 (sequence verum – placebo), seventeen patients (mean age 42 ± 9 years) to group 2 (sequence placebo – verum). There was no significant difference between the groups according to age, gender, CTG-repeat length or disease duration. Cr and placebo were administered in identical powder form along with a 5.3 g measuring cup. Patients were advised to dissolve the powder in fluid (not in hot drinks and coffee), and to take it once daily with a small meal. We analysed disease severity in all patients according to the functional scale by Scott et al. [7]. This scale scores 20 different motor functions, the maximum sum score in a healthy individual is 40, the minimum score is 0. The average sum score of our patients was 27 ± 7 (range 14 to 40), there was no significant difference among the two groups. Before and after each treatment period response to treatment was evaluated (in total 4 assessments), using Medical Research Council Scales (MRC), Quantitative Strength Measurement (QMA), Neuromuscular Symptoms Score (NSS), Lean Body Mass (LBM), Vital Capacity (VC), and patients' global assessment of improvement. Patients confined to bed or wheelchair or with renal insufficiency were excluded.

Physical examinations, routine blood chemistry and laboratory tests such as blood cell count and serum enzyme levels were carried out at each assessment visit to control for the safety of both study treatments. The study protocol was approved by the local ethics committee, and was performed in accordance to the 1964 Declaration of Helsinki. All patients gave written informed consent.

Tests

Testing was performed by two experienced neurologists after sufficient training with study procedures (reliability assessment: intraclass correlation coefficient ICC > 0.84 for MRC, ICC > 0.87 for QMA).

Muscle strength was examined bilaterally according to the Medical Research Council Scale (MRC). MRC sum scores were evaluated before and after each treatment period.

Quantitative muscle strength (QMA) was assessed using the Multi Muscle Tester M3 Diagnos System (Schnell Company, Germany). Maximum bilateral strength of biceps and quadriceps muscle was measured isometrically by torque measurement; results were indicated as % of maximum torque difference. Measurements were repeated three times, the best result was recorded.

Fourteen daily-life activities were evaluated by Neuromuscular Symptom and Disability Functional Score (NSS).

Body cell mass (BCM), lean body mass (LBM), fat mass, total body water (TBW), and intracellular water (ICW) were assessed from reactance and resistance measurements with bioelectrical impedance analysis (single frequency of 50 kHz, hand held, four electrodes; B. I. A. 2000-S Body Impedance Analyzer, Precon, Basel, Switzerland). Measurements were made on midday after a six hours fast and after urination before each measurement.

Electrodes were placed on the right hand and right foot according to the manufacturer's guidelines. Subjects were supine, with their arms 30 degrees away from their bodies, and they were instructed to keep their legs apart. The body weight, age, sex, and height for each subject were recorded. Reactance, resistance and phase angle measurements were then processed with the B. I. A. 2000-S Body Impedance Analyzer.

Spirometry was performed by forced Vital Capacity (% predicted VC) and PImax (kPa) and was assessed before and after each treatment cycle.

For exploration of patients' global assessment of treatment, patients were asked about subjective improvement after each treatment period, using a 3-point scale (better/same/worse).

Statistics

Test-retest reliability of the performances of the 2 investigators was assessed for the QMA and the MRC grading system. ICCs were calculated to compare the data between sessions. Sample size calculations were based on the estimated response to the primary outcomes of the study. The sample size was estimated using a delta/sigma ratio of $d = 0.5$ as a minimum important difference for the MRC sum score. We calculated that a sample size of 32 evaluable patients would allow superior efficacy of Cr over placebo to be shown, with an α -level of 0.05, a 1-β-level of 0.80, and a correlation between the data of both crossover periods or $\rho = 0.5$. Usual descriptive statistics were calculated for each group separately according to sequence of treatment. Comparison of baseline scores at the begin of each crossover period (age, sex, MRC, QMA, NSS, LBM, VC) in both groups was evaluated by using Mann-Whitney-Wilcoxon-test and Fisher's exact test, respectively, on significance level < 0.05. Using MRC and NSS as primary parameters, efficacy of Cr treatment was evaluated by non-parametric rank-sum techniques. The overall significance level of $\alpha = 0.05$ was split to $\alpha^* = 0.025$ for each of the two main outcome parameters, using the Bonferroni procedure. Reference parameters were the differences between sum scores before and after each treatment period; they were analysed by use of Lehmacher's [8] crossover method which allows to test for treatment, carryover and period effects. Safety analysis was performed by standardized rating of adverse events including new or, compared with baseline, worsened findings in physical examinations and laboratory assessments. All patients who received treatment were included both in the efficacy and the safety analysis. A differentiation between intention-to-treat and per-protocol-analysis was not performed, because there was no serious protocol injury.

Results

Muscle strength (MRC)

Comparing differences in MRC sum scores before and after each treatment cycle, we found no significant difference between both treatments (Table 1, Fig. 2a). Though there was a slightly larger improvement in the Cr group than in the placebo group ($p = 0.1127$), no statistically or clinically relevant benefit of Cr could be shown. Fig. 2a demonstrates that this outcome was mainly caused by the placebo treatment when administered as first treatment in the respective crossover sequence. The expected result was only found in the second crossover period ($p = 0.0049$), where Cr-treated patients improved whilst placebo treated patients worsened with respect to muscle strength.

Neuromuscular Symptom Score (NSS)

As with the MRC scores, the two groups did not differ in the test for treatment effects within the crossover trial ($p = 0.1507$). Again, Cr and placebo showed similar improvements when applied as first treatment (Table 1, Fig. 2b) but the expected result was observed in the second crossover period ($p = 0.0636$).

Table 1 Mean changes in efficacy measures

Efficacy Measures	Creatine	Placebo	Treatment p-value	Carryover p-value	Period p-value
MRC sum score	2.0±3.5	0.6±4.6	0.1127	0.2206	0.0103
NSS sum score	1.7±3.4	0.7±3.1	0.1507	0.4158	0.0034
QMA Biceps (Nm)	0.5±15.2	−2.3±7.5	0.0668	0.8206	0.9272
QMA Quadriceps (Nm)	7.8±34.4	−0.7±34.4	0.4500	0.5083	0.0375
PImax (kPa)	0.4±1.8	0.5±1.8	0.2446	0.2979	0.8469
Lean body mass (kg)	1.3±3.5	1.1±3.4	0.6882	0.7756	0.5401
Body weight (kg)	0.9±2.1	1.2±3.6	0.9544	0.2385	0.5955

Remarks: The table reports mean ± standard deviations for data pooled across crossover periods with identical treatments. The p-values reported are associated with crossover tests (Mann-Whitney U-tests) according to Lehmacher [6].

Quantitative Muscle Strength (QMA)

Compared with all other efficacy variables, the treatment effects were most pronounced in QMA (biceps: $p = 0.0668$), but again, similar changes between both treatments within begin and end of the first crossover period failed to demonstrate any favorable efficacy of Cr (Table 1, Fig. 2c).

Lean body mass and vital capacity

No differences could be shown for these 2 variables which were less sensitive for treatment effects than the muscle strength measures or the NSS (Table 1).

Patients' global assessment of improvement

Improvement within each cycle was rated by the patients. Eighteen percent of patients could assign improvement to verum phase, 73 % of patients did not feel a considerable difference between treatments, and 9 % of patients felt improvement during placebo administration (data not shown).

Adverse events

Throughout treatment, no clinically relevant adverse events were found.

Laboratory findings

Physical examinations, routine blood chemistry and laboratory tests such as blood cell count and serum enzyme levels showed no clinically relevant changes during the study period. In particular, there was no relevant raise of CK-levels during Cr supplementation.

Discussion

The aim of this study was to evaluate efficacy and safety of Cr supplementation in patients with DM1. Muscle strength and daily activities as main outcome measures of the study as well as quantitative measurements (QMA) of muscle strength did not reveal a positive effect of Cr supplementation in the global crossover test. However, in the second crossover period improvement in the Cr group and worsening in the placebo group were observed. In the first crossover period, we observed considerable placebo effects that prevented an overall positive outcome of the trial. Furthermore, period effects were detected in the crossover analysis with improvement in the second period for both groups that may indicate a training effect. In the light of these findings a parallel group design might be better suited as compared to a cross-over design. However, this would require larger sample sizes, and compliance of patients may be reduced according to possible assignment to the placebo group.

In summary, we can not rule out entirely that Cr might be a beneficial supplementary therapy for patients with myotonic dystrophy. Recent positive trials have been reported for patients with muscular dystrophy [6], inflammatory myopathies [2] and McArdle [5] disease, whereas no effect on muscle strength could be found in patients with hereditary neuropathies [9]. In mitochondrial cytopathies, the effect of Cr supplementation was inconsistent [3, 4]. These conflicting results regarding the benefit of Cr supplementation in neuromuscular disorders may be related to muscle pathophysiology such as differences in energy metabolism among the different disease groups. MR spectroscopy revealed lower muscle phosphocreatine (PCr) storage and more rapid PCr depletion during exercise in skeletal muscle of boys with Duchenne dystrophy, if compared with healthy age-matched control subjects [10, 11]. Similarly, muscle PCr and/or total Cr concentration were significantly lower in patients with mitochondrial

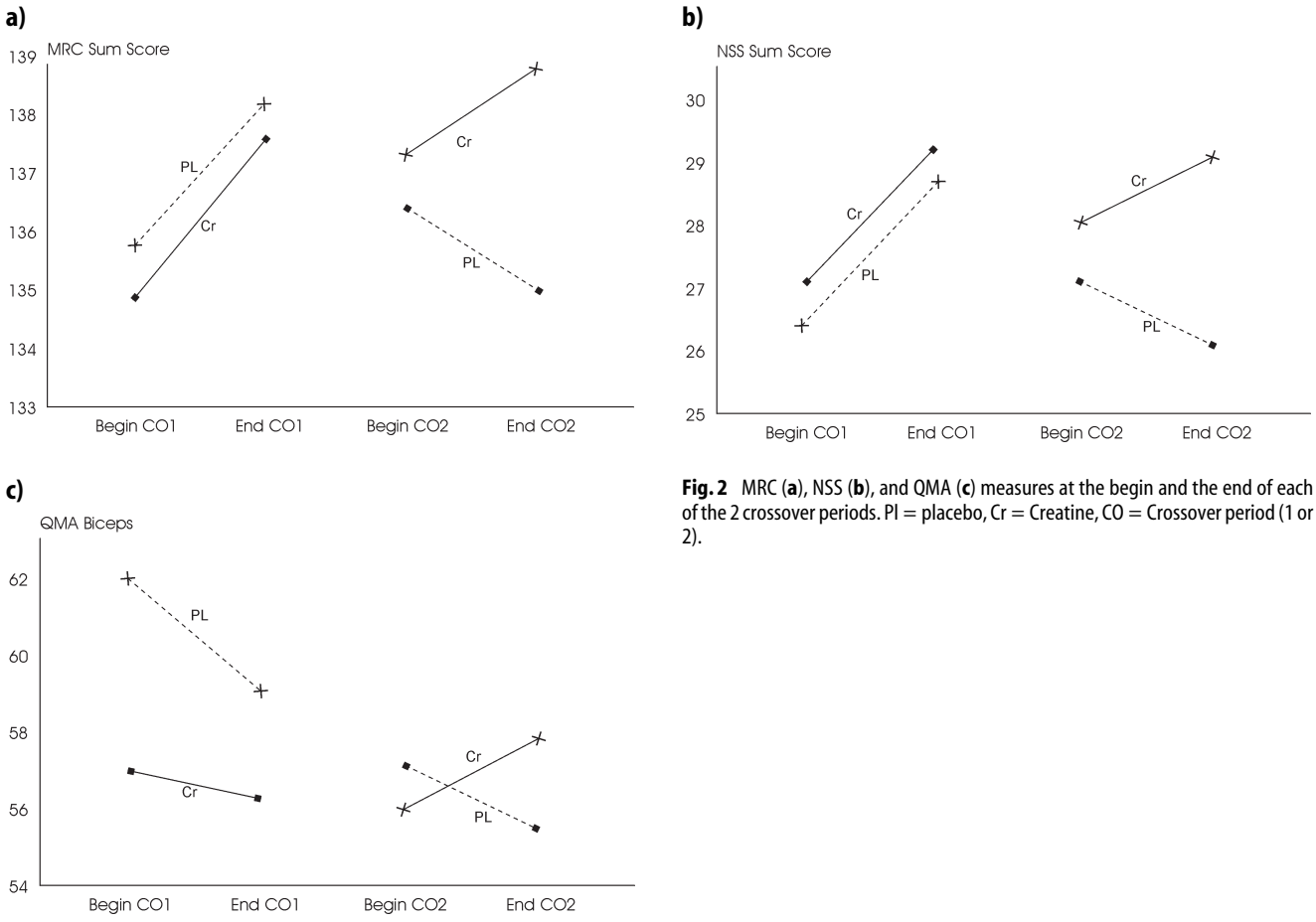

Fig. 2 MRC (**a**), NSS (**b**), and QMA (**c**) measures at the begin and the end of each of the 2 crossover periods. Pl = placebo, Cr = Creatine, CO = Crossover period (1 or 2).

cytopathy with ragged-red fibers and with inflammatory myopathies [9]. In DM1, mild abnormalities in the bioenergetics of skeletal muscle both at rest and during exercise were demonstrated [12], affecting both mitochondrial and glycogenolytic function, whereas PCr/ATP ratios were not altered significantly. Since energy metabolism is only slightly impaired in DM1, Cr treatment may be less efficient as compared to muscular dystrophy.

Cr supplementation was reported to increase lean body mass and muscle strength in healthy individuals [13]. However, we did not detect an increase in lean body mass during the study duration. Similar findings are obtained in patients with hereditary neuropathy during Cr administration [9]. It remains to be seen whether this finding, no increase in lean body mass, correlates with missing therapeutic efficacy of Cr. In conclusion, low-dose Cr supplementation has no beneficial effects in DM1. A small to moderate treatment effect may be detectable in DM1 patients on long-term treatment, larger sample sizes, higher Cr dose, or modifications of the design.

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