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BRIEF COMMUNICATION

L-carnitine Reduces Muscle Cramps in Patients With Cirrhosis

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We performed a prospective study to evaluate the ability of L-carnitine, which is involved in the β-oxidation of fatty acids, to reduce muscle cramps in patients with cirrhosis. Consecutive patients with cirrhosis and muscle cramps were given L-carnitine 300 mg, 3 times/day (900 mg/day, n = 19) or 4 times/day (1200 mg/day, n = 23) for 8 weeks. The frequency of muscle cramps was assessed by questionnaires, and the degree of muscle cramping was assessed by using the visual analogue scale (VAS). Muscle cramping was reduced in 88.1% of all subjects at the end of the 8-week study period and disappeared for 28.6% of patients. Overall VAS scores decreased significantly from 69.9 ± 22.5 at baseline to 26.2 ± 29.1 after 8 weeks ($P < .0001$). The dose of L-carnitine was significantly associated with percentages of patients with reduced muscle cramps after 8 weeks (43.5% in the 1200 mg/day group vs 10.5% in the 900 mg/day group, $P = .037$) and VAS scores at 8 weeks (9.9 ± 13.5 in the 1200 mg/day group vs 39.6 ± 31.9 in the 900 mg/day group, $P = .003$). No adverse events were reported. Therefore, L-carnitine appears to be safe and effective for reducing liver cramps in patients with cirrhosis.

Keywords: Liver Fibrosis; Lipid Metabolism; Fatty Acid; Clinical Trial.

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Muscle cramps associated with cirrhosis are an important complication of this disease.[1–3] General health-related quality of life measured by instruments such as the Medical Outcome Study Short Form-36, the Nottingham Health Profile questionnaires, and the Chronic Liver Disease Questionnaire is diminished in cirrhotic patients with muscle cramps.[4–7] The etiology of muscle cramps in patients with liver disease remains largely unknown, and effective treatments have not been established.

L-carnitine (L-beta-hydroxy-gamma-N-trimethyl aminobutyric acid) plays an important role in lipid metabolism by being an obligatory cofactor for β-oxidation of fatty acids. L-carnitine improves minimal hepatic encephalopathy in cirrhosis patients.[8] However, the effect of L-carnitine treatment for muscle cramps in patients with cirrhosis is not known. This study aimed to evaluate the efficacy of L-carnitine for muscle cramping in cirrhosis patients.

Materials and Methods

Patients

A total of 42 consecutive patients with cirrhosis that was complicated by muscle cramps were enrolled in this study between September 2012 and May 2014. Cirrhosis was diagnosed on the basis of clinical, radiologic, and laboratory parameters and/or liver biopsy. Patients with cramps had ongoing symptoms defined by painful, involuntary contraction of skeletal muscles, occurring at rest or strong enough to wake the patient from sleep more than twice during the preceding 4 weeks. Patients with evidence of disease associated with muscle cramps, such as vascular occlusive disease, peripheral neuropathy, end-stage renal disease on hemodialysis, and congestive heart failure, were excluded. Patients with previous administration of carnitine-containing supplements were not included. The patients were treated with L-carnitine 300 mg 3 times a day (900 mg group) or 4 times a day (1200 mg group) for 8 weeks, according to the attending physician's discretion.

Assessment of Treatment Efficacy

The frequency and duration of muscle cramps were assessed by questionnaires, and the severity of muscle cramps was assessed by using scores of the visual analogue scale (VAS). VAS is a horizontal line, 100 mm in length, anchored by word descriptors at each end. The left end indicates totally without pain, and right end indicates unbearable pain. The patient marks on the line the point that they believe represents their perception of their current state. The VAS score is determined by

Abbreviations used in this paper: ATP, adenosine triphosphate; BCAA, branched chain amino acid; VAS, visual analogue scale.

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measuring millimeters from the left-hand end of the line to the point that the patient marked. However, 11 cases did not respond for VAS score at baseline or after 8 weeks of treatment because they could not understand the meaning of VAS score. After the attachment of sufficient explanation, the VAS data were consecutively obtained. The questionnaires contained questions related to the frequency (number of cramps/day, week, or month) and duration of cramps (in minutes or seconds) and VAS. The questionnaires and VAS scores were obtained before and 8 weeks after the administration of L-carnitine. The protocol was undertaken in accordance with the World Medical Association's Declaration of Helsinki and was approved by the institutional review board of Musashino Red Cross Hospital, Tokyo, Japan.

Statistical Analysis

Values for continuous variables were presented as means ± standard deviation. The paired or non-paired Student *t* test was used to assess the significance of the differences in the comparison of continuous data, whereas numeric variables were assessed by the Fisher exact test. *P* values below .05 were considered to be statistically significant. These analyses were performed by using SPSS version 17.0 software (SPSS Inc, Chicago, IL).

Results

Patients

The clinical backgrounds of the patients who were prescribed L-carnitine 3 times a day or 4 times a day were compared retrospectively, and this revealed no differences.

Treatment Efficacy

The questionnaire revealed that the frequency of muscle cramps had reduced from 5.1 ± 5.9 to 1.7 ± 3.0

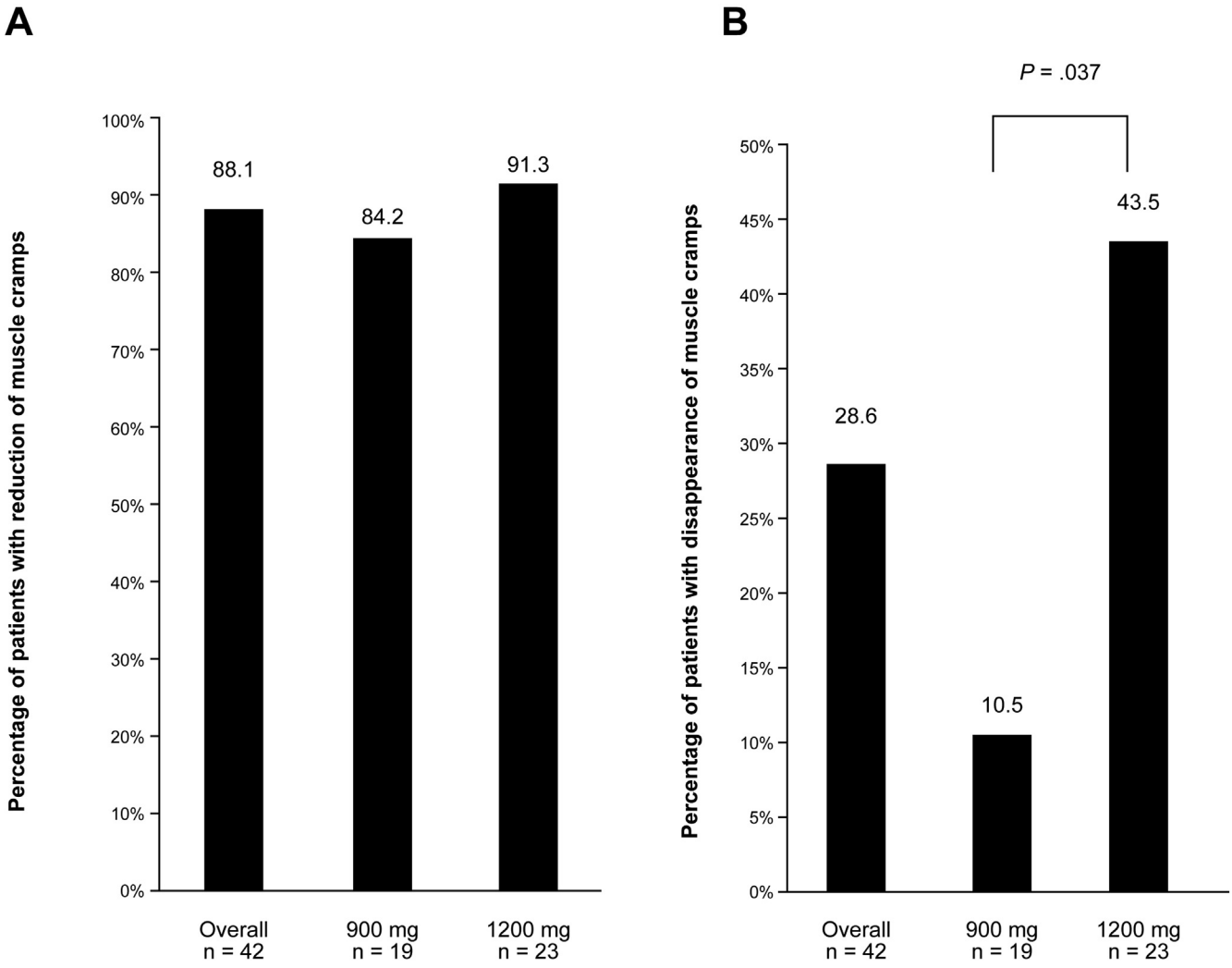

Figure 1. Efficacy of L-carnitine treatment for the reduction or disappearance of muscle cramps. Percentages of (*A*) reduction and (*B*) disappearance of muscle cramps are shown. Muscle cramping was reduced in 88.1% and disappeared in 28.6% of patients after 8 weeks of therapy. The dose of L-carnitine was an important factor associated with disappearance of muscle cramps.

times a week ($P = .0019$), and the cramps had reduced in 88.1% of patients and disappeared in 28.6% of patients after 8 weeks of therapy (Figure 1). The VAS score was analyzed in 31 patients, and the baseline value ranged from 19 to 100, with a mean of 69.9 ± 22.5. After 8 weeks of treatment, the VAS scores reduced in 27 patients (87.1%), remained unchanged in 1 patient (3.2%), and increased in 3 patients (9.7%). The mean value of the VAS score was reduced to 26.2 ± 29.1 after 8 weeks of therapy and was significantly lower than the baseline ($P < .0001$, Figure 2*A*).

Factors Associated With Treatment Efficacy

Clinical variables were compared in terms of treatment efficacy. The dose of L-carnitine was a significant factor associated with the disappearance of muscle cramps. The rate of disappearance of muscle cramps was 43.5% in the 1200 mg group and was significantly higher than 10.5% for the 900 mg group ($P = .037$, Figure 1*B*). The baseline VAS score did not differ between the 2 groups (71.4 ± 24.4 vs 69.7 ± 21.7, $P = .837$), but the VAS scores after 8 weeks of therapy were significantly lower in the 1200 mg group than in the 900 mg group (9.9 ± 13.5 vs 39.6 ± 38.1, $P = .003$; Figure 2*B*). In this study, 24 cases (57.1% of patients), 10 cases (52.6% in the 900 mg group), and 14 cases (60.7% in the 1200 mg group) were on branched chain amino acid (BCAA) supplementation at baseline, but there was no patient newly treated by BCAA after L-carnitine administration. The rate of disappearance of muscle cramps was not statistically different between patients with or without oral supplementation of BCAA (33.3% [8 of 24] vs 22.2% [4 of 18], $P = .51$).

Treatment Compliance

All 42 patients received more than 80% of the planned daily dose of L-carnitine. No adverse reactions caused by L-carnitine administration were identified in any patient.

Discussion

Here we showed that L-carnitine administration for muscle cramps was safe and highly effective in patients with cirrhosis. Muscle cramps reduced in 88.1% of patients and disappeared in 28.6% of treated patients. The treatment was well-tolerated, and no adverse event

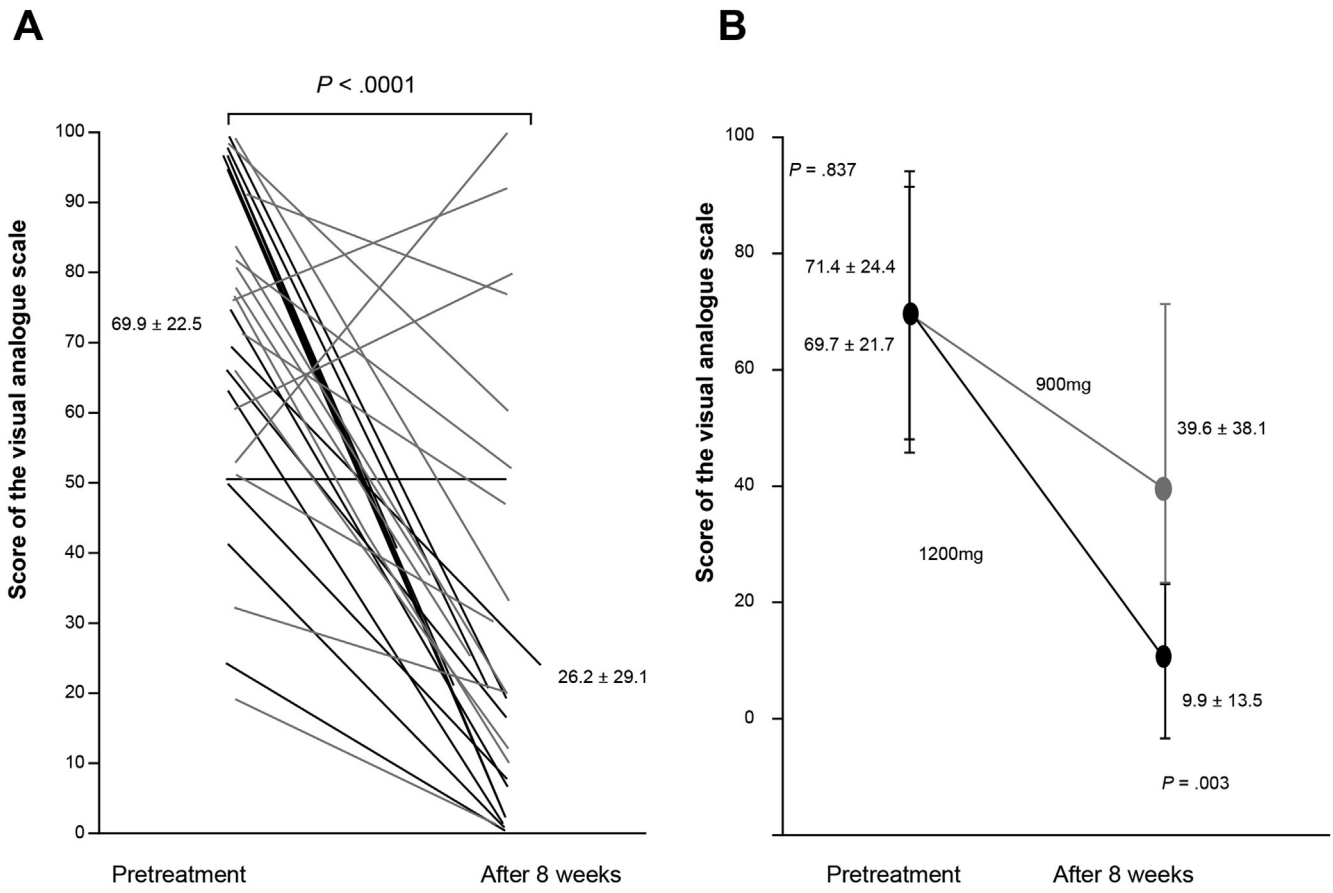

Figure 2. Scores of VAS before and after 8 weeks of L-carnitine treatment are shown. *Black* and *gray lines* indicate the 1200 mg group and 900 mg group, respectively. (*A*) Overall, the mean value of VAS score was reduced significantly from 69.9 ± 22.5 to 26.2 ± 29.1 after 8 weeks of therapy. (*B*) According to the dose of L-carnitine, VAS scores after 8 weeks of therapy were significantly lower in 1200 mg group than in 900 mg group.

was reported. The preliminary results suggest a dose-dependent effect. This report shows safe and efficacious administration of L-carnitine for muscle cramps related to cirrhosis.

The exact pathophysiology of muscle cramps continues to be poorly understood, and there are no significant predictors in the occurrence of muscle cramps.[5,6] A potential cause of altered energy metabolism in cirrhosis is reduction in adenosine triphosphate (ATP) production.[5] Moller et al[9] performed skeletal muscle biopsies in 10 cirrhotic patients and found a reduction in ATP, phosphocreatine, and total adenine nucleotide levels. Cramps occur when muscles are unable to relax properly. When skeletal muscles relax, myosin fibers disassociate from actin, and for this process, ATP must attach to myosin. A deficiency of ATP results in insufficient dissociation of myosin from actin.[10] L-carnitine improves the breakdown of fats and fatty acids and converts them into energy in the form of ATP.[11] Carnitine deficiency results in a lack of ATP in skeletal muscles, and this can cause malfunction of calcium adenosine triphosphatase pumps and a subsequent increase of intracellular calcium levels and inadequate muscle contraction.[12] Therefore, carnitine deficiency may be a cause of muscle cramps in cirrhosis patients. The notable efficacy of L-carnitine administration also supports this hypothesis.

The limitations of the present study are that there was no control group, and the patients were not randomized into 2 doses. Further dose-ranging randomized controlled trials are necessary in the near future.

In conclusion, the administration of L-carnitine may be a promising treatment for cirrhosis patients with painful muscle cramps. The preliminary results suggest a dose-dependent effect. Further studies are needed to validate the efficacy and safety of this treatment and to determine the optimal dose and duration.

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The authors disclose no conflicts.

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