L-Carnitine for the Treatment of Overt Hepatic Encephalopathy in Patients with Advanced Liver Cirrhosis

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(Received December 31, 2017)

Summary Hepatic encephalopathy is a major complication in patients with advanced cirrhosis and is associated with poor prognosis. To evaluate the effectiveness of l-carnitine supplementation in patients with overt hepatic encephalopathy (OHE), outcomes were retrospectively analyzed in patients with OHE who were treated with intravenous branched-chain amino acids (BCAA), with or without intravenous l-carnitine. Twenty-six patients were treated with intravenous BCAA in addition to conventional agents such as lactulose and non-absorbable antibiotics (Group A), and 19 patients were treated with these agents plus intravenous l-carnitine (Group L). Changes in blood ammonia concentrations, hepatic coma grade and the Glasgow Coma Scale (GCS) were compared in the two groups. Recurrence-free survival (RFS) was evaluated in the two groups and in patients who were and were not administered oral l-carnitine supplementation. At baseline, GCS scores were significantly lower and deterioration in liver function greater in Group L. After 3 d of intravenous l-carnitine, however, GCS showed a significantly greater improvement in Group L than in Group A. Blood ammonia levels improved stably over time in Group L. Overall survival and RFS were similar in Group L and Group A, but median RFS was significantly longer in patients who did than did not receive oral l-carnitine supplementation (735 versus 497 d, \( p=0.03 \)). Although these findings are preliminary, l-carnitine supplementation may be a therapeutic option for patients with OHE and disturbed consciousness.

Key Words l-carnitine, hepatic encephalopathy, branched-chain amino acid, cirrhosis

Hepatic encephalopathy (HE) manifests with various abnormal neuropsychiatric symptoms and is one of the major complications frequently found in cirrhotic patients (1, 2). HE can be classified as covert (CHE) or overt (OHE), depending on its severity (3, 4). The onset of OHE has been associated with poor prognosis (5, 6) and with high socioeconomic and emotional burdens on patients and their families (7, 8). Various factors are thought to contribute to HE, with ammonia regarded as a major contributor (9, 10).

Treatments for OHE include the removal of precipitating factors, such as infection and variceal bleeding, as well as the administration of non-absorbable disaccharides such as lactulose and non-absorbable antibiotics (1, 2). Pharmaceutical interventions are regarded as first-line treatments, followed, if necessary, by liver transplantation (1, 2). Non-absorbable disaccharides, such as lactulose, reduce blood ammonia concentrations by reducing the numbers of ammoniagenic bacteria and by converting ammonia to non-absorbable ammonium. Recent meta-analyses showed that these treatments improved HE (risk ratio [RR], 0.58) and prolonged survival (RR, 0.59) (11, 12). Non-absorbable antibiotics such as rifaximin have also been shown effective in patients with HE (13, 14), and are regarded as an alternative first-line treatment in patients with OHE (1). Non-absorbable antibiotics react with gut microbiota, reducing the production and absorption of gut-derived neurotoxins such as ammonia.

A recent meta-analysis of 16 randomized controlled trials showed that supplementation with branched-chain amino acids (BCAA) had clinical benefits in patients with OHE (RR, 0.73) (15). That analysis, however, did not determine the beneficial effects of BCAA on mortality, quality of life or nutritional parameters (15). BCAA supplementation has also been reported to have harmful effects, including increases in cataplerosis and ammonia formation (16). Moreover, the ability of BCAA supplementation to restore disturbed consciousness was shown to differ according to liver function (17). Although further investigations are required to ascertain the effectiveness of BCAA supplementation, its lack of major adverse effects makes its use feasible to treat patients with HE (18). Japanese treatment guidelines for patients with HE therefore include BCAA supplementation (19), with intravenous BCAA regarded as useful for OHE patients with disturbed consciousness because their oral intake is frequently impaired.

L-Carnitine, a vitamin-like biofactor in lipid metabolism, has been shown to reduce blood and brain ammonia concentrations and to improve HE (20–23). L-Carnitine transfers acyl-coenzyme A to the mitochondria,
activates the tricarboxylic cycle and induces ureagenesis, reducing ammonia concentrations. A recent detailed evaluation of carnitine dynamics and their effects on hyperammonemia in cirrhotic patients showed that serum and liver carnitine concentrations were well correlated and that L-carnitine supplementation reduced blood ammonia levels in parallel with increased total carnitine levels (24).

Randomized placebo-controlled trials have shown that oral L-carnitine administration reduced blood ammonia concentrations in patients with HE (20, 22). Few studies to date, however, have assessed the clinical significance of L-carnitine supplementation, especially intravenous supplementation, in patients with HE. Furthermore, a single larger dose of carnitine supplementation (4 g/d) was evaluated in previous studies (20–23); the effectiveness of L-carnitine supplementation in daily clinical practice remains unclear. This retrospective study therefore analyzed the effects of L-carnitine supplementation in patients with OHE in clinical practice settings.

**METHODS**

**Selection of patients.** This single-center, retrospective, observational study included cirrhotic patients who were hospitalized with OHE and treated with intravenous BCAA (Aminolevan®, Otsuka Pharmaceutical Co. Ltd, Tokyo, Japan), with or without intravenous L-carnitine (L-carnitine chloride, L-cartin FP®, Otsuka Pharmaceutical Co. Ltd.), between April 2015 and April 2017 (Fig. 1). OHE was diagnosed by experienced (>10 y) hepatologists according to the following criteria: 1) liver cirrhosis, diagnosed by liver biopsy, radiological examination, or laboratory results such as reduced platelet count (25); 2) disturbed consciousness in the absence of other causes, such as intracranial diseases, systemic serious infection, hypoglycemia, electrolyte disorders, and drug or alcohol abuse; 3) blood ammonia concentration higher than baseline; and 4) presence of asterixis. Criteria 1 and 2 were considered essential for the diagnosis of OHE, with criteria 3 and 4 providing additional diagnostic information.

**Data collection.** The medical records of all included patients treated with intravenous BCAA with or without L-carnitine were reviewed retrospectively and their baseline characteristics recorded, including sex, age, etiology of cirrhosis, liver function markers, liver fibrosis markers, nutritional status, degree of hepatic coma and Glasgow Coma Scale (GCS). The Model for End-Stage Liver Disease (MELD) score was calculated based on serum bilirubin and creatinine concentrations, the international normalized ratio for prothrombin time, and the need for hemodialysis (26). Liver fibrosis markers included the aspartate aminotransferase-to-platelet ratio index (APRI) and Fib-4 index (27, 28), and nutritional status was evaluated using the screening tool for controlling nutritional status (CONUT) (29), which has been associated with prognosis of patients with end-stage liver diseases (30). Patients with hepatocellular carcinoma (HCC) requiring treatment were defined as having viable HCC. Patients with HCC were diagnosed and treated according to the guidelines of the Liver Cancer Study Group of Japan (LCSGJ) (31). Patients with serious liver failure or advanced HCC who died within 1 wk after intravenous BCAA treatment were excluded from this analysis. The study protocol was approved by the Institutional Review Board Ethics Committee of Toyama University (No. 26-96) and was in agreement with the 1975 Helsinki Declaration as revised in 1983.

**Treatment of hepatic encephalopathy.** All patients with cirrhosis were treated according to Japanese clinical practical guidelines (19). Patients who developed OHE with disturbed consciousness were intravenously administered 500 mL of BCAA-containing fluid, in addition to conventional therapies such as removal of precipitating factors and administration of lactulose. Patients with a severe disturbance of consciousness were administered lactulose by enema. Some patients with HE were treated with 1,000 mg of intravenous L-carnitine per 500 mL intravenous BCAA. During consciousness disturbance, patients were administered intravenous fluids, including intravenous BCAA, with these treatments stopped when the consciousness level improved and oral intake could be restarted. The dose of lactulose was adjusted to yield soft stools 2–3 times per day.

At the discretion of their attending physicians, some patients who could be discharged from hospital were administered 1,500–2,000 mg per day oral L-carnitine (L-cartin FP®, Otsuka Pharmaceutical Co. Ltd.) (Fig. 1). Conventional baseline therapies for prevention of OHE, including lactulose, non-absorbable antibiotics and oral BCAA, were also administered.

**Statistical analysis.** Statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY). Data were shown as median and range, with the dos-
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Recurrence-free survival (RFS) and overall survival (OS) after intravenous L-carnitine administration were analyzed by the Kaplan-Meier method, and compared by log-rank tests. A p value ≤0.05 was considered statistically significant.

RESULTS

Patient characteristics

The characteristics of patients who were treated with intravenous BCAA alone (Group A) or intravenous BCAA plus intravenous L-carnitine (Group L) are shown in Table 1. Eight patients who died within 1 wk were excluded from this study. Baseline characteristics were generally similar in these two groups, but median blood ammonia levels were higher in Group L than Group A patients (140 versus 91 μg/dL, p=0.02). Median MELD scores (14.6 versus 10.2), APRI (3.1 versus 2.2) and Fib-4 index (9.2 versus 7.4) were higher in Group L than Group A, whereas median CONUT scores were similar (10 versus 9). This study included patients with severely deteriorated liver function, advanced liver fibrosis and low nutritional status, with about one-third of patients in both groups having viable HCC. Evaluation of patients with advanced HCC showed LCSGJ Stages I, II, III, IVa and IVb tumors in 1, 2, 6, 3 and 5 patients,
respectively, in Group A and 0, 2, 4, 3 and 3 in Group L, respectively (32). Patients with lower GCS, indicating poorer liver function, were preferentially included in Group L.

**Intravenous therapy with BCAA and l-carnitine**

Table 2 shows the treatments for OHE in Group A and Group L. The duration of intravenous therapy and the average daily dose of intravenous BCAA (593 ± 198 versus 591 ± 197 mL, *p* = 0.88) were similar in Group A and Group L. The average daily dose of intravenous l-carnitine in Group L was 1,182 ± 395 mg, and the median total dose was 4.5 g. Other agents, including lactulose, oral BCAA and non-absorbable antibiotics, were similar in the two groups. Because rifaximin was not approved in Japan for treatment until September 2016, patients were treated with the non-absorbable antibiotic kanamycin. All patients in both groups who developed OHE were treated with lactulose. Pretreatment median ammonia concentrations were significantly lower in Group A than Group L (91 versus 140 μg/dL, *p* = 0.02). After intravenous treatment for 3 d, median ammonia levels in these groups were reduced to 118 and 93 μg/dL, and after 7 d to 89 and 85 μg/dL, respectively (Fig. 2A). Compared with their baseline concentrations, blood ammonia concentrations on day 3 were significantly reduced in both Group A (*p* = 0.04) and Group L (*p* = 0.02). After 7 d, ammonia concentrations were significantly lower than baseline in Group L (*p* < 0.01), but not in Group A (*p* = 0.11). The rate of change from day 0 to day 7 was significantly greater in Group L than Group A (*p* < 0.01, Fig. 2B).

Although median GCS at baseline was significantly higher in Group A than Group L (8 versus 7, *p* = 0.03), indicating greater deterioration in Group L, median

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**Fig. 2. Effects over time of intravenous BCAA with or without intravenous l-carnitine on (A) blood ammonia concentrations, (B) changes in blood ammonia concentrations relative to day 0, (C) hepatic coma grade, and (D) Glasgow Coma Scale. Each data set is shown as mean and the 95% confidence interval. * Statistically significant difference between group A and group L. # Statistically significant difference within each group compared with day 0.**

**Fig. 3. Overall survival curves in patients treated with intravenous BCAA with or without intravenous l-carnitine. Results were plotted by the Kaplan-Meier method and compared by log-rank tests. MST, median survival time.**

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GCS after 3 d of intravenous l-carnitine supplementation was significantly lower in Group A (10 versus 11, \( p=0.02 \)), with no significant difference on day 7 (GCS: 13 versus 15, \( p=0.12 \)). No patient in either group experienced adverse events associated with intravenous l-carnitine or BCAA administration. Following recovery from OHE, bowel movements in most patients were controlled by lactulose and oral BCAA supplementation. Recurrence-free survival after l-carnitine treatment

Seven patients in Group A and four in Group L died within 1 mo after treatment (Table 2). About one-third of these patients died of OHE progression, which was not surprising, as this study included patients with advanced HCC and severely deteriorated liver function. The causes of death in these patients were all liver-related death, including HCC or liver failure. Median OS after intravenous BCAA with or without l-carnitine treatment was 534 d (95% confidence interval [CI] 173–895 d) in Group A and 392 d (95% CI 110–674 d) in Group L (\( p=0.76 \); Fig. 3). Median RFS was 620 d (95% CI 466–774 d) in Group A and 497 d (95% CI 191–803 d) in Group L (\( p=0.14 \); Fig. 4A).

Interestingly, median RFS was significantly longer in patients who were than were not administered oral l-carnitine (735 versus 497 d, \( p=0.03 \); Fig. 4B). The average daily dose of oral l-carnitine was 1,833 ± 258 mg, and the median total dose was 885 g. There were no statistically significant differences in the Child-Pugh score, MELD score, APRI, Fib-4 index, CONUT score, or HCC staging between patients who were administered oral l-carnitine and those who were not (data not shown). These findings suggested oral l-carnitine supplementation could prevent the recurrence of OHE in cirrhotic patients with severely deteriorated liver function in clinical practice settings.

DISCUSSION

This retrospective study showed that blood ammonia concentrations were reduced more by treatment with intravenous l-carnitine and intravenous BCAA than with intravenous BCAA alone. Although patients in Group L showed greater deterioration in liver function, OHE improved equally in both groups or better in l-carnitine administered patients than in only BCAA administered patients, indicating that intravenous l-carnitine supplementation is effective in patients with OHE and disturbed consciousness. Furthermore, recurrence of HE was better prevented in patients given oral l-carnitine supplementation plus conventional therapies than in those given conventional therapies alone. These results indicate that l-carnitine supplementation is effective in the management of HE, and that intravenous l-carnitine supplementation may be a treatment option for patients with OHE and disturbed consciousness.

The present study found that the blood ammonia level was significantly reduced by intravenous l-carnitine supplementation in patients. Although such ammonia-lowering effect by intravenous l-carnitine supplementation has been reported in previous studies (21, 23), the present study confirmed the effect in patients with deteriorated liver function or accompanying HCC by lower dose of l-carnitine (4 g/d in former studies versus 1.18 g/d in the present study). l-Carnitine has been shown to decrease blood ammonia concentrations in animal models (33, 34). This reduction in ammonia was due to the conversion of α-ketoglutarate to glutamate by the enzyme glutamate dehydrogenase and by improved pyruvate oxidation and tricarboxylic acid cycle flux (33, 34). The significance of ammonia in the development of HE is unclear (35, 36). However, we found that the GCS improved earlier in patients treated with intravenous l-carnitine plus BCAA than with intravenous BCAA alone, providing further evidence for the effectiveness of intravenous l-carnitine supplementation in treating OHE. Furthermore, ammonia is thought to act on organs other than the liver, including the muscles and the brain, suggesting that these organs are also involved in the removal of ammonia from the circulation (37, 38). Further investigations are required to determine whether l-carnitine supplementation contributes to the improvement of OHE. l-Carnitine supplementation has also been shown

Fig. 4. (A) Recurrence-free survival curves in patients treated with intravenous BCAA with or without intravenous l-carnitine. Results were plotted by the Kaplan-Meier method and compared by log-rank tests. MST, median survival time. (B) Recurrence-free survival curves of patients who did (solid line) and did not (dashed line) receive oral l-carnitine supplementation. Results were plotted by the Kaplan-Meier method and compared by log-rank tests.
effective in patients with HE, although most of these studies were from a single center and all from Italy with a higher dose of L-carnitine (4 g/d) (20–23, 39, 40). Several randomized, placebo-controlled trials have shown that oral L-carnitine supplementation was effective to reduce blood ammonia levels and improve HE in patients with minimal to mild HE (20, 22, 39, 40), with the present study confirming that oral L-carnitine could effectively prevent the recurrence of HE at a lower dose (1.83 g/d). Oral L-carnitine was also found to reduce blood ammonia levels in patients with HCC (41). Thus the effectiveness of oral L-carnitine supplementation to improve and prevent HE can be expected in patients with cirrhosis even when concomitant with HCC. On the other hand, regarding intravenous L-carnitine supplementation, two randomized controlled trials showed that administration of intravenous L-acetylcarnitine for 1 and 3 d to patients with hepatic coma reduced blood ammonia concentrations and improved electroencephalography (EEG) and GCS results (21, 23), with improvements in neurological findings observed within several hours after intravenous L-carnitine supplementation (21). Intravenous supplementation with L-carnitine may promptly counteract any carnitine deficiency, leading to earlier improvement in OHE. These findings suggested that the activity of L-carnitine in HE is both direct and strong. Moreover, these studies reported no serious adverse events following L-carnitine supplementation, regardless of the administration route (20–23, 39, 40). Patients with OHE frequently show disturbances in oral intake, and many patients with advanced cirrhosis experience hepatic edema, leading to intestinal edema and resulting in the impairment of intestinal absorption. Collectively, intravenous L-carnitine supplementation may be an effective therapeutic modality for patients having OHE with coma. To date the effectiveness of intravenous L-carnitine supplementation for OHE in clinical settings was limited, especially in Japan. Further studies to confirm the effectiveness of intravenous L-carnitine supplementation and to optimize its administration are desired.

This study had several limitations. First, this study was retrospective in design and included relatively few patients. Furthermore, many of the patients in this study had advanced HCC, which may have masked the therapeutic and survival benefits of L-carnitine supplementation. Although there were few statistically significant differences between groups of patients who did and did not receive L-carnitine, randomized, controlled prospective trials in patients who do not have advanced HCC are required to raise the evidence level. Another limitation of the present study was the method of diagnosing OHE, which was based on the clinical judgment of each attending physician. More objective methods may be preferred, including results on the number connection test or neurophysiological testing such as EEG (2). This type of functional testing might also help in evaluating the mechanism of action of L-carnitine supplementation.

Another limitation was the lack of measurement of carnitine concentrations. In daily clinical practice, carnitine concentrations cannot be routinely measured in cirrhotic patients. In this study, patients administered intravenous L-carnitine supplementation recovered from OHE and patients administered oral L-carnitine showed a reduction of OHE recurrence. These results suggested that advanced liver cirrhosis was accompanied by a severe deficiency in L-carnitine. A previous study showed that carnitine deficiency was found in cachectic cirrhotic patients, and such hypocarnitinemic cirrhotic patients showed decreased levels of carnitine in the liver, muscles or brain (42). The findings of this study confirmed that worsening of the nutritional state in cirrhotic patients correlated with disease progression (30). Advanced cirrhosis may therefore be characterized by nutritional deficiencies, including carnitine. A recent study reported that serum carnitine levels were maintained within standard levels in cirrhotic patients and that blood carnitine and ammonia concentrations did not show significant correlations (24). However, L-carnitine supplementation showed an ammonia-lowering effect in cirrhotic patients with normal blood carnitine levels (24), suggesting that cirrhotic patients require more carnitine than healthy individuals and that they have relative carnitine deficiency. Carnitine deficiency is frequently accompanied by deficiencies in skeletal muscle, suggesting that carnitine concentrations be measured in muscle or brain, in addition to blood or liver, in patients with advanced cirrhosis and HE, thereby clarifying the association between carnitine and HE. In practice, however, it is difficult to measure carnitine in muscle or brain, suggesting the need for alternative functional tests or evaluations with experimental models.

In conclusion, this study indicated that intravenous L-carnitine administration is effective in patients with OHE. Although these results are preliminary, L-carnitine supplementation might be a therapeutic option for OHE with disturbed consciousness. Additional studies are required to determine the optimal route of L-carnitine administration and its mechanism of action.

Source of funding

We had no financial support for the present study.

REFERENCES

4) Bajaj JS, Cordoba J, Mullen KD, Amadio P, Shawcross DL, Butterworth RF, Morgan MY. International Society for


