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ORIGINAL ARTICLE

Acetyl-L-carnitine reduces depression and improves quality of life in patients with minimal hepatic encephalopathy

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Abstract

Background. Minimal hepatic encephalopathy (MHE) represents a common complication present in well-compensated cirrhotic patients that impairs patients' daily functioning and health-related quality of life (HRQL). Acetyl-L-carnitine (ALC) has been shown to be useful in improving blood ammonia and cognitive functions in cirrhotic patients with MHE. ***Objective.*** This study evaluated the effects of ALC treatment on HRQL and depression in patients with MHE. ***Study design.*** This was a randomized, double-blind, placebo-controlled study. Sixty-seven patients with MHE were recruited to the study. They were randomly assigned to two groups and received either 2 g acetyl-L-carnitine twice a day ($n = 33$) or placebo ($n = 34$) for 90 days. The primary efficacy measures were changes in aspartate aminotransferase, alanine aminotransferase, γ-glutamyl-transpeptidase, albumin, alkaline phosphatase, prothrombin time, and ammonia. Clinical and laboratory assessments, psychometric tests and automated electroencephalogram (EEG) analysis were performed for all patients. ***Results.*** At the end of the study period, between the two groups, we observed a significant difference in physical function ($p < 0.001$), role physical ($p < 0.001$), general health ($p < 0.001$), social function ($p < 0.05$), role emotional ($p < 0.05$), mental health ($p < 0.05$), Beck Depression Inventory ($p < 0.001$), TMT-B s ($p < 0.001$), State Trait Inventory ($p < 0.001$), urea ($p < 0.05$), NH_4^+ ($p < 0.001$), and bilirubin ($p < 0.001$). ***Conclusions.*** This study shows that ALC treatment is associated with significant improvement in patient energy levels, general functioning and well-being. The improvement of quality of life is associated with reduction of anxiety and depression.

Key Words: *Acetyl-L-carnitine, depression, minimal hepatic encephalopathy, quality of life*

Introduction

Minimal hepatic encephalopathy (MHE) represents a common complication present in well-compensated cirrhotic patients [1]. In recent years, quality of life has been increasingly recognized as an important outcome of medical treatment and represents an important goal of all health interventions. MHE is an important disorder that impairs patients daily functioning and health-related quality of life (HRQL) [2,3]. In fact, patients with MHE had a significant impairment in daily functioning, such as social interaction, alertness, emotional behavior, sleep, work, home management and recreation and pastimes as compared with patients who did not have MHE [4–6]. HRQL, which comprises the physical mental and social effects of disease, is measured by assessing somatic symptoms: psychological status, social interactions, physical cognitive and psychosocial functioning, and sense of well being and emotional status. Several studies have shown that MHE can negatively affect the physical and mental well-being of patients through development of short- and long-term complications, physical symptoms and

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lifestyle changes, and feelings of helplessness and emotional distress [2,7]. Acetyl-L-carnitine (ALC) is an endogenous molecule synthesized in mitochondria by the enzyme ALC transferase and is the predominant acylcarnitine in normal tissues. Acylcarnitine is the fatty acid-bound form of carnitine and has an important role in the transport of long-chain fatty acid into mitochondria and their β-oxidation [8–10]. Serum acylcarnitine is mainly composed of short-chain fatty acid carnitine, especially ALC. Although 99% of the carnitine amount is intracellular, the relationship between serum acylcarnitine and free carnitine is highly sensitive to intramitochondrial metabolic alterations [11]. ALC has been shown to be useful in improving blood ammonia and cognitive functions in cirrhotic patients with MHE [12]. The aim of this study was to evaluate whether ALC treatment may improve HRQL and reduce depression in patients with MHE.

Materials and methods

Study design

This was a randomized, double-blind, placebo-controlled study. The study was conducted between April 2002 and November 2005 and the study participants were recruited from Cannizzaro Hospital, Catania, Italy. This study was designed and conducted in compliance with the ethical principles of Good Clinical Practice Guidelines and the Declaration of Helsinki [13]. The study protocol was approved by the research ethics committee of Cannizzaro Hospital, Catania, Italy. Informed consent was obtained from patients before any study procedures were initiated. Seventy-two patients with diagnosis of MHE were enrolled in the study. Sixty-seven patients (age 34–67 years) were randomly assigned by a computer-generated randomization schedule to receive a 90-day supply of either ALC or placebo. Thirty-four patients were allocated to placebo group and 33 were allocated to ALC group (Figure 1). The treatment was for 90 days. The measurements were made every month, both for efficacy tests and for tolerability.

Eligibility criteria

All patients diagnosed as having cirrhosis at the outpatient Internal Medicine of the Department of Senescence were candidates for enrolment. The diagnosis of cirrhosis was based on clinical, biochemical and ultrasonographic or liver histological data.

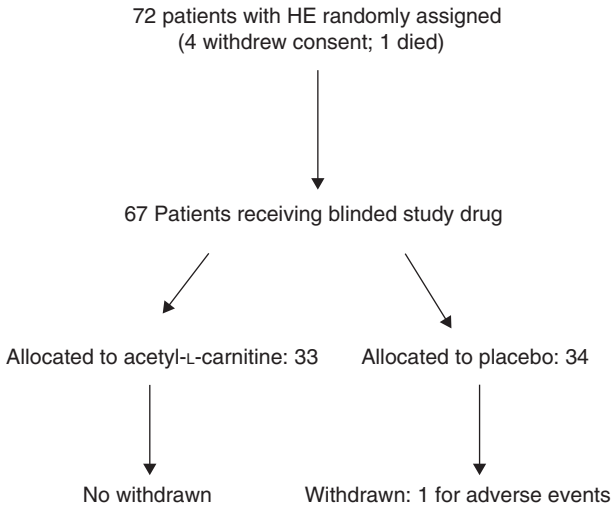

Figure 1. Trial profile of acetyl-L-carnitine treatment.

Exclusion criteria

Exclusion criteria were overt hepatic encephalopathy (HE) or a history of overt HE; history of recent alcohol intake; infection; recent antibiotic use or gastrointestinal bleeding; history of recent use of drugs affecting psychometric performances like benzodiazepines, antiepileptics or psychotropic drugs; a history of shunt surgery or transjugular intrahepatic portosystemic shunt for portal hypertension; electrolyte imbalance; renal impairment; hepatocellular carcinoma; severe medical problems such as congestive heart failure, pulmonary disease or neurological or psychiatric disorder that could influence quality of life measurement; inability to perform neuropsycological tests. Patient characteristics, including educational status, Child–Turcotte Pugh class, and etiology of the cirrhosis are listed in Table I. Male patients were considered to have alcohol-related cirrhosis if daily alcohol intake was more than 50 g and female patients if daily intake was more than 30 g for more than 5 years and if testing showed no viral, metabolic or immunologic cause. Chronic hepatitis B and C were diagnosed when testing was positive for the viral markers HbSAg and antiHCV, respectively. None of the patients received antiviral treatment before or during the study.

Data collection

Baseline characteristics of the patients were recorded on entry into the study. We collected information regarding demographic profile (age, sex, and educational status) etiology of cirrhosis, hemogram (hemoglobin, total white blood cell and platelets) liver and

Table I. Clinical characteristics of patients at randomization.

Parameters	Group A, ALC	Group B, Placebo	*p*-Value
Male/Female	20/13	19/15	NS
Age (range)	37–65	34–67	NS
SBP mmHg	148 ± 25.4	144 ± 26.2	NS
DBP mmHg	80 ± 11	79 ± 12	NS
Heart rate (bpm)	78 ± 12	81 ± 10	NS
Cirrhosis etiology			
Post-hepatitis B	13	12	NS
Post-hepatitis C	15	15	NS
Alcoholism	2	3	NS
Unknown	3	4	NS
Child–Pugh class			
Grade A	21	20	NS
Grade B	12	14	NS
Ascites	4	5	NS

Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; NS = not significant.

kidney functions (bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin, creatinine, Na^+ and K^+, prothrombin time).

Prerandomization phase

The subjects were required to document all caloric intake with the use of a diary, completed every 2 days. This prerandomization period was designed to nullify the effects of dietary changes on metabolic markers. During the initial 4 weeks phase, subjects were instructed by a dietitian to follow an ad libitum diet as classified by the National Cholesterol Education Program [14]. Their protein intake was not restricted. Ascites was controlled with salt restriction and a combination diuretic therapy consisting of torasemide or furosemide and spironolactone. Nonselective β-blockers were used for prophylaxis of variceal bleed. These medications were continued during the study period.

Randomization phase

Throughout the trial, ALC was supplied in vials with 2 g ALC taken orally twice a day. All drugs and placebos were identical in appearance, and neither investigators nor patients were informed of the selected agent until the end of the study phase. Dosing instructions were provided with each patient pack. All trial medication was instructed to be taken as prescribed. Subjects were considered compliant if the number of returned vials was between 80% and 120% of the planned treatment regimen. For the duration of the trial any concomitant drugs were administered at the lowest possible therapeutic dosage and, as far as possible, were not changed.

L-Carnitine determination

Patients were studied in the morning between 08.00 and 10.00 after an overnight fast. The patients were first asked to empty their bladder. Then, venous blood samples were drawn into tubes containing EDTA or heparin, and serum or plasma was obtained by centrifugation. A spot urine sample was obtained 10 min after the collection of the blood sample. Serum was measured immediately; plasma and urine were stored at −20°C until analysis. The L-Carnitine concentration in plasma and urine was measured by a method described by Cederblad and Lindstedt [15] and modified by Brass and Hoppel [16]. Plasma was treated with perchloric acid (final concentration of 3% vol:vol) and centrifuged for 2 min at 10,000 × g. Long-chain acylcarnitines (LCACs) were measured in the pellet after alkaline hydrolysis, and free and short-chain acylcarnitines (SCACs) were measured in the supernatant fluid. The inter-assay CVs were 3.8%, 3.9%, and 4.1%, respectively; the intra-assay CVs were 5.4%, 5.8%, and 6.4%, respectively. Addition of LCACs, together with the free and SCACs yields the total acyl-carnitine. In urine no perchloric acid precipitation was performed (LCACs are normally not found in urine). Free carnitine and SCACs were measured in plasma. The within-assay CVs were 4.1% and 3.9%, respectively; the between-assay CVs were 5.2% and 5.8%, respectively.

Efficacy assessment

Throughout the randomization phase of the study, thrice-weekly alimentary diary cards were used to collect efficacy data. The primary efficacy measures were changes in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltranspeptidase (γ-GT), albumin, alkaline phosphatase (ALP), prothrombin time, and ammonia. Measurements were made at the beginning and at the end of the study period. Data were collected in the morning, after an overnight fast.

Tolerability assessment

Laboratory assessments were monitored at baseline and monthly until the end of the trial. These data included hemochrome, glycemia, creatininemia, and blood urea. After providing informed consent,

each subject in the two groups underwent ultrasonography (US) examination of the liver. Electrocardiogram and blood pressure were monitored with the use of standard techniques.

Methods

Clinical and laboratory assessments, psychometric tests and automated electroencephalogram (EEG) analysis were performed for all patients. A detailed clinical neurological examination was performed to exclude evidence of clinically overt HE and any focal neurology. The diagnosis of HE grade was made on the basis of the evaluation of consciousness, intellectual functions, behavior and neuromuscular functions, and was made when appropriate laboratory and diagnostic testing excluded other causes of mental status changes. The investigators were blinded to the patients' ammonia levels. Patients whose clinical course was not consistent with HE were excluded. Mental status was assessed and graded on admission according to the West–Haven criteria introduced by Conn [17].

Neuropsychological assessment

The use of neuropsychometric battery tests have been limited to research of minimal HE. Although results from most studies have not been easy to compare because of the array of different tests, the common finding in cirrhotic patients is impaired psychomotor speed, visual perception and attention, while verbal ability is unimpaired. The Number Collection Test has been considered as the most sensitive diagnostic test for the detection of HE. Recently, the Psychometric Hepatic Encephalopathy Score (PHES) has been introduced, which consists of five psychometric tests that measure psychomotor speed and precision, visual perception, visuo-spatial orientation, visual construction, concentration, attention and memory [18]. This uses the Line Drawing Test, the Serial Dotting Test and the Trail Making Test (TMT A and B), to examine motor speed and accuracy, visual perception visuo-spatial orientation, visual construction concentration, attention and to a lesser extent memory. The Serial Dotting Test consists of 10 rows of 10 circles, and the subject is timed on how quickly he or she can place a dot in the center of each circle. The Line Drawing Test requires the subject to draw a continuous line between two parallel (winding) lines, and scores include completion time and errors. This small neuropsychological battery is simple to perform, can be completed in less than 20 min and has a sensitivity of 96% and a specificity of 100% in the diagnosis of HE.

Trail making test

The TMT was used to evaluate abstract reasoning, tactile performance, tactile visual and spatial memory, rhythm perception and memory, speech-sound perception, primary motor speed, intelligence, psychomotor speed, sequencing abilities, language function, sensory function, grip strength and personality functioning. The TMT is part of the Halsted–Reitan test battery [19]. Time was recorded in seconds. This test included part A and B. In part A, patients were asked to serially connect digits that were scattered on a page as quickly as possible. In part B, patients were asked to sequentially alternate numbers and letters (i.e. 1-A-2-B-3-C) as quickly as possible. A decrease in the time indicated an improvement in neuropsychological function. The score on each part represent the amount of time required to complete the task.

SF-36

The 36-item short-form (SF-36) includes one multi-item scale that assesses eight health concepts: (1) limitations in physical activities because of health problems; (2) limitations in social activities because of physical or emotional problems; (3) limitations in usual role activities because of physical health problems; (4) bodily pain; (5) general mental health (psychological distress and well-being); (6) limitations in usual role activities because of emotional problems; (7) vitality (energy and fatigue); and (8) general health perceptions. The survey was constructed for self-administration and for administration by a trained interviewer [20]. All raw scores were converted to 0–100 scale with higher scores indicating higher levels of functioning or well-being.

Beck depression inventory (BDI)

Candidates were asked to complete BDI (BDI1) in their first visit. The questionnaire was completed by an assistant for uneducated subjects. Accordingly, BDI score was calculated. Index score of ≤ 9 is considered to be within normal range, a score of 10–15 shows minimal depressive symptomatology, a score of 16–31 points toward mild depression, a score of 32–47 is in favor of moderate depression and a score of >47 indicates severe depression [21].

State-trait anxiety inventory (STAI)

The state of anxiety of the individuals was assessed by the S-anxiety questionnaire of the STAI. Patients responded to 20 statements by rating each question with a score ranging from 1 (not at all) to 4 (very much so). The scale is scored by summing the 20 responses (range 20–80) [22].

Neurophysiological assessment

The EEG was recorded using standardized techniques. Five electrodes were attached to the skin at the positions T3, T4, O1, O2 and Cz according to the international '10–20 system'. Electrode impedance was kept lower than 5 kQ. After applying the usual handpass filters (0.53–35 Hz), two runs of 100 s each were recorded and compared for reproducibility. Patients were graded into different studies of HE according to their mean dominant frequency and the relative powers of δ and θ activity [23]. The EEG is the only test that classifies HE in five grades of severity (from normal to coma) just as the clinical grading.

Grade 0: normal, regular a rhythm.
Grade 1: irregular background activity (α and θ rhythm).
Grade 2: continuous θ activity, occasionally δ activity.
Grade 3: prevalence of θ activity, transient polyphasis complexes of spikes and slow waves.
Grade 4: continuous δ activity, abundant complexes of spikes and slow waves [24].

Liver function assessment

The Child–Pugh score was determined to assess the severity of cirrhosis, including three biochemical variables (serum albumin, bilirubin and prothrombin time) and two clinical characteristics (presence or absence of ascites and clinical HE). A patient had a Child–Pugh score A cirrhosis if the score was ≤6 points, a Child–Pugh B cirrhosis if the score was 7–9 points and a Child–Pugh C cirrhosis if the score was greater than 9 points. Patients without signs of ascites were scored as two points for ascites [25]. We also evaluated the presence and severity of the portosystemic shunt, by the portal vein flow, by the presence and size of the esophageal varices and by splenic size.

Venous ammonia concentration

The ammonia was determined according to the enzymatic determination of ammonia with glutamate dehydrogenase in a rapid and interference-free photometric determination (340 nm) of NH_4^+ in native blood plasma as according to Da Fonseca–Wollheim method [26]. Owing to the reasons of safety, blood was immediately taken by refrigerated transport sent to the laboratory for immediate determination of NH_4^+ (within 15 min from blood sampling).

Safety parameters

Safety parameters included blood tests (hemoglobin, hematocritus, white blood cell count and thrombocytes) and liver function tests (ALT, AST, γ-GT, cholinesterase activity, serum bilirubin concentrations, prothrombin time and partial thromboplastin time) on days 0, 30 and 60.

Statistical analysis

We calculated that a sample size of at least 25 patients in each arm would be required to detect a difference in improvement in HE, that is, the proportion of patients with HE at 2 months, with a 5% type 1 error and 90% power for a two-tailed log-rank test. Descriptive statistics were prepared from the study sample and results have been expressed as mean ± standard deviation. Statistical significance in contingency tables was evaluated using χ^2 and Fisher's exact test. Student's test for unpaired data, one-way analysis of variance and Mann–Whitney rank sum test were used for comparisons of continuous variables. Statistical analysis was performed using appropriate tests for repeated measures as well as by controlling for multiple comparisons with correction of Duncan procedure. Difference in tolerability was assessed from χ^2 test comparing the proportions permanently withdrawn from all study drugs or placebos.

Results

Baseline values

Clinical characteristics of patients at randomization in both groups are presented in Table I. The two groups were homogeneous for demographic characteristic, etiology, casting of disease and Child–Pugh grade. Serum NH_4^+ fasting concentrations were not significantly different before the treatment. No statistical differences were observed between the two groups about prothrombin time and serum albumin, bilirubin, AST and ALT. No statistical differences have been observed in the two groups in the administered neuropsychological test and in EEG (Table I).

Neuropsychological response

Effects of ALC on PHES. After 90 days in the ALC treatment group there were significant differences in TMT-A s ($p < 0.001$ CI 4.48–9.12), TMT-B s ($p < 0.001$ CI 8.28–14.92), Line tracing (seconds) ($p < 0.001$ CI 8.19–19.21), Line tracing (errors) ($p < 0.001$ CI 1.71–3.09) and Serial dotting (seconds) ($p < 0.05$ CI 1.26–8.74). When comparing group A and group B we observed a significant difference in TMT-B s −11.5 vs. −1.8 ($p < 0.001$) and Line tracing (errors) −2.4 vs. −0.6 ($p < 0.001$) (Table II).

Effects of ALC on HRQL. After 90 days in the ALC treatment group there were significant differences in physical function ($p < 0.001$ CI −13.18 to −4.82); role physical ($p < 0.05$ CI −9.72 to −0.48); general health ($p < 0.001$ CI −9.47 to −2.53); vitality ($p < 0.05$ CI −7.01 to −1.39); social function ($p < 0.001$ CI −8.46 to −2.14); role emotional ($p < 0.05$ C.I. −9.98 to −1.02), mental health ($p < 0.001$ C.I. −10.71 to −4.69). When comparing group A and group B we observed a significant difference in physical function 9 vs. 2.3 ($p < 0.001$), role physical 5.1 vs. 3 ($p < 0.001$), general health 6 vs. 2.3 ($p < 0.001$), social function 5.3 vs. 0.7 ($p < 0.05$), role emotional 5.5 vs. −1.2 ($p < 0.05$), mental health 7.7 vs. −1.2 ($p < 0.05$) (Table II).

Effects of ALC on depression and anxiety. After 90 days in the ALC treatment group, we observed significant differences in BDI ($p < 0.001$ CI 4.04–7.16) and State Trait Inventory ($p < 0.001$ CI 5.80–12.40). In the comparison between the two groups there were significant differences in BDI −5.6 vs. −2.2 ($p < 0.001$) and State Trait Inventory −9.1 vs. −2.9 ($p < 0.001$) (Table II).

Neurophysiological response

We did not observe significant differences in the EEG after treatment in both groups.

Biochemical responses

Effects of ALC on ammonia and urea. At the end of treatment in the group treated with ALC we observed significant differences in Urea ($p < 0.001$ CI 4.80–12.20) and NH_4^+ ($p < 0.001$ CI 18.08–27.52). In the comparison between groups there were significant differences in Urea −8.5 vs. −2.2 ($p < 0.05$) and NH_4^+ −22.8 vs. −4.8 ($p < 0.001$) (Table III).

Effects of ALC on liver function. At the end of treatment in the group treated with ALC we observed significant differences AST ($p < 0.001$ CI 44.57–60.43), ALT ($p < 0.001$ CI 57.75–74.65), prothrombin time ($p < 0.05$ CI 0.41–1.99), bilirubin ($p < 0.001$ CI 0.17–0.63) (Table III).

L-Carnitine in plasma and urine. In the ALC group, significant differences were observed in the following markers after treatment compared with baseline: free

Table II. Comparison of physical and mental markers between treatment groups[1].

	Group A, ALC ($n = 33$)		Group B, Placebo ($n = 34$)	
	Before treatment	After 90 days	Before treatment	After 90 days
Physical function	62.4 ± 8.6	71.4 ± 8.4***^{A}	61.2 ± 5.7	63.5 ± 5.5*^{A}
Role physical	69.1 ± 9.5	74.2 ± 9.3**^{A}	61.6 ± 6.1	64.6 ± 6.4*^{A}
Body pain	61.6 ± 11	66.5 ± 10.4*^{C}	62.2 ± 8.3	64.7 ± 8.6*^{C}
General health	54.9 ± 7	60.9 ± 7.1***^{A}	64.7 ± 7.1	67.1 ± 6.7*^{A}
Vitality	60 ± 6.1	64.2 ± 5.3**^{C}	60 ± 7.1	61.4 ± 6.8*^{C}
Social function	61.6 ± 6.9	66.9 ± 5.9***^{B}	64.3 ± 5.8	64 ± 4.2*^{B}
Role emotional	62.5 ± 9.6	68 ± 8.6**^{B}	64.4 ± 7.4	63.2 ± 4.8*^{B}
Mental health	59 ± 6.5	66.7 ± 5.7***^{B}	64.8 ± 6.3	63.6 ± 4.5*^{B}
Beck Depression Inventory	23.6 ± 2.8	18 ± 3.5***^{A}	23.5 ± 2.6	21.3 ± 2.6*^{A}
TMT-A s	42.8 ± 5.5	36 ± 3.8***^{C}	39.6 ± 5.6	38 ± 5.4*^{C}
TMT-B s	57.8 ± 7	46.2 ± 6.5***^{A}	63.5 ± 5.7	59.4 ± 5.5*^{A}
Serial dotting (seconds)	50.4 ± 8	45.4 ± 7.2**^{C}	46.1 ± 5.7	44.3 ± 4.8*^{C}
Line tracing (seconds)	81.3 ± 10.1	67.6 ± 12.2***^{C}	71.2 ± 11.3	67.8 ± 11.2*^{C}
Line tracing (errors)	7.5 ± 1.5	5.1 ± 1.3***^{A}	7.1 ± 0.9	6.5 ± 0.7*^{A}
State Trait Inventory	49.6 ± 7.6	40.5 ± 5.7***^{A}	49.2 ± 6.5	46.3 ± 6.6*^{A}

[1]All values are expressed as mean ± SD.
Comparison within group A and within group B according to the values before the treatment *p = NS; **$p < 0.05$; ***$p < 0.001$.
Comparison between groups A and B after 90 days of treatment $^A p < 0.001$; $^B p < 0.05$; ^{C}NS.

Table III. Comparison of clinical parameters between treatment groups[1].

	Group A, ALC (n = 33)		Group B, Placebo (n = 34)	
	Before treatment	After 90 days	Before treatment	After 90 days
Urea	52.7 ± 6.9	44.2 ± 8.1^{***B}	50.2 ± 7.4	48 ± 6.4^{*B}
NH_4	64.8 ± 8.1	42 ± 10.9^{***A}	63.6 ± 10.4	58.7 ± 7.6^{*A}
AST	102.1 ± 15.2	49.6 ± 17^{***C}	80.4 ± 19.8	54.6 ± 15.6^{*C}
ALT	117.4 ± 16	51.2 ± 18.3^{***C}	90.2 ± 14.3	55.4 ± 14.1^{*C}
Prothrombin time	16.5 ± 1.6	15.3 ± 1.6^{**C}	15.8 ± 1.6	14.7 ± 1.2^{*C}
Albumin	3.3 ± 0.3	3.4 ± 0.2^{*C}	3.4 ± 0.2	3.4 ± 0.2^{*C}
Bilirubin	2.3 ± 0.6	1.9± 0.3^{***A}	1.6 ± 0.6	1.6 ± 0.4^{*A}

Abbreviations: AST = aspartate transaminase; ALT = alanine transaminase.
[1]All values are expressed as mean ± SD.
Comparison within group A and within group B according to the values before the treatment $^{*}p$ = NS; $^{**}p < 0.05$; $^{***}p < 0.001$.
Comparison between groups A and B after 90 days of treatment $^{A}p < 0.001$; $^{B}p < 0.05$; ^{C}NS.

plasma carnitine (5.2 μmol/L, $p < 0.05$ CI −9.06 to −1.34), plasma concentrations of total plasma carnitine (7.7 μmol/L, $p < 0.001$ CI −12.08 to −3.32), plasma LCAC (0.3 μmol/L, $p < 0.05$ CI −0.52 to −0.08), and SCAC (2.3 μmol/L, $p < 0.001$ CI −3.49 to −1.11). No significant differences of levocarnitine concentrations were observed in the urine. In the placebo group, the plasma concentrations of free L-Carnitine and LCAC and the urinary excretion of free L-Carnitine and SCAC did not show significant differences compared with baseline. At the end of the study period, compared with placebo, the ALC-treated patients showed significant improvements in the following markers: plasma concentrations of total L-Carnitine (7.7 compared with 1.8 μmol/L, $p < 0.001$) and plasma SCAC (2.3 compared with −0.1 μmol/L, $p < 0.001$) (Table IV).

Discussion

MHE is associated with a poor quality of life, decreased work performance and increased progression to overt HE [27,28]. Quality of life is an essential assessment component of patients with chronic diseases. Issues pertaining to quality of life are also central to most patient complaints in cirrhosis. Groeneweg et al. studied the Sickness Impact Profile in a cohort of cirrhotics being tested for MHE [27]. A recent study by Prasad et al. confirmed these findings in MHE patients in all spheres apart from communication, which was similar between patients with or without MHE [2]. Numerous studies have demonstrated that HRQL is reduced regardless of the severity of liver disease or psychiatric comorbidities [29–32]. This study shows that ALC treatment is associated with significant improvement in patient energy levels, general functioning and well-being. The improvement of quality of life is associated with reduction of anxiety and depression. Confirmation of these findings is important because they imply that the increased quality of life is related to the decrease of ammonium. This study also indicates that HRQL benefits of ALC treatment occur in MHE. Few studies were conducted in metabolic encephalopathy and in hepatocerebral degeneration. In previous study, we have demonstrated the beneficial effects of carnitine and ALC in neuropsychiatric

Table IV. Comparison of plasma and urinary concentrations of L-Carnitine between treatment groups[1].

	Group A, ALC (n = 33)		Group B, Placebo (n = 34)	
	Before treatment	After 90 days	Before treatment	After 90 days
Free plasma carnitine (μmol/L)	46.7 ± 8.1	51.9 ± 7.6^{**C}	50 ± 7.3	51.8 ± 7.3^{*C}
Plasma SCAC (μmol/L)	10.7 ± 2.7	13 ± 2.1^{***A}	7.7 ± 1.8	7.6 ± 1.1^{*A}
Plasma LCAC (μmol/L)	2.9 ± 0.5	3.2 ± 0.4^{**C}	3.1 ± 0.4	3.1 ± 0.3^{*C}
Total plasma carnitine (μmol/L)	60.4 ± 9.3	68.1 ± 8.5^{***A}	60.9 ± 7.8	62.7 ± 7.6^{*A}
Free urinary carnitine (μmol/L)	13.8 ± 1	14 ± 0.7^{*C}	13.9 ± 0.7	14 ± 0.7^{*C}
Urinary SCAC (μmol/L)	12.8 ± 0.4	12.7 ± 0.3^{*C}	13.3 ± 0.7	13.3 ± 0.6^{*C}

Abbreviations: SCAC = short-chain acylcarnitine; LCAC = long-chain acylcarnitine.
[1]All values are expressed as mean ± SD.
Comparison within group A and within group B according to the values before the treatment $^{*}p$ = NS; $^{**}p < 0.05$; $^{***}p < 0.001$.
Comparison between groups A and B after 90 days of treatment $^{A}p < 0.001$; $^{B}p < 0.05$; ^{C}NS.

syndrome in patients with encephalopathy associated with cirrhosis and portal hypertension [12,33]. Multiple studies have revealed that cirrhosis reduces quality of life. This decrease may be related to the impact of HE on cognitive abilities, such as attention, memory functioning, personality changes (e.g. euphoria or anxiety), response inhibition, psychomotor slowing, visuoconstructive disabilities and executive function [12,34]. Impaired quality of life has also been demonstrated using the Short Form 36 (SF-36) in MHE populations in several studies across the world [4,5]. There is much interest in L-Carnitine and ALC treatment in various neural disorders, such as Alzheimer's disease and in HE [35]. Although the mechanisms by which carnitine provides neurological protection are unknown, some researchers confirmed that ALC is promising as a safe and effective treatment for HE [12,36]. One possible mechanism of carnitine action is its reduction of serum ammonia levels leading to improved SF-36 [33,37]. Current hypotheses propose that HE is secondary to the effects of several toxins on the brain, the most important being ammonia. Ammonia undergoes a high degree of extraction in the liver; thus, portal-systemic shunts induce a rise in plasma ammonia, which may explain why HE develops frequently in patients with cirrhosis that undergo transjugular intrahepatic portosystemic shunt or surgical shunts. ALC is neuroprotective when administered at supraphysiological concentration [38]. Although such uncertainty in the success of the use of carnitine and its short-chain acyl-esters may be due to various reasons, it might be that a successful and efficacious treatment with L-Carnitine may require raising of plasma carnitine concentrations to supraphysiological levels in order to achieve an increase in L-Carnitine in the target organs [39]. If a supraphysiological increase of the acetyl-coA pool in liver mitochondria is associated with accelerated gluconeogenetic flux, an increase of acetyl-coA in muscle mitochondria may also affect glucose utilization. The protective effect of carnitines against ammonium toxicity seems to be produced due to the action of glutamate against neurotoxicity, with an increase in the binding affinity of glutamate receptors [40]. Extracellular glutamate accumulation could produce damage by excitotoxicity with the consequent increase in frequency of seizures. On the other hand, glutamate production through to excess of ammoniemia could lead to depletion of α-glutarate in the brain which produces a block in Krebs cycle [41]. When cells are energy deficient no matter the cause – hypoxia, starvation, metabolic toxins – they become susceptible to excitotoxic injury [42,43]. ALC may have a dual protective effect by enhancing the energy dynamics of the cell and also inhibiting cell membrane hyperexcitability. Excitotoxic damage via upregulation of glutamate/*N*-methyl-D-aspartate (NMDA) receptors is heavily dependent on the energy state of the cell. Hyperammoniemia involves also excitotoxicity injury through NMDA receptors. The association between psychiatric disturbances and MHE is strong; more than half patients with MHE show signs of clinical depression and or anxiety, which dramatically affect HRQL. Although hyperammoniemia is presumed to be the principal neurotoxin there is evidence that other neurochemical alterations may also be involved. Tryptophan (precursor for serotonin) and 5-hydroxyindoleacetic acid (metabolite of serotonin) are increased under hyperammoniemia and can be oxidized to quinolonic acid, an excitotoxin acting on NMDA receptors [44,45]. ALC has also been proposed for the recovery of cerebral energy deficits induced by ammonium. The mean role of carnitine is to shuttle acyl-coA derived from fatty acids across the inner mitochondrial membrane. Once inside the mitochondria the acyl-coA molecule undergoes beta oxidation producing acetyl-coA that can enter the tricarboxylic acid (TCA) cycle leading to the production of ATP [44,46]. It has been shown that ALC is able to enhance the restoration of ATP and phosphocreatine levels. The protective effect of ALC may be due to the restoration of the cytochrome C oxidase activity [46,47]. Aside from being an essential component of fatty acid metabolism, ALC is also a free-radical scavenger and may contribute to the protection of cells against oxidative stress [48,49]. Cells with a normal energy are very resistant to such toxicity. Our study indicates that ALC shows a beneficial effect in improvement of quality of life and in consequently reduction of anxiety and depression.

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