Journal of Critical Care 45 (2018) 128–132

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

A pilot trial of L-carnitine in patients with traumatic brain injury: Effects on biomarkers of injury

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ARTICLE INFO

Keywords:
L-Carnitine
Traumatic brain injury
Neuron specific enolase
Outcome

ABSTRACT

Objective: To investigate the effects of L-Carnitine on neuron specific enolase (NSE) as a marker of inflammation in patients with traumatic brain injury (TBI).
Methods: Forty patients with severe TBI were randomized into 2 groups. The (LCA-) group received standard treatment with placebo while the (LCA+) group received L-Carnitine 2 g/day for one week. NSE was measured on days 1, 3 and 7 after the initiation of the study. Neurocognitive and neurobehavioral disorders were recorded on the first and third months.
Results: Neurocognitive function and NSE significantly improved within one week in both groups. Patient mortality was similar in LCA+ and LCA- groups (*P* value: 0.76). Brain edema was present in 7 patients in LCA+ group and 13 patients in LCA-group (P value: 0.044). While there was no difference in NSE levels between the two groups. Neurological function was preserved in the LCA+ group with an exception of attention deficit, which was frequent in the LCA+ group.
Conclusion: We concluded that despite improvements in neurobehavioral function and the degree of cerebral edema, 7-days of treatment with L-Carnitine failed to reduce serum NSE levels or improve mortality rate at 90 days in patients with TBI.

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1. Introduction

The pathophysiologic response to traumatic brain injury (TBI) is complex and interdependent. It starts a cascade of events that impair normal cell function and lead to inflammatory responses, oxidative stress and mitochondrial dysfunction. Research has been focused on replacement of metabolic substrates that can improve cerebral recovery after TBI [1]. Exogenous L-carnitine is metabolized in brain to acetyl coenzyme A and subsequently enters the tricarboxylic acid cycle. L-Carnitine improves mitochondrial dysfunction and contributes to neuroprotective effects in animal models of cerebral ischemia and spinal cord injury [2]. L-Carnitine further increases the endogenous pool of antioxidant reserve [3,4] and optimizes mitochondrial enzyme complex function [5]. Scafidi et al. showed that L-Carnitine administration in acute phase of TBI resulted in improvement of neurobehavioral function and reduced level of injury in immature rats [6]. Karalija et al. showed that L-Carnitine has a therapeutic potential (anti-inflammatory) in the early treatment of traumatic spinal cord injury in adult rats [7].

Neuron specific enolase (NSE) is a glycolytic enzyme which is predominantly located in neurons and other ectodermal cells. NSE is one of the most promising markers of brain damage and recovery after TBI [8]. It can be measured in cerebrospinal fluid and peripheral blood samples. Multiple trials have demonstrated an inverse correlation between serum levels of NSE with Glasgow Coma Scale (GCS) and have verified its validity as a short and long-term predictor marker after TBI [9,10].

There are few existing studies that have examined the effect of L-Carnitine on both clinical and biochemical markers of brain injury after TBI. In this trial, our aim was to evaluate the impact of L-Carnitine on both clinical outcome and blood levels of NSE in patients with TBI. We hypothesized that daily administration of LCA would decrease the frequency of poor outcome and also reduce serum levels of NSE within 7 days after TBI.

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https://doi.org/10.1016/j.jcrc.2018.01.029
0883-9441/Published by Elsevier Inc.

2. Patients and methods

The study design was prospective randomized placebo-controlled clinical trial examining the effect of L-Carnitine on surrogates of brain injury and clinical outcome after TBI. After obtaining approval from the institutional Ethics Committee of the affiliated university the trial was registered with the Iranian Registry for Clinical Trials (IRCT201410312582N9).

2.1. Sample size determination

We calculated sample size based on the study by El-Maraghi et al. where the predictive value of NSE on the outcome of patients with TBI was examined [11]. These investigators reported NSE levels of 5.1 ± 2.1 as a good outcome and 11.1 ± 5.1 as a poor outcome. Good outcome was defined as recovery from TBI and poor outcome was defined as severe disability from TBI. Sample size determination was performed using an online power calculator available from the University of British Columbia website (www.stat.ubc.ca/~rollin/stats/ssize/n2html). A minimum of 4 patients with an unfavorable outcome in each treatment group was needed in order to make a reasonable prediction. As the risk of post TBI mortality ranges 20–25% in our trauma center for the patient with initial GCS scores of ≤8, a total of 20 patients were determined to be randomized in each group to maintain a power of 80% when alpha was set at 0.05.

2.2. Inclusion and exclusion criteria

Adult patients (18–70 years old) with severe traumatic, non-penetrating brain injury and GCS ≤8 during first 24 h of the trauma. Exclusion criteria were patients with chronic kidney injury, documented allergy to L-Carnitine, a history of L-Carnitine use, heart failure and liver failure. Additionally, the patients were excluded if their family (next of kin/healthcare proxy) refused to consent for enrollment.

2.3. Study design and randomization

All patients with TBI with admitting GCS scores of <8 were screened for the presence of inclusion and exclusion criteria (See the CONSORT Diagram on Fig. 1). Informed consent was obtained from the next of kin or healthcare proxy for voluntary participation. Patients were then randomized 1:1 ratio using a computer-generated list (RandList 4) on Microsoft Excel by a research pharmacist and the study drug was delivered to the ICU. The treatment group (LCA+) received L-Carnitine one gram every 12 h through the feeding tube for a period of one week, while the placebo (LCA-) group received a similar volumes or water for the same period of time. All patients received enteral feeding with following guideline of care: 30–45° head elevation, prophylaxis for seizure, deep vein thrombosis and stress ulcer, hyperthermia management, antibiotic therapy if needed and appropriate management for sedation/analgesia.

2.4. Clinical, behavioral and radiographic assessment of the patients

Secondary outcome variables included neurocognitive function, brain edema development and death within 90 days of the trauma event. Neurological examinations of all surviving patients were carried out immediately after their admission to the hospital by the Neurosurgeon member of the study team (GS) and a Neurointensivist. Intubation and sedation procedures of the patients with GCS ≤ 8 were performed after the examination following standard protocol in the institution for trauma patients by a certified intensive care anesthesiologist. Demographic, and clinical information including the GCS scores were recorded along with the radiographic findings for all participants. A trained clinical psychologist who was blinded to group assignment recorded neurocognitive. Neurobehavioral abnormalities on the first and third months after the index event were recorded using validated testing methods.

A single radiologist who was also blinded to the randomization reviewed all computerized tomographic(CT) cranial scans for the

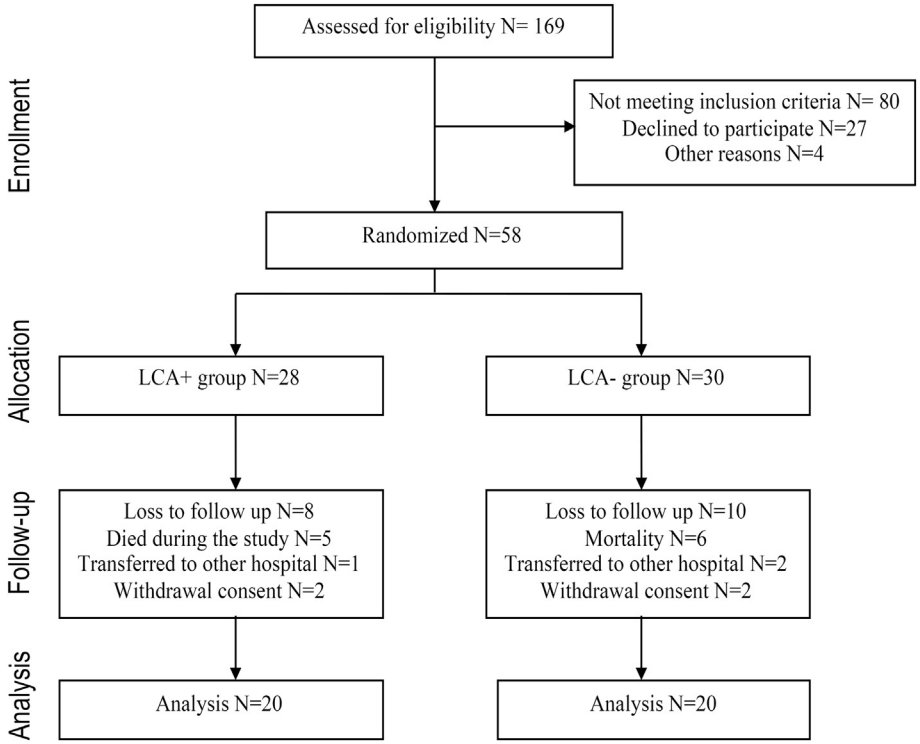

Fig. 1. CONSORT flow diagram of the study design for enrollment, allocation, follow-up and analysis.

presence of cerebral contusions and edema, and any sign of parenchymal, subarachnoid, subdural, or epidural bleeding. Presence of brain edema was assessed as a binomial variable with serial CT images and it was based on the loss of differentiation between white and gray matter on non-enhanced CT images.

2.5. Blood sampling and biochemical analysis

The primary endpoint of the study was NSE concentrations on admission (T0) and 72 h after admission (T3). Peripheral blood samples were obtained within one hour of admission and was repeated at T3 and on the 7th day of admission (T7). Following centrifugation at 3000 rpm for 15 min, serum samples were separated and frozen in minus 80 °C until analyzed. All samples assayed for NSE using an enzyme-linked immunoassay (ELISA) kit commercially available from Eagle Biosciences (Cat. No. ABIN366571, CusaBio, Wuhan, China). The minimum detection level for this kit is 0.78 ng/mL, which was calculated based on the absorbance at A450 nm.

Statistical Analysis: Statistical analyses were performed using Statistical Program for Social Sciences (SPSS) software Version 24.0 (IBM®, Inc., Chicago, IL). All numerical variables were tested for the normality of distribution by Kolmogorov-Smirnov test. Normally distributed continuous variables were compared via independent sample *t*-tests, and those without a normal distribution were analyzed with a non-parametric using Mann Whitney *U* test. Data were expressed as mean ± standard deviation for normally distributed variables and as median with interquartile range (IQR) for those without a normal distribution. Descriptive statistics were analyzed using Fisher's exact test with Bonferroni adjustment for categorical variables expressed as number and percentage for categorical variables. A general linear regression model with repeated measured was constructed to assess the changes in NSE in either group. A p value of <0.05 was considered significant.

3. Results

From 169 patients with severe TBI who were screened for enrollment, 58 were randomized (28 patients for LCA+ and 30 patients for LCA- groups). Five out of 28 patients died early in the LCA+ group and 6 out of 30 patients died in the LCA- group (*P* value: 0.76) before the treatment course was completed and therefore they were excluded from further analyses. Three patients (1 from the LCA+ group and 2 from the LCA- group) were lost to follow-up. After 4 patients (2 from each group) withdrew their consent, 20 patients in each group completed their treatment course and were considered for analysis (Fig. 1, CONSORT Diagram).

Nine women and 31 men with average age of 44.9 ± 19.5 years old completed the full study protocol. Epidural hematoma and subarachnoid hemorrhage were the most frequent type of TBI in each group. Table 1 shows demographic characteristics of patients after randomization. There was no difference between the two groups in the frequency of comorbid diseases. Table 2 reveals characteristics of patients in each group with minimal difference between two groups. In each group, mean arterial pressures, GCS scores and triglyceride concentrations were significantly improved from T1 to T7. (See Table 3.)

Table 1
Demographic characteristics of patients.

	LCA+ group (*N* = 20)	LCA- group (N = 20)	*P*-Value
Age (years)	43.9 ± 19.5	45.9 ± 19.5	0.73
Sex (male/female)	16/4	15/5	0.69
Ischemic heart disease (%)	3 (15%)	1 (5%)	0.6
Hypertension (%)	7 (35%)	4 (20%)	0.28
Diabetes mellitus (%)	5 (25%)	7 (35%)	0.49
APACHE II score	24 [IQR: 4]	24 [IQR: 4]	0.96

Table 2
Information of patients in each group during the study period.

	Day	LCA+ group	LCA- group	P-Value
Seizure (%)	T0	5 (25)	7 (35)	0.49
	T3	2 (10)	2 (10)	>0.99
	T7	2 (10)	0 (0)	0.48
Increased intracranial pressure (%)	T0	20 (100)	20 (100)	–
	T3	13 (65)	17 (85)	0.14
	T7	3 (15)	2 (10.5)	0.67
Glasgow coma scale	T0	6 (IQR:2)	6 (IQR:0)	0.26
	T3	7 (IQR:5)	7 (IQR:3)	0.76
	T7	11(IQR:9)	12 (IQR:8)	0.96
Triglyceride (mg/dL)	T0	186 (IQR:70)	167 (IQR:59)	0.26
	T3	178 (IQR:64)	150 (IQR:62)	0.24
	T7	180 (IQR:68)	165 (IQR:65)	0.40
Mean arterial pressure (mmHg)	T0	76 (IQR:11)	78 (IQR:12)	0.09
	T3	77 (IQR:10)	79 (IQR:8)	0.54
	T7	79 (IQR:9)	81 (IQR:12)	0.47

But patients in LCA+ group showed a non-significant decrease in ICP and triglyceride levels during the study period when compared to the LCA-group. Brain edema was present in 7 patients in the LCA+ group and 13 patients in control group after 7 days of treatment that was statistically significant (*P* value: 0.044). Changes in NSE levels between the two groups are shown in Fig. 2. While there was no difference in serum concentrations of NSE at any time point between the LCA+ and LCA- group, the patients who died during the study period had a significantly higher NSE levels compared to those who survived. There were 2 additional deaths in each treatment group within 90-day. Table 4 shows findings on development of neurobehavioral complications and the status of neurocognitive function after discharge. Except the lack of attention, the frequencies of all other complications were non-significantly, with a tendency to be lower in the LCA+ group, compared to the LCA- group.

4. Discussion

The main therapeutic goals for patients with TBI include supportive care and early detection of events that may lead to further irreversible damage to the central nervous system that may potentially lead to function recovery of the patients. To the best of our knowledge, this study is the first attempt to examine the potential neuroprotective effects of L-Carnitine therapy and its role in changing NSE levels of neuroinflammation following TBI. It is well known that TBI is capable of inducing primary neuronal injury with cell death that leads to delayed neurologic dysfunction. Though the current study failed to demonstrate any difference in NSE levels or mortality following TBI, NSE remained a valid marker of brain injury with a significant prognostic value. The only significant finding of this study was the ability of L-Carnitine treatment for 7 days in decreasing the frequency of cerebral edema after TBI. Additionally, L-Carnitine has demonstrated some beneficial effects in reducing the long-term neurological sequelae by improving neurobehavioral and neurocognitive function of patients following TBI. This was particularly evident in the first three months of treatment.

L-Carnitine is a naturally occurring substance that is an important transmitochondrial membrane transporter of long-chain fatty acids for beta oxidation and in supraphysiologic concentrations has shown

Table 3
Changes in NSE levels in two groups during the study.

	Non-survivors	Survivors	P
Day 1	40.6 ± 7.4	18.7 ± 2.4	<0.001
Day 3	29.9 ± 8.2	13.7 ± 2.2	<0.001
Day 7	26.3 ± 10.2	10.0 ± 2.7	<0.001

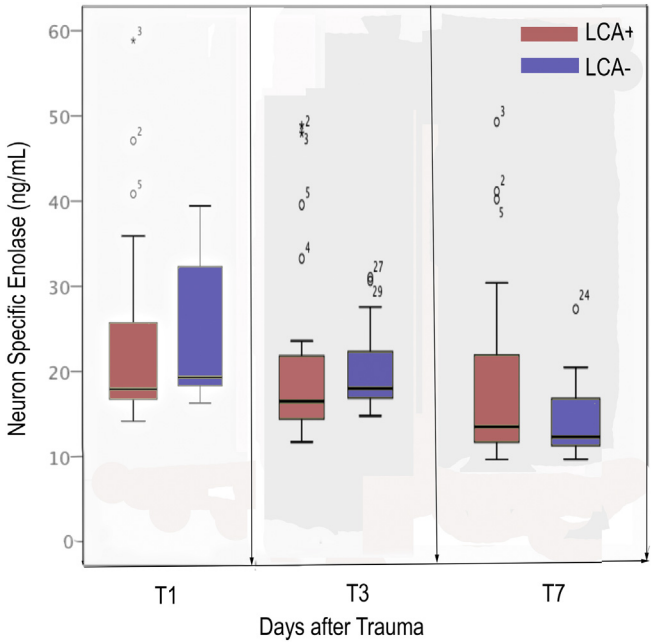

Fig. 2. The box plot of serum levels of neuron-specific enolase (y-axis) for LCA+ and LC- groups measured at three (T0, T3 and T7) time points.

neuroprotective effects [12]. L-Carnitine increases ATP levels and decreases lactate levels of the brain tissue after an ischemic event and thereby decreasing post-ischemic markers of oxidative stress both in brain tissue and the cerebrospinal fluid [13-15]. It also inhibits mitochondrial permeability transition and inhibits acute and chronic cell death after insult [16,17]. It is likely that L-Carnitine improves cerebral energy metabolism and lessens the chance of necrotic cell death caused by metabolic failure evident from previous experiments. Because of these neuroprotective mechanisms and its theoretical advantages, L-Carnitine has shown some offerings as a neuroprotective drug in patients with cerebral inflammatory state and edema like TBI. In addition, there is an abundance of experimental studies showing that L-Carnitine administration is able to enhance neuronal biosynthesis of glutathione which is the main free radical scavenger within the central nervous system [18-20]. Improvement in cellular redox state is probably the main mechanism that contributes to the neuroprotective roles of L-Carnitine in TBI [21,22].

L-Carnitine has also shown a neuroprotective effect after ischemic spinal cord injury as its administration in high doses resulted in significant improvements in motor function [23-25]. Taglialatela et al. and Angelucci et al. in different studies showed that L-Carnitine enhanced the neuroprotective response of PC12 cells to nerve growth factor (NGF) by upregulation the expression of its receptors [26,27]. Karalija et al. in their study showed that continuous intrathecal infusion of L-Carnitine reduced neuronal degeneration, microglial reaction and inflammation after an injury to the spinal cord in rats [7]. Patel et al. in another study showed that L-Carnitine can be a great pharmacologic potential for treating the victims of traumatic spinal cord injury [28].

Compared to the doses that have been used in animal models of TBI (100 mg/kg), we used a modest dose of L-Carnitine (2 g administered daily through the feeding tube). Importantly, in animal studies that showed neuroprotective effects, L-Carnitine treatment administered within one hour of the injury. Calikoglu et al. in their study evaluated the effect of L-Carnitine in preventing secondary injury in rats with traumatic brain injury and demonstrated that L-Carnitine has neuroprotective, anti-edema and anti-inflammatory effects when administered in the acute phase of injury [29].

It is important to note that none of these studies measured L-Carnitine levels and the administered dose was not high compared to other studies. In order to assure the adequate levels following various doses, concentrations of L-Carnitine should be measured the serum of patients. In view of its favorable safety profile, and some modest improvements in neurobehavioral and neurocognitive functions, its use in victims of trauma suffering from clinical cases of TBI may be justified. Early control of brain edema by L-Carnitine may contribute to this favorable outcome and better neurobehavioral function of these patients [30,31].

An important limitation of this study was its low sample size because it was conducted in only one center. Currently, there is no available outcome data for patients with TBI analyzing L-Carnitine levels. We therefore used NSE levels as the primary endpoint of the study and based our power analysis on the differences of this serum biomarker among the survivors and non-survivors of the TBI patients. This sample size was probably appropriate if the comparison was made according to the mortality factor, as we were able to demonstrate this difference in patients who succumbed to TBI. We also confirmed that NSE levels, particularly when it is obtained within 72 h of TBI, is good biomarker of mortality in these patients. However, when we tried to generalize our finding to calculate the samples in the treatment and placebo group, the numbers of the patients were too small to detect the difference in NSE levels or mortality. Additionally, our follow up period was 3 months so future studies will be necessary to determine whether treatment with L-Carnitine improves long-term neurologic outcome, reduces cortical lesions and delays cell death.

We conclude that there is association with early L-Carnitine treatment and reduction of brain edema and improvement of long-term neurological function after TBI. Although NSE levels have been identified as strong predictors of mortality among these patients, its role as a guide for initial treatment with L-Carnitine is highly questionable. This study has shown favorable associated outcome. We believe L-Carnitine has a safe pharmacologic profile and it is worthy of being reexamined in future with a particular emphasis on its dosing. Future studies may consider L-Carnitine as a first-line intervention since its

Table 4
Neurobehavioral and neurocognitive disorders after discharge.

		LCA+ group	LCA-group	P-Value
Apathy	Not assessable	0	1 (7.1)	
	Positive	3 (20)	4 (28.6)	
	Negative	12 (80)	9 (64.3)	
Impulsive behavior	Not assessable	0	1 (7.1)	
	Positive	6 (40)	7 (50)	0.43
	Negative	9 (60)	6 (42.9)	
Aggression	Not assessable	0	0	
	Positive	6 (40)	8 (57.1)	0.35
	Negative	9 (60)	6 (42.9)	
Inattention	Not assessable	0	1 (7.1)	
	Positive	5 (33.3)	7 (50)	0.31
	Negative	10 (66.6)	6 (42.9)	
Diminished alertness	Not assessable	0	2 (14.3)	
	Positive	3 (20)	3 (21.4)	0.15
	Negative	12 (80)	9 (64.3)	
Self-centered attitude	Not assessable	1 (6.7)	2 (14.3)	
	Positive	1 (6.7)	3 (21.4)	
	Negative	13 (86.7)	9 (64.3)	
Memory disorders	Not assessable	1 (6.7)	1 (7.1)	
	Positive	9 (60)	10 (71.4)	
	Negative	5 (33.3)	3 (21.4)	
Sexual dysfunction	Not assessable	4 (26.7)	4 (28.6)	
	Positive	1 (6.7)	2 (14.3)	
	Negative	10 (66.7)	8 (57.1)	
Learning disorder	Not assessable	21 (13.3)	1 (7.1)	
	Positive	4 (46.7)	7 (50)	0.42
	Negative	9 (60)	6 (42.9)	
Decreased processing speed	Not assessable	0	1 (7.1)	
	Positive	10 (66.7)	12 (85.7)	
	Negative	5 (33.3)	1 (7.1)	
Speech disorders	Not assessable	1 (6.7)	0	
	Positive	3 (20)	4 (28.6)	
	Negative	11 (73.3)	10 (71.4)	

administration during the early hours of injury has the potential to improve the neurologic outcome of TBI. In view of the abundance of the experimental evidence of neuroprotection, future studies can be designed to initiate the treatment at the scene of the trauma by the EMT personnel (point of care treatment).

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