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

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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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## 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

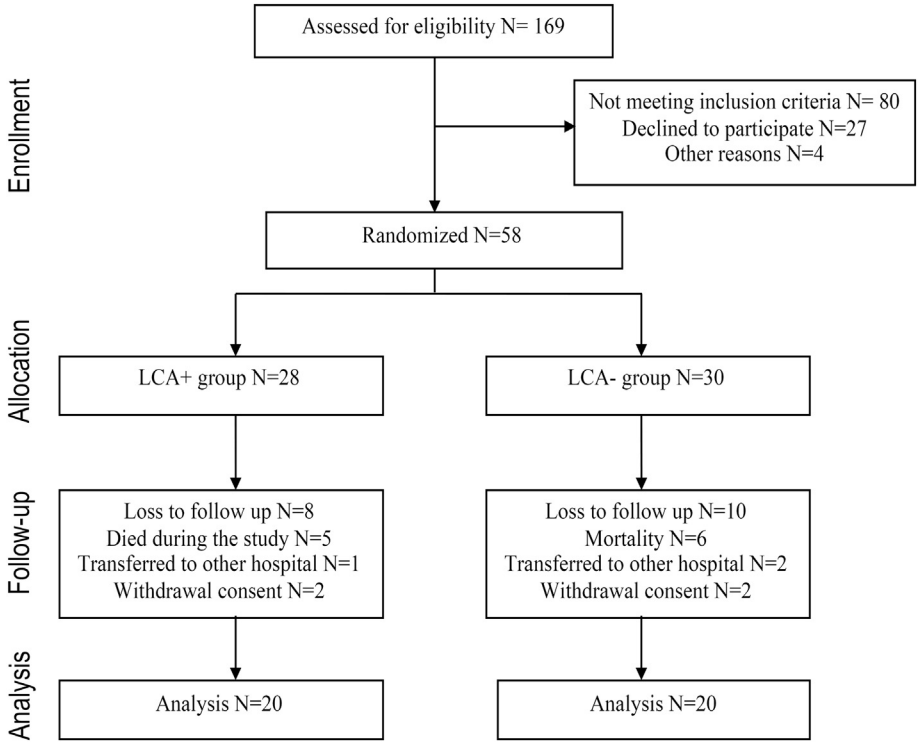


**Fig. 1.** CONSORT flow diagram of the study design for enrollment, allocation, follow-up and analysis.