The effects of L-Carnitine supplementation on inflammatory markers, clinical status, and 28 days, mortality in critically ill patients: A double-blind, randomized, placebo-controlled trial

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Abstract

Aim: Critical ill patients experience catabolic stress which results in the systemic inflammatory response. The inflammatory response is associated with increased complications including infection, multi-organ dysfunction, increased length of ICU stays, and mortality. L-Carnitine supplementation may play an important role in these patients by regulating inflammatory cell function. The purpose of the present study was to investigate the effect of L-Carnitine supplementation on clinical status, inflammatory markers, and mortality rate in critically ill patients admitted in the intensive care unit(ICU) Methods: This randomized, double-blind, placebo-controlled trial was performed on critically ill patients. Subjects were randomly assigned into placebo (n=27) and L-Carnitine (n=27) groups. L-Carnitine (3000mg/day) was administered via nasogastric tube for the intervention group for 7 days while the other group received a placebo for the same duration. Serum levels of inflammatory markers including C-reactive protein (CRP) and interleukin-6 (IL-6) were measured. Nutritional status and the acute physiology and chronic health evaluation (APACHE) score, sequential organ failure assessment (SOFA) score, and 28-day mortality were also recorded. Results: Fifty-one critically ill patients completed the study. L-Carnitine supplementation significantly reduced the levels of CRP (mean change± SE: -34.9 ± 6.5) and IL-6 (mean change ±SE: -10.64 ± 2.16) compared to the baseline, which are both statistically significant compared with the control group ($p<0.05$). The SOFA and APACHE scores were significantly reduced in the L-Carnitine group compared with the placebo group ($p=0.02$ and $p<0.001$, respectively). Conclusions: L-Carnitine supplementation has substantial beneficial effects on inflammatory and clinical outcomes of critically ill patients.

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Short Title; L-carnitine supplementation in ICU patients

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ABSTRACT

Aim : Critical ill patients experience catabolic stress which results in systemic inflammatory response. Inflammatory response is associated with increased complications including infection, multi-organ dysfunction, increased length of ICU stays and mortality. L-Carnitine supplementation may play an important role in these patients by regulating inflammatory cell function. The purpose of the present study was to investigate the effect of L-Carnitine supplementation on clinical status, inflammatory markers, and mortality rate in critically ill patients admitted in the intensive care unit(ICU)

Methods : This randomized, double-blind, placebo-controlled trial was performed on critically ill patients. Subjects were randomly assigned into placebo (n=27) and L-Carnitine (n=27) groups. L-Carnitine (3000mg/day) was administered via nasogastric tube for the intervention group for 7 days while the other group received placebo for the same duration. Serum levels of inflammatory markers including C-reactive protein (CRP) and interlukin-6 (IL-6) were measured. Nutritional status and the acute physiology and chronic health evaluation (APACHE) score, sequential organ failure assessment (SOFA) score, and 28-day mortality were also recorded.**Results** : Fifty-one critically ill patients completed the study. L-Carnitine supplementation significantly reduced the levels of CRP (mean change± SE: -34.9 ± 6.5) and IL-6 (mean change ±SE: -10.64 ± 2.16) compared to the baseline, which are both statistically significant compared with the control group ($p<0.05$). The SOFA and APACHE scores significantly reduced in the L-Carnitine group compared with the placebo group ($p=0.02$ and $p<0.001$, respectively).**Conclusions** : L-Carnitine supplementation has a substantial beneficial effects on inflammatory and clinical outcomes of critically ill patients.

Keywords : L-Carnitine, Inflammation, Supplement, Critically ill patient, Intensive care unit

WHAT'S KNOWN (What is already known about this topic)?

Regarding this case study, that critically ill patients because of their high phases and inflammation and high mortality, we are always looking for a solution that can reduce mortality, hospitalization costs and length of hospital stay in these patients.

WHAT'S NEW(What does this article add)?

The aim of this study was to use a L-Carnitine supplement in critically ill patients. Since in previous studies in cardiovascular patients this supplement had reduced inflammation, we decided to use this supplement due to high inflammation in critically ill patients, which in our study was also Inflammatory factors were significantly reduced and mortality was reduced for 28 days mortality. This study is a starting point for future plans that are currently reviewing and conducting an L-carnitine supplementation plan in Covid 19 patients to reduce infection and inflammation in imam reza hospital**.**

Introduction

Critically ill patients have considerable inflammatory response which affects metabolism and metabolic changes may occur due to different etiologies including stroke, sepsis, multiple trauma, burns, and respiratory failure. Metabolic changes are associated with systemic inflammatory response that leads to increased multi-organ failure, sepsis, immunosuppression, duration of mechanical ventilation, length of hospital stay, and higher mortality rate (1-3). Various reasons are considered for malnutrition during hospitalization including

severe inflammation, increased metabolic requirements, oxidative stress, delayed or stop in enteral and parenteral nutrition for medical intervention treatment that may worsen catabolic status (4, 5). L-Carnitine (B-hydroxy- γ- trimethyl l- aminobutyric acid, LC) is an essential compound that is synthesized from lysine and methionine in the liver and kidney or its mainly supplied from animal diet sources such as meat and dairy product (6). L-Carnitine is necessary for beta-oxidation of long-chain fatty acids and fatty acid transport via Carnitine palmitoyltransferase I (CPT1) into the inner membrane of mitochondria. Therefore, L-Carnitine plays a critical role in energy metabolism (7). L-Carnitine deficiency may result in mitochondrial dysfunction and failure in lipid utilization by vital organs (8, 9). L-Carnitine deficiency leads to beta-oxidation disorder due to depletion in fatty acyl coenzyme A (CoA), which is required for lipid oxidation, and depletion of CoA enzyme pool. Therefore, mitochondrial dysfunction will occur and result in metabolic changes and multi-organ dysfunction. Oami*et al.* showed that carnitine deficiency occurs in 23.4 % of critically ill patients (10). It has been shown that L-Carnitine supplementation at a dose of 1-3 gr decreases the effect of inflammation in non-communicable disease (11-13). Therefore, L-Carnitine may have the potential effect in inflammatory disease by reducing inflammatory markers, including C - reactive protein (CRP) and interlukin-6 (IL-6). To the best of our knowledge, the anti-inflammatory effect of L-Carnitine supplementation in critically ill patients was poorly investigated. In addition, there is no published study, which assessed the effects of L-Carnitine supplementation for seven days on inflammatory and clinical outcomes of the intensive care unit (ICU) patients who fed only with enteral nutrition Therefore, the purpose of this study was to evaluate the effects of L-Carnitine supplementation (with dose 3000 mg/day) on clinical status, inflammatory markers, and 28-days mortality in critically ill patients who admitted to the ICU.

Methods

Study design and participants

We conducted a double-blinded, parallel-group randomized placebo-controlled trial on critically ill patients between June 2018 and August 2019. Critically ill patients were recruited from general ICUs of Emam Reza hospital, Mashhad, northeast of Iran. We obtained patient or surrogate consent in case the patient was unconscious. The inclusion criteria were as follows: age >18 years, and being diagnosed with critical illnesses. The exclusion criteria were as follows: patients with renal or liver disease, patients undergoing dialysis, cancer patients undergoing chemotherapy, pregnant or lactating patients. Patients using antioxidant or anti-inflammatory supplements or multivitamin supplement were also excluded. The study protocol was approved by the Research Ethics Committee of Mashhad University of Medical Sciences (registration code: IR.MUMS.fm.REC.1396.671) and was registered in the Iranian Registry of Clinical Trials (registration code: IRCT 20151108024938N2).

Intervention, Randomization and blinding

We enrolled 54 critically ill patients in this study. Patients were randomly assigned using block randomization with fixed block size of 4 to placebo (n=27) or L-Carnitine (LC) group (n=27). The intervention group received 3000 mg/day L-Carnitine divided into 3 equal doses of 1 gram L-carnitine as a liquid form (BSK, Zist Takhmir Co, Tehran-Iran) with daily enteral feeding for 7-days and the placebo group (Distilled water) with same dose and duration. L-carnitine and placebo are same regarding the color, shape, odor and size, thus, patients, and physicians and investigators were blinded. Furthermore, the laboratory personnel and statisticians were blinded to the treatment allocation.

In both groups, after 24-48 hours of admission and when hemodynamic resuscitation and stabilization were carried out, enteral nutrition was initiated to provide 80-100% of the energy requirements of each patient. Energy requirement was calculated to provide 25 kilocalories of energy per kilogram of the body weight of each patient.

Study size

Sample size calculation was made based on 80% power and an alpha error of 5% to detect the inflammation effect based on changes in IL-6 by LC supplementation (Control group: 0.3±0.2, Intervention group: 0.1±0.2)

using the findings of Lee *et al.* (16).

Outcome measures and data collection

The primary outcome of this study was IL-6, CRP, SOFA, and APACHEII. A checklist was designed to obtain information according to the selection criteria of the study including age, sex, medical history, drug history, and underlying diseases. Disease severity scores, including the acute physiology and chronic health evaluation (APACHE) and sequential organ failure assessment (SOFA) scores were calculated. The weight (using bed scales; Seca-Germany), estimated height, NUTRIC score, required energy intake and received energy (Kcal/kg/day) were also calculated by the nutritionist for each patient and all patients received standard hospital gavages. Serum and plasma were extracted from the blood samples by adding EDTA and centrifugation at 3000 rpm for 15 minutes at 4 ^{o}C. Plasma samples were stored at -80 ^{o}C immediately after centrifugation until analysis.

After the finishing of intervention, serum CRP level was measured following the method of immunoturbidity measurement (Kit: Quantitative determination of CRP in human blood by latex turbidimetry assay using BT3500 Biotecnica Instruments SpA –Italy). IL-6 as an inflammatory marker measured by ELISA method using Karmagene kit (Kerman-Iran), and also 28-day mortality was measured and recorded by telephone and follow-up of patients after intervention.

Statistical analyses

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 16(SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.). continuous and categorical variables were reported as mean±SD and frequency(percentage), respectively. The normal distribution of continuous variables was evaluated using the Kolmogorov- Smirnov test and Q-Q plot. Non-normality positive skewed data were subjected to logarithmic transformation. Comparison of basic continuous and categorical variables of study subjects between the placebo and LC groups was performed using independent sample t-test and chi-squared test. Paired samples t-test was used for for comparing before and after the intervention continuous variables in each study group. Analysis of covariance (ANCOVA) was used for comparing the mean values of continuous outcomes at the end of study between two groups and adjustment was made for baseline values. The repeated measures analysis of variance (ANOVA) was used to compare changes in SOFA score between two groups which was measured repeatedly during the study course. Muchly test of sphericity was evaluated and when it was violated we adopted multivariate analysis of variance for repeated measures ANOVA. Comparison of study qualitative outcomes between groups was done by the chi-squared test or Fisher exact test. A p-value less than 0.05 was considered as statistically significant.

Results

Characteristics of participants

In this study, 54 patients were recruited based on inclusion and exclusion criteria. From 54 patients in the baseline, three in LC group (2 patients died and 1 patient started on hemodialysis) were excluded from study. Therefore, 51 patients (LC (n = 24) and placebo (n = 27)) completed the trial (Figure 1).

The mean ± standard deviation (SD) OF age was 57.7 ± 14.9 years in LC and 57.8 ± 14.9 years in placebo groups (P=0.85). In this study, 56.9% of the patients. Table 1, shows that baseline characteristics of the critically ill patient were comparable between two groups (All P>0.05). At the beginning of the study, no significant difference was observed between groups in terms of comorbidities (All P>0.05)(Table 2).

Effects of L-Carnitine supplementation on levels of inflammatory markers

The mean levels of inflammation markers before and after supplementation on 7 days are shown in Table 3. A significant decline was observed in serum IL-6 levels in the LC group (p<0.001), while IL-6 levels significantly increased in the placebo group (P=0.001), and the mean change between groups was statistically significant (P<0.001) in which LC group showed both clinical and statistical significant decline compared to placebo group. Likewise, in comparison to the baseline, at post intervention, CRP significantly decreased in the LC

group though it did not change in the placebo group, and the difference between groups was statistically significant (P=0.009).

Effects of L-Carnitine supplementation on the clinical outcomes and 28-day mortality

A significant decrease was observed in SOFA score during the LC intervention (P<0.001), while no significant change was observed in placebo group (P=0.08) and the mean decrease over the study period was statistically significant in LC group compared to placebo group (P=0.021) [Figure2]. The APACHE score was significantly decreased in LC group (P<0.001), it was significantly increased in the placebo group and the mean decrease was statistically and clinically significant in LC group compared to placebo group (P=0.001) (Table 3). The 28-day mortality rate was significantly lower in LC group compared to the placebo group (29.2% VS 59.3%, P=0.048). Although we did not observe significant difference in the duration of hospital and ICU stay between two groups, however the observed difference were clinically notable. we found a significant decrease in duration of mechanical ventilation in LC group compared with the placebo group and also ICU discharge was significantly shorter in the LC group compared with placebo group (Table 4).

DISCUSSION

In this study, we found that critically ill patients who received LC at a dose of 3 gr/day for 7-day had significantly reduced levels of inflammation markers and 28-day mortality in the intervention group compared with the control group. Lee et al reported that daily consumption of 1 g LC for 12 weeks significantly reduced levels of IL-6, CRP, and Tumor necrosis factor-α (TNF-α) in patients with cardiovascular diseases (13). Recent evidence has demonstrated that LC supplementation prevents oxidative stress in patients with coronary artery disease (CAD) by regulating and reducing lipid peroxidation and increasing antioxidant enzymes for scavenging free radicals and reactive oxygen species (ROS) (14-16). Furthermore, ROS and other radicals, can increase inflammation and up-regulate nuclear factor kappa-light-chain-enhancer of activated B cells)NF-Kβ(pathway (17-19), which is a transcription factor and regulator of multiple gene expression in immune-inflammatory responses and reduces gene expression of proinflammatory cytokines including IL-6, IL-1, CRP, and enhances gene expression of anti-inflammatory cytokines IL-10 (20-22). Consequently, LC could decrease inflammatory markers in patients with chronic inflammation including critically ill patients with the same mechanism. In their study, Shakeri et al. reported that consumption of 1 gr/day of oral LC resulted in a 29% decrease in baseline CRP and 61% decrease in IL-6 levels in hemodialysis patients (23). Dastan et.al supplemented cardiovascular patients with 3 g/day of LC for 5 days and reported a significant reduction in CRP levels (12). In recent years, two clinical studies have shown that supplementation with 20 mg/kg/day LC may decrease CRP levels in hemodialysis patients (11, 24). However, two other clinical studies, it has been shown that LC supplementation had no effect on the inflammatory markers, including CRP and IL-6, in obese healthy subjects (25, 26). This lack of effect in healthy people may be due to the fact that healthy subjects do not have high levels of inflammation, while in our study, all subjects had high levels of inflammation with CRP levels higher than 1 mg/dl and IL-6 levels higher than 1.5 pg.ml. In the present study, supplementation with LC resulted in a significant reduction in IL-6 and CRP levels in critically ill patients. Results of the previous meta-analysis showed a significant reduction in CRP due to LC supplementation in comparison to the control group . Recently, Haghighatdoost et al. conducted another systematic review and meta-analysis, which included 13 clinical trials to assess the effect of LC supplementation on inflammation and inflammatory markers (IL-6, CRP). Findings of this study showed that supplementation with LC led to a significant reduction in CRP and IL-6 levels compared with the control group (P = 0.001 and p=0.002 respectively) (28). The mentioned study showed that LC reduced inflammation in patients, especially in studies that supplementation continued for more than two weeks at a dose higher than 2 g/day. Although in our study, LC was used for one week, intervention among critically ill patients with high levels of inflammatory markers and using mega-dose of 3 gr/day might be the main reason causes similar findings of our study with the recent meta-analysis findings.

Pharmacological studies have reported that the bioavailability of oral dose of LC is low and it is absorbed only by 5 to 16%, so it has been suggested that doses higher than 2 g/day might have a greater effect (29, 30). Therefore, the additional effect of LC on the level of inflammatory markers can be dose and time-

dependent. Besides, LC is able to regulate the Peroxisome proliferator-activated receptor gamma is a type of nuclear receptor (PPAR γ) pathway, which is a key factor in the regulation of oxidative stress pathways and liver inflammation (31). Another study showed that LC may be able to improve the inflammatory response of the liver by regulating the PPAR γ signaling pathway, which is a transcription factor for lipolytic genes including carnitine palmitoyltransferase 1 (CPT1) (32, 33). They also reported that SOFA score was significantly associated with LC deficiency in these patients, and no significant difference was observed in clinical outcomes, length of hospital stay between LC deficient patients and non-deficient patients. They did not mention any mechanism for the increase in SOFA score but one explanation could be due to the important role of LC in transporting long-chain fatty acyl CoA into the mitochondrial matrix for beta-oxidation by carnitine palmitoyltransferase 1 (CPT1) (10). LC deficiency disrupts B-oxidation of fatty acid in critically ill patients. Since most of the acyl-CoA in the body is used to bond with fatty acid, in case of depleted CoA pool, due to metabolic dysfunction in mitochondrial function, the multi-organ failure and mortality is increased (34). Jones et al. assessed the effect of high-dose LC supplementation in 250 sepsis patients. LC was administered three doses of 6 g, 12 g, and 18 g during the first 24 hours of admission. They reported that the SOFA score reduced in the first 48 hours and also treatment with carnitine was significantly decreased 28 days mortality. The effect of LC was dose dependent but the difference in LC did not statistically significant. The proposed mechanism for this finding could be that LC may decrease the metabolic effects of sepsis by promoting and increasing the fatty acids transportation into the mitochondria, and thereby reducing the inhibitory effects of acetyl-CoA on pyruvate dehydrogenase (35). Puskarich et al reported that supplementation with 12 gr LC led to a greater reduction in SOFA score and mortality compared to the control group in 31 sepsis patients. The mortality was reported 50% (8 of 16) in the LC group in the mentioned study while mortality occurred in 80% (12 of 15) of patients in the control group (36)(38). Chung et al. measured plasma levels of acylcarnitine in sepsis patients and evaluated its association with multi-organ dysfunction and mortality. They reported that plasma levels of acylcarnitine may reflect the severity of multi-organ dysfunction, inflammation, infection, and sepsis and may serve as a predictive biomarker for mortality. These findings suggested that carnitine deficiency and disorder in B-Oxidation of fatty acids lead to defects in lipid utilization by vital organs, especially the liver and kidney, which may lead to mitochondrial dysfunction in patients who died of sepsis (33). In the present study study, critically ill patients who were supplemented with LC reduced the duration of ventilation compared to the control group, and 37.5% of patients in the LC group were discharged from the ICU. Goetzmen et al, studied long-chain acyl-CoA dehydrogenase deficiency in relation to pulmonary surfactant dysfunction. They showed that fatty acid oxidation was increased in the lungs similar to the liver, and that the inhibition of fatty acid oxidation by acyl-CoA can lead to abnormal synthesis of surfactants (37). The main function of LC is the esterification and transfer of long-chain fatty acids into the mitochondrial membrane and production of energy, therefore, LC supplementation may improve clinical outcomes by decreasing inflammatory mediators in critically ill patients.

Although this is the first study investigating the effects of a mega dose of oral LC supplementation for seven days among critically ill patients, some limitations could be acknowledged. First, the present study was conducted in the general ICUs with the heterogenic patients. The second limitation was the duration of LC supplementation (7-day). We suggest that larger and longer intervention studies are required to document the effects of L-Carnitine on inflammatory markers and clinical status in ICU patients.

Conclusion

The findings of this study showed that L-Carnitine supplementation at a dose of 3 g/day has substantial beneficial effects in decreasing the inflammation status, improve clinical outcomes and reduce mortality in critically ill patients.

Conflict of interest

The authors declare no conflict of interest.

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Figure legends:

Figure 1. This is the flow chart of the study

Figure 2. The SOFA figure has to include all patients having at least 2 points, Changes in SOFA score during the study period (Obtained from repeated measure ANOVA Test)

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`Table 1.docx` available at https://authorea.com/users/733647/articles/711201-the-effects-of-l-carnitine-supplementation-on-inflammatory-markers-clinical-status-and-28-days-mortality-in-critically-ill-patients-a-double-blind-randomized-placebo-controlled-trial

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`Table 2.docx` available at https://authorea.com/users/733647/articles/711201-the-effects-of-l-carnitine-supplementation-on-inflammatory-markers-clinical-status-and-28-days-mortality-in-critically-ill-patients-a-double-blind-randomized-placebo-controlled-trial

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`Table 3.docx` available at https://authorea.com/users/733647/articles/711201-the-effects-of-l-carnitine-supplementation-on-inflammatory-markers-clinical-status-and-28-days-mortality-in-critically-ill-patients-a-double-blind-randomized-placebo-controlled-trial

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`Table 4.docx` available at https://authorea.com/users/733647/articles/711201-the-effects-of-l-carnitine-supplementation-on-inflammatory-markers-clinical-status-and-28-days-mortality-in-critically-ill-patients-a-double-blind-randomized-placebo-controlled-trial