



Journal of Acute Disease

Original Article



jadweb.org

doi: 10.4103/jad.jad_51_24

Impact Factor® 0.5

Effects of *L*-carnitine on treatment outcomes of COVID-19 patients hospitalized in intensive care units: A double-blind randomized clinical trial

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ABSTRACT

Objective: To assess the effects of *L*-carnitine on the outcomes of patients with moderate to severe coronavirus disease 2019 (COVID-19) in intensive care unit (ICU).

Methods: This double-blind clinical trial was carried out in 2022–2023. 64 Patients with COVID-19 were selected from Amiralmomenin and Khansari hospitals in Arak, Iran. They were randomly assigned to the control and the *L*-carnitine treatment group *via* block randomization. Venous blood gases, disease severity, and levels of D-dimer, lactate dehydrogenase, ferritin, and C-reactive protein were daily assessed during the seven days of the intervention, and the length of ICU stay, the need for endotracheal intubation, and mortality rate were documented.

Results: There were significant differences in length of ICU stay, the need for endotracheal intubation, and levels of D-dimer, lactate dehydrogenase, ferritin, APACHE II score, and C-reactive protein between the two groups ($P < 0.05$). However, the groups did not significantly differ in mortality rate and venous blood gas indexes ($P > 0.05$).

Conclusions: *L*-carnitine can improve outcomes of patients with COVID-19. Therefore, it can be used as an adjuvant therapy for these patients.

Trial registration: Iranian Registry of Clinical Trials identifier IRCT20141209020258N165.

KEYWORDS: *L*-carnitine; COVID-19; ICU; Critically ill; Mortality; Clinical outcome

1. Introduction

Coronaviruses are a large family of viruses. Seven types of coronaviruses have so far been identified. Coronaviruses mostly attack the respiratory system and sometimes cause gastrointestinal symptoms[1,2]. Coronaviruses primarily cause infection in the mucociliary system in the nose and the throat with symptoms like the common cold. Sometimes, they cause severe infections such as bronchitis and pneumonia or aggravate the existing asthma or chronic bronchitis in elderly people and those with immunodeficiency[1,3].

Coronavirus disease 2019 (COVID-19) is an airway infection

Significance

The effects of *L*-carnitine (LC) on patients with COVID-19 is unclear. Our study shows that the length of ICU stays, need for endotracheal intubation, CRP level and APACHE II score decreased in the LC group in compared to control group. It suggests that LC can improve outcomes of patients with COVID-19.

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How to cite this article: Modir H, Mahmoudieh B, Shahtaheri SY, Farokhi F. Effects of *L*-carnitine on treatment outcomes of COVID-19 patients hospitalized in intensive care units: A double-blind randomized clinical trial. J Acute Dis 2024; 13(3): 100–105.

Article history: Received 10 April 2024; Revision 30 April 2024; Accepted 12 July 2024; Available online 25 July 2024

caused by a mutated species of coronaviruses[4,5]. During the COVID-19 pandemic, the death rate of COVID-19 is estimated at 1.88 per 100 000 general population, but it differs depending on the disease's underestimation and lack of testing[6]. Around 5% of afflicted patients are hospitalized in intensive care units (ICU) (5%) and around half of the hospitalized patients in ICU need oxygen therapy[5,7]. Meta-analyses of patients who need ICU and mechanical ventilation showed a mortality rate of 40%-45%[8,9].

Despite global efforts to determine effective strategies for the management and control of the COVID-19 pandemic, therapeutic strategies are mostly preventive and supportive, and current strategies mostly focus on reducing the risk of transmission through physical distancing and restrictions on traveling to high-risk areas. At the time of hospital admission, patients with severe COVID-19 show lymphocytopenia, leucopenia, high C-reactive protein (CRP), and an arterial oxygen saturation of less than 93%. Patients with severe COVID-19 suffer from severe hypoxemia and acute respiratory failure and show laboratory findings of septic shock and organ dysfunction or failure[10,11].

The most effective preventive measures for COVID-19 management are the identification of afflicted patients and asymptomatic individuals, breaking the chain of transmission through distancing and disinfecting, and personal protection. Therefore, early diagnosis, isolation, and treatment of afflicted patients are the major strategies for controlling the primary source of infection and reducing its transmission[1,4,7]. Currently, there is no specific antiviral treatment for COVID-19 and no specific vaccine for its effective management. COVID-19 treatment focuses mainly on symptom management and the principal intervention for patients with severe COVID-19 is oxygen therapy. Mechanical ventilation is essential in patients with respiratory failure who show resistance to oxygen therapy, and hemodynamic support is essential for the management of patients with septic shock[3,5,7,10]. L-carnitine (LC) is a non-protein amino acid produced from lysine and methionine amino acids. It facilitates the beta-oxidation of long-chain fatty acids, participates in the metabolism of branched-chain amino acids, and stabilizes cell membranes[1,12]. It also has antioxidant effects and protects antioxidant enzymes against oxidative injury[12].

Several studies also indicated that acetyl LC positively influenced the growth and maturity of T lymphocytes and immune response to viral agents[12,13]. It also helps inhibit the production of reactive oxygen species and the reproduction of the cytokine network of the systemic inflammatory response syndrome[14,15]. Therefore, LC, as a supportive and therapeutic agent, may be useful in reducing inflammation among patients with COVID-19[15]. Our literature search revealed that studies in this area were mostly on patients with pneumonia and there were few studies on the effects of LC on patients with COVID-19. We conducted this study to assess the effects of LC on the outcomes of patients with moderate to severe COVID-19 hospitalized in the ICU.

2. Patients and methods

2.1. Study setting

This double-blind clinical trial was carried out from March 2022 to March 2023 in the ICUs of Amiralmomenin and Khansari Hospitals, in Arak, Iran.

2.2. Inclusion and exclusion criteria

Inclusion criteria were affliction by COVID-19; no need for endotracheal intubation, hospitalization in ICU; APACHE II score less than 25; age between 28 and 75 years; no pregnancy or breastfeeding; no affliction by acute asthma, acute pulmonary bleeding, lung tumor, or unmanaged pneumothorax; no oral anticoagulant therapy (such as warfarin); and no history of renal or hepatic disorder, diabetes mellitus, and seizure.

2.3. Intervention

The eligible patients were recruited and randomly assigned to a control and an LC group by block random allocation. The block size is considered as 4.

The national guidelines for COVID-19 by Iran's National Ministry of Health and Medical Education (MOHME) were used and patients were managed according to WHO and MOHME recommendations[2,16-18]. The dosage was based on the national and WHO guidelines[16,17]. In addition to routine treatments, patients in the LC group daily received 1 g LC tablet for seven consecutive days. Their counterparts in the control group received routine treatments as well as a placebo. As routine COVID-19 treatments included anticoagulant therapy and participants were at risk for bleeding, we daily tested participants' venous blood gas instead of arterial blood gas testing.

2.4. Measurements

Using the APACHE II, an anesthesiologist classified patients into mild, moderate, and severe groups based on COVID-19 severity. The length of ICU stays and the need for endotracheal intubation were also documented and daily venous blood samples were taken for seven consecutive days to assess the levels of D-dimmer, lactate dehydrogenase (LDH), and CRP.

2.5. Ethical statement

This study protocol is approved by the Ethics Committee of Arak University of Medical Sciences, Arak, Iran by code: IR.ARAKMU.REC.1400.124. Moreover, it is registered in the Iranian Registry of Clinical Trials by code: IRCT20141209020258N165.

2.6. Statistical analysis

Sample size calculation was done by considering the results of a recent study[19], with a study power of 80% and, a confidence interval of 95% based on the following formula.

$$n = \frac{(s_1^2 + s_2^2) (z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2}{(\bar{x}_1 - \bar{x}_2)^2}$$

The data were analyzed at a significance level of less than 0.05 using SPSS version 20 (SPSS Inc., Chicago, IL, USA). The Chi-square test and independent *t*-test were used. In addition, repeated measures analysis of variance was used to compare the trend of changes in LDH, ferritin, and D-dimer between groups at different times. *P*<0.05 is considered a significant difference.

3. Results

Sixty-four eligible patients with moderate to severe COVID-19 were selected (Figure 1). Participants' age varied from 29-75 years with a mean of (54.3±14.8) years. Most patients were male (34, 53.1%). Groups did not significantly differ from each other respecting age and sex (*P*>0.05, Table 1).

The length of ICU stays and the need for endotracheal intubation in the LC group were significantly less than in the control group (*P*<0.05, Table 1). However, there was no significant difference between the groups in terms of mortality rate, pH, PaCO₂, and HCO₃ (*P*>0.05, Table 1). CRP level and APACHE II score showed a significant decrease in the LC group compared to the control group (*P*<0.05, Table 1).

There was no significant difference in D-dimer and ferritin levels between the two groups on the 1-3 days (*P*>0.05), while D-dimer and ferritin in the LC group were significantly less than the control group on days 4-7 (*P*<0.01, Figure 2A&B). The repeated measures analysis of variance also showed a significant change in D-dimer level as the day passed (*P*<0.01).

There was no significant difference in LDH level between the two

groups on days 1-5 (*P*>0.05). LDH in the LC group significantly decreased compared with the control group on the 6th and 7th day (*P*<0.05) and the results of the repeated measures analysis of variance also showed significant change in LDH as the day passed (*P*=0.01, Figure 2C).

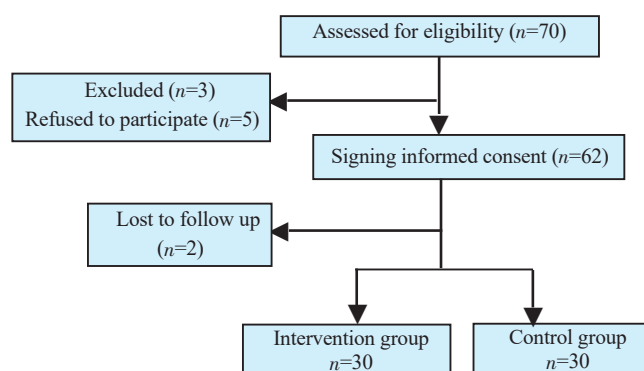


Figure 1. The study flowchart.

4. Discussion

This study assessed the effects of LC on the outcomes of patients with moderate to severe COVID-19 hospitalized in the ICU. Findings showed that the length of ICU stay, the need for endotracheal intubation, D-dimer, LDH, ferritin, APACHE II score, and CRP in the LC group were significantly less than the control group. However, it had no significant effect on mortality rate and venous blood gases. LC is a non-protein amino acid produced from the lysine and methionine amino acids.

Our findings revealed a significant increase in the level of CRP among patients with COVID-19 and a reduction in the LC group. CRP reduction can indicate a reduction in disease severity. This finding agrees with the findings of two previous studies which showed increased levels of CRP among hospitalized patients with COVID-19 in Wuhan, China[20] and Iran[21]. A study reported the

Table 1. Baseline data and clinical characteristics (n=60).

Variables	LC group	Control group	$\chi^2/U/t$	P
Age (years, mean±SD)	54.2±14.7	54.5±15.1	0.840	0.933
Male (n, %)	18 (52.94%)	14 (46.87%)	0.251	0.616
Length of ICU stay (Days, mean±SD)	7.00±1.29	8.62±1.09	5.410	0.001
Endotracheal intubation (n, %)	12 (37.5)	21 (65.62)	5.060	0.020
Mortality rate (n, %)	6 (18.75)	7 (21.87)	0.410	0.565
Change in blood pH (mean±SD)	-0.04 (-0.04, 0.03)	-0.01 (-0.03, 0.02)	1.680	0.185
Change in PaCO ₂ (mmHg, median, Q1, Q3)	4 (1, 8)	4 (1, 6)	-0.420	0.676
Change in HCO ₃ (mEq/L, median, Q1, Q3)	2.00 (-1.75, 3.00)	2.00 (-0.75, 3.00)	-0.150	0.882
Change in CRP (mg/L, median, Q1, Q3)	-1 (-2, -1)	-0.50 (-1.75, 0.00)	3.600	0.001
Change in APACHE II score (median, Q1, Q3)	-1 (-2, -1)	-1 (-1, -1)	2.320	0.024

ICU: intensive care unit; CRP: C-reactive protein.

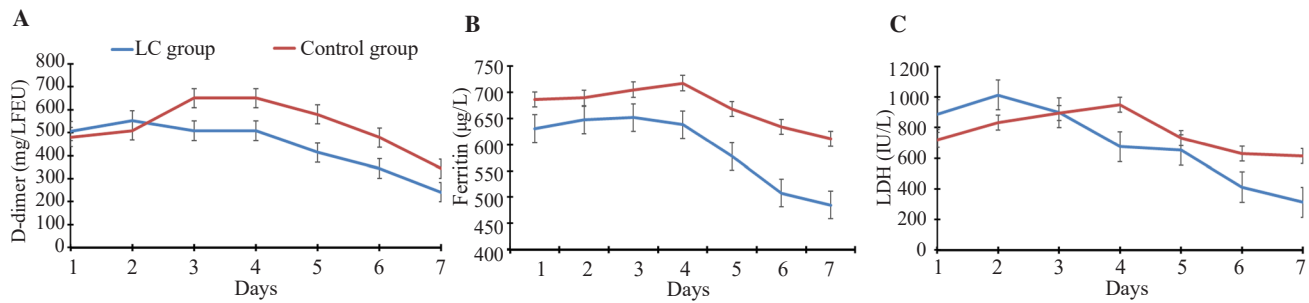


Figure 2. D-dimer (A), ferritin (B), and LDH (C) between two groups. LC: *L*-carnitine; LDH: lactate dehydrogenase.

effectiveness of LC supplementation in reducing inflammation and CRP among patients with hemodialysis[22]. LC and its active form, *i.e.*, acetyl LC, can reduce systemic inflammation by reducing inflammatory factors and cytokines such as CRP, interleukin 6, and tumor necrotizing factor- α [23]. Given the significant role of the cytokine storm in the progression of COVID-19, LC intake can prevent infection progression[24]. Moreover, LC inhibits lipid peroxidation, reduces oxidative stress, improves mitochondrial function, and thereby, plays a pivotal role in reducing inflammation[25]. It also boosts the immune system through different mechanisms, such as improving macrophage function, and hence, reduces inflammation and infection[26].

We also found that reduced level of LDH in the LC group. LDH is largely found in all body cells and has a direct role in energy metabolism. Any increase in LDH level may show a defect in any body organ or tissue. Some patients with COVID-19 may show an LDH increase due to injuries to tissues such as the muscles. A study reported that LC reduces injuries to body organs such as muscles and kidneys and thereby, reduces LDH[27].

Our findings also showed that the need for mechanical ventilation was reduced in the LC group. This may be due to significant improvement in arterial oxygen saturation. COVID-19 may affect and destroy lung cells and reduce arterial oxygen saturation through specific angiotensin-converting enzyme 2 receptors. High levels of LC can increase arterial oxygen saturation, reduce COVID-19 severity, and accelerate recovery probably by reducing the expression of the angiotensin-converting enzyme 2 receptors and inhibiting the binding of the virus to the lung cells[28]. Carnitine is synthesized in the muscles and the liver and appears in some foodstuffs such as poultry, red meat, fish, and some dairy products and is also a food supplement. Its main role in the body is to facilitate metabolism and change food to energy[29]. The L isomer of carnitine is biologically active, while its D isomer is inactive in the body[30]. LC acts as an essential factor in the oxidation of fatty acids in the mitochondria and recent studies reported the great importance of its antioxidant

and anti-inflammatory effects[12,13,26]. Its protective effects against oxidative stress can increase the overall antioxidant capacity of the cells[31]. A study also indicated that LC has protective effects against stress and tissue injuries caused by COVID-19[1].

Some experimental studies reported that LC can improve primary hemodynamic parameters and reduce mortality rates[15,22,27,32]. Another study on patients with pneumonia found that LC reduced free radical lipid peroxidation, improved antioxidant defense, and accelerated recovery. A study also revealed that LC improved endothelial function in pulmonary vessels but highlighted the need for further studies to produce firmer evidence respecting the effects of LC[33]. Moreover, a study on premature neonates with respiratory distress syndrome highlighted that LC supplementation may increase the blood level of carnitine and thereby, reduce the need for surfactant administration and shorten the duration of mechanical ventilation[34].

The findings of the present study revealed that the length of hospital stay was shortened in the LC group. A study on patients with pneumonia reported that LC reduced free lipid peroxidation, improved antioxidant status, accelerated recovery, and shortened treatment course[35]. Another study on thirteen fetal lambs also indicated that LC may improve pulmonary endothelial function[33]. Moreover, a study on premature infants with respiratory distress syndrome found that LC supplementation may increase carnitine levels, shorten the course of mechanical ventilation, and reduce the need for surfactants[34].

We attempted to minimize the effects of potential confounders through for example not including patients with comorbid conditions. Our study was conducted in a single center. However, future studies are recommended to compare the effects of LC with other medications for COVID-19 management to determine the most effective treatments.

In conclusion, this study suggests that seven-day LC therapy can improve outcomes of patients with COVID-19. Therefore, LC can be used as an adjuvant therapy for these patients.

Conflict of interest statement

The authors report no conflict of interest.

Funding

This study received no extramural funding.

Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

Study concept and design: HM and SYS; Analysis and interpretation of data: FF, BM, and HM; Drafting of the manuscript: HM, FF, and BM; Critical revision of the manuscript for important intellectual content: FF, BM, and SYS; Statistical analysis: BM.

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Edited by Tan BJ, Chen SR