Research in Pharmaceutical Sciences, February 2022; 17(1): 66-77
Received: 30-08-2021
Peer Reviewed: 14-09-2021
Revised: 20-09-2021
Accepted: 03-10-2021
Published: 11-11-2021

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Original Article

L-carnitine supplementation ameliorates insulin resistance in critically ill acute stroke patients: a randomized, double-blinded, placebo-controlled clinical trial

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Abstract

Background and purpose: Insulin resistance (IR) can negatively affect clinical outcomes in acute ischemic stroke (IS) patients. Safe and cost-saving interventions are still needed to improve glycemic indices in this population. The primary objective was to evaluate L-carnitine (LC) effects in acute IS patients' homeostatic model assessment of IR (HOMA-IR).

Experimental approach: In this randomized, double-blind placebo-controlled clinical trial, critically ill IS patients were allocated to receive daily oral L-carnitine (1.5 g) or a placebo for six days. Fasting serum levels of glucose, insulin, C-reactive protein, LC, and HOMA-IR were measured on days 1 and 7. Mechanical ventilation duration, ICU/hospital duration, illness severity score, sepsis, and death events were assessed.

Findings/Results: Forty-eight patients were allocated to the research groups, 24 patients in each group, and all were included in the final analysis. LC administration showed a decrease in mean difference of HOMA-IR and insulin levels at day 7 compared to placebo, -0.94 ± 1.92 *vs* 0.87 ± 2.24 ($P = 0.01$) and -2.26 ± 6.81 *vs* 0.88 ± 4.95 ($P = 0.03$), respectively. However, LC administration did not result in significant improvement in clinical outcomes compared to placebo. The short duration of intervention and low sample size limited our results.

Conclusion and implication: Supplementation of L-carnitine improved HOMA-IR index in acute IS patients admitted to the critical care unit. Supplementation of LC would be a potential option to help to control IR in critically ill acute IS patients.

Keywords: Critical care; Insulin resistance, Ischemic stroke; L-carnitine, HOMA-IR, Hyperglycemia.

INTRODUCTION

Globally, over 80 million people live with a history of a stroke and over 13.7 million new stroke cases each year. Stroke is the second cause of mortality worldwide and one of the most important reasons for a disability, which requires new modalities for improving outcomes (1). Along with other possible changes in the acute phase of stroke (2), hyperglycemia could develop during the acute stress phase of a critical condition like stroke and result in an ominous prognosis in this condition (3). There is growing evidence that hyperglycemia in the acute phase of ischemic stroke (IS) is associated with poor prospects and increased mortality (4,5), larger infarct size (6), and hemorrhagic transformation (7).

Access this article online	
	Website: http://rps.mui.ac.ir
	DOI: 10.4103/1735-5362.329927

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Insulin resistance (IR) plays a prominent role in emerging stress-induced hyperglycemia. A high IR level, independent of hyperglycemia and stroke severity, has a prognostic value in the acute IS (8,9). IR is one of the predictive factors for poststroke functional dependency and can deteriorate clinical outcomes after acute IS, irrespective of age, sex, stroke subtype, and stroke severity (10). Fasting blood glucose and insulin levels are usually used to calculate the homeostasis model assessment of IR (HOMA-IR), which considers IR.

Conclusively, IR is a crucial therapeutic target in improving functional outcomes in patients experiencing acute IS and necessitates an appropriate intervention with a low risk of hypoglycemia (9,11). However, we could not find any published study that evaluated an intervention to reduce IR or hyperglycemia associated with IR in patients within the IS's acute or subacute stages.

Only one study assessed pioglitazone's effect, as a therapy directed at improving insulin sensitivity, on stroke or myocardial infarction in nondiabetic subjects with recent stroke or transient ischemic attack and IR for 4.8 years. It should be mentioned that the screening blood test was performed at least 14 days after the index event. This study revealed a lower risk of stroke or myocardial infarction in patients who received pioglitazone than placebo. The risk of diabetes and HOMA-IR index were lower in the pioglitazone group, while the dangers of weight gain, edema, and fracture were more severe than in the placebo group (12).

A few studies also assessed the effect of different stress-induced hyperglycemia interventions in intensive care unit (ICU) patients. Supplementation of vitamin D (13), an alanyl-glutamine dipeptide (14), α-lipoic acid (15), and a loading dose of intravenous magnesium sulfate (16) were modalities that could improve IR indices in critically ill patients. It seems supplements with a safe profile of adverse effects that could ameliorate IR without hypoglycemia are appropriate interventions for glycemic control and improve IS prognosis.

L-Carnitine (LC) with previous studies in sepsis, hemodialysis patients to improve anemia and its beneficial effects on liver enzymes and survival in liver transplant setting (17-19) is another supplementation that revealed beneficial effect in managing IR among outpatients with impaired glucose metabolism, prediabetics, type-2 diabetes mellitus, and also controlling metabolic syndrome, nonalcoholic steatohepatitis, chronic ambulatory peritoneal dialysis, coronary artery disease, polycystic ovarian syndrome, and obesity (20); which all present a kind of chronic IR.

Given the popularity of LC as a food supplement due to its safety profile (21), antioxidant activity (22), availability, and suggested effects on energy metabolism pathways, it is actively studied for various indications. However, we lack data on using LC in an acute care setting. The available information is derived from research in chronic critically ill patients that presented carnitine depletion symptoms (23), and little has been studied about the concentration of LC and its utility in the early phase of the critical condition (24). Moreover, based on recent evidence, the IR's early evaluation is mainly related to IS patients' functional outcomes (9). Thus, we performed the present study to explore LC's IR modifying effect as a safe and available food supplement during IS patients' subacute stage with critical conditions.

We hypothesized that LC supplementation could ameliorate glycemic indices and IR relative to baseline values and placebo group.

MATERIALS AND METHODS

Study design and setting

We performed this randomized, double-blind placebo-controlled clinical trial at the general ICU of AL-Zahra hospital, a tertiary academic hospital affiliated with Isfahan University of Medical Sciences, with 80 active ICU beds. In this center, critical stroke patients were admitted to the ICU. IS was diagnosed based on evidence of IS on brain CT, MRI, or both performed within 24 h of hospitalization, together with the clinical course of the sudden onset of a nonconvulsive, focal neurologic deficit.

Sample size, randomization, and blinding

We considered the significance level of 0.05 and 90% power (β = 0.1), with HOMA-IR (mean ± standard deviation) of 1.9 ± 0.7 and effect size of 0.7 for sample size formula (25). Therefore, based on the calculated sample size, we determine 24 patients to enroll in each study group.

The eligible patients were randomly assigned to study arms using a random list generated by a computer with a 1:1 allocation of study groups in an arbitrary block size of two, four, or six. Indeed the random sequences generated in blocks by the computer were written on the cards and placed in locked opaque packets, respectively. After that, a packet was assigned for each patient in order to the study recruitment, and related intervention was applied.

The participants, care providers, and data collectors were blinded to allocation until the end of the study. The corresponding author made the blinded preparations and unblinded the codes after the end of the study.

Patient Population

ICU admitted adult patients (> 18 years) with the first-ever or recurrent acute ischemic stroke who could tolerate oral intake or enteral nutrition, with no seizure history and no active participation in another trial were enrolled. Patients with a drug history of LC in the last month or known allergy to LC, those undergoing dialysis, and those unable to obtain consent were not allocated to the study groups, along with patients not followed up due to death or hospital discharge earlier than seven days after study recruitment.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human patients were approved by the Ethics in Research Committee of Isfahan University of Medical Sciences, IR.MUI.MED.REC.1397.199. Written informed consent was obtained from all patients or their family members.

The study was registered at the Iranian Registry of Clinical Trials, https://en.irct.ir/; with the registration identification number of IRCT20200509047365N1.

Patients received 500 mg every 8 h of LC tartrate tablets orally or *via* nasogastric tube for six days (cumulative dose of 9 g) in the intervention group.

Based on pharmacokinetic data, supplemental LC's bioavailability decreases with increasing oral dose; for example, the bioavailability of a two-gram single dose of LC was 10-20%, and for a single dose of 6 g was only 5% (26). So, we decided to evaluate a daily dose lower than 2 g with a single dose of as low as 500 mg on glycemic indices to optimize absorption while minimizing gut metabolism. As we aimed to assess the effects of the intervention during the acute phase of ICU stay; we set the duration of six days for LC supplementation.

The placebo group received the same amount of orally or *via* nasogastric tube placebo tablets with identical appearance three times daily for the study period. The same pharmaceutical company (Karen Pharma, Iran) manufactured both the supplement and placebo tablets; therefore, the appearance and taste of the tablets were similar. Three patients in the LC group and two in the placebo group were on the oral diet.

Study endpoints and measurement

The primary study outcome was evaluating the difference in HOMA-IR within and between groups during seven days. IR was assessed by using the HOMA-IR formula (27,28). The HOMA-IR value was calculated as the fasting blood sugar level (FBS measured in mg/dL) times the fasting insulin level (μU/mL) divided by 405. The Blood samples collected from fasting patients to measure the baseline FBS and fasting insulin were taken in the stroke's subacute phase. The cutoff points for defining IR when using HOMA-IR were considered 1.85 and 2.17 in women and men, respectively (29). The cutoff of 12.94 μU/mL was also used for IR based on insulin level (30). In our study, hyperglycemia was also defined as FBS > 110 mg/dL (4,5).

We also assessed C-reactive protein (CRP) and LC on the first and the last day of the study. Carnitine deficiency was defined at a level of free-LC < 36 nmol/mL (24).

The length of mechanical ventilation support, ICU and hospital stay, and mortality rate in 28 days were also reported as secondary outcomes in study groups.

For evaluating primary outcomes, 10 mL peripheral venous blood sample was drawn from patients after 8-h overnight fasting, before starting the intervention, and seven days later. Eight mL of the blood specimen was immediately processed to measure the serum level of glucose, insulin, and CRP. The remained 2 mL of each sample was seeded in an anticoagulated tube and centrifuged at 5000 *g* for 5 min. The plasma was stored at -70 °C until the LC level was analyzed on the first thaw. All blood samples were obtained in the early morning between 4:00 to 6:00 AM.

We used Roche® Elecsys/E170 insulin assay to analyze serum insulin level. Glucose and CRP were assayed following enzymatic (GOD-POD) colorimetric and turbidimetry procedures, respectively.

The ELISA method was performed to measure the LC levels based-on instructions outlined by the provider; Hangzhou East Coast Biopharmaceutical.

The energy requirement for ICU patients was set at 25 kcal/kg body weight; so, hyperglycemia from overfeeding (> 25-35 calories per kg of body weight) could be avoided. We adjusted the dextrose infusion rate at a maximum of 4 mg/kg body weight per min to prevent infusion-related hyperglycemia. In our study, any calories, including parenteral dextrose, were withheld in fasting hours, and insulin therapy was limited. All patients received standard interventions to prevent and treat hyperglycemia, to maintain the recommended level of 140-180 mg/dL, based on the standard protocol of subcutaneous insulin administration. Total calories received during the study *via* enteral nutrition (1 Kcal/mL) in each group were also documented.

We gathered the patients' background characteristics and clinical data, including sex, age, body mass index (BMI) category, the reason for ICU admission of the stroke patients, history of diabetes mellitus, and other chronic diseases on ICU admission. Glasgow coma scale (GCS), acute physiology and chronic health evaluation (APACHE II), and sequential organ failure assessment (SOFA) scores were also calculated on study recruitment. Moreover, we recorded daily changes in GCS and SOFA scores. Two score increase in daily SOFA score was considered as suspicion for sepsis (31). We also recorded administration data of medications such as insulin, glucocorticoids, antioxidants, vasopressors.

Statistical analysis

Descriptive and statistical analyses were performed by the SPSS version 25 (IBM Corporation) software. The Kolmogorov-Smirnov test assessed normality distributions of continuous variables, and related data were represented as mean ± SD or median (IQR1-IQR3) according to the distribution. Categorical variables were reported as frequencies, and any association between categorical variables and study groups was detected by performing the Chi-squared or Fisher's exact test. We used the independent t-tests and Mann-Whitney U test to analyze differences in continuous variables for parametric and nonparametric variables, respectively. The paired t-test or related nonparametric Wilcoxon Signed Ranks test assessed the differences of a continuous dependent variable within the groups before and after the intervention, while the McNemar test was used for the dichotomous dependent variable. We used analysis of covariance (ANCOVA) for parametric variables to control some confounding factors, including baseline levels of FBS, LC, SOFA, GCS score, and each variable-related baseline that might influence our study results. Moreover, the mean of changes was measured by subtraction after intervention values from baseline, and the independent t-test was performed to find the difference between study groups based on this variable. The level of statistical significance for all analyses was set at $P \leq 0.05$.

RESULTS

Study population

From March 2019 to August 2020, we evaluated a total of 113 IS patients to include in the study. Of these, 48 patients who met the inclusion criteria were randomly allocated to the research groups, 24 each (Fig. 1).

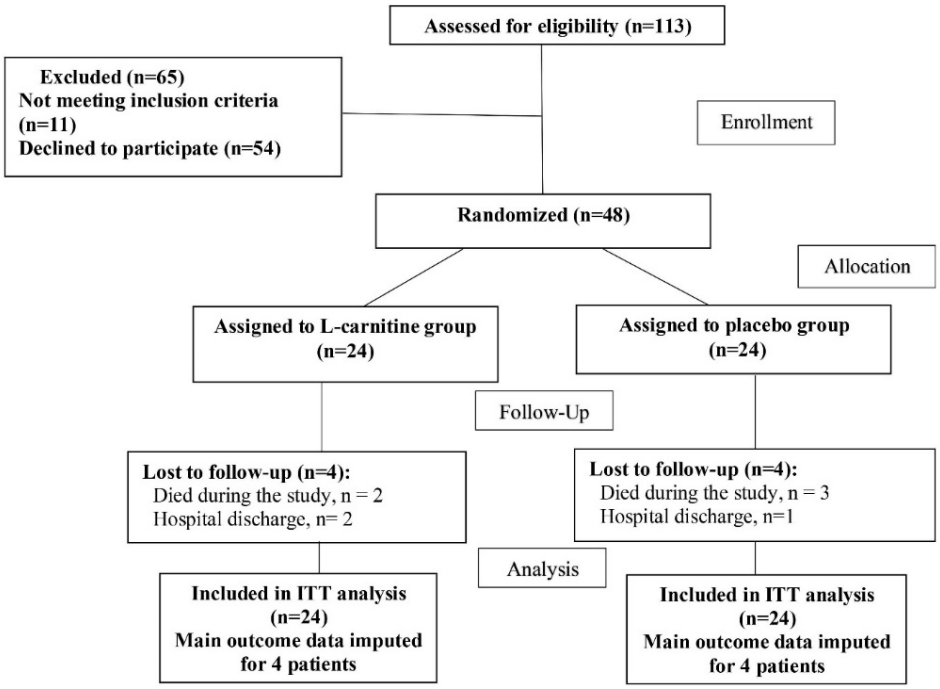

Fig. 1. The CONSORT patient flow diagram.

These patients were admitted to the ICU from emergency or neurology wards with an identical ratio. The time from hospital admission to collect baseline blood samples to determine study endpoints were comparable between study groups (10.9 ± 9.96 versus 8.65 ± 8.43 days in the LC and placebo group, respectively; P = 0.34, Table 1).

Demographic and baseline characteristics

The patients' mean age was 64.1 ± 15.48 years, 31 (64.58%) were male, and 41.66% were overweight or obese. Table 1 illustrated the demographic and clinical characteristics of the patients on ICU admission. Among these variables, the baseline levels of FBS, LC, GCS, and SOFA scores were significantly different between placebo and LC groups (P = 0.03, 0.03, 0.01, and 0.02, respectively) were considered as confounding factors in relevant analyses. However, other glycemic indices including fasting insulin and HOMA-IR levels were not significantly different between the groups at the time of admission to the ICU (P = 0.24 and 0.16, respectively). Moreover, the percentages of patients with hyperglycemia and IR based on both HOMA and insulin level were comparable between groups (P = 0.13, 0.37, and 0.09, respectively), and all participants had sufficient levels of LC at the beginning of the study (Table 1). The overall prevalence of hyperglycemia was 65% in our patients. As shown in Tables 2 and 3, other baseline laboratory findings and concomitant drugs were also comparable between study groups. The mean calories that patients received during the study were 1555.29 ± 296.71 kcal in placebo and 1747 ± 450 kcal in the LC group; P = 0.15.

Outcomes

Assessment of IR and other glycemic indices within groups

On day 7, we observed improvements in HOMA-IR within the LC group (P = 0.05), but there were no differences in FBS and insulin levels (P = 0.32 and 0.10, respectively). In the placebo group, FBS levels deteriorated at day 7 (P = 0.03) with no difference in insulin levels and HOMA-IR score (P = 0.77 and 0.19, respectively) (Table 4).

Table 1. Baseline demographic data and clinical status of participants.

Characteristics	L-carnitine group (n = 24)	Placebo group (n = 24)	*P*-value
Demographic data			
Age (year), median (IQR†)	68 (59-79.75)	61 (55-69.50)	0.20*
Male sex, n (%)	18 (75)	13 (51.16)	0.13**
BMI† class, n (%)			0.63**
< 18.5 (below normal weight)	0	1 (4.16)	
≥ 18.5 and < 25 (normal weight)	14 (58.33)	13 (54.16)	
≥ 25 and < 30 (overweight)	6 (25)	4 (16.66)	
≥ 30 and < 35 (class I obesity)	4 (16.66)	5 (20.83)	
≥ 40 (class III obesity)	0	1 (4.16)	
Reperfusion therapy and other interventions, n (%)			0.36**
Tissue plasminogen activator	4 (16.66)	2 (8.33)	
Thrombectomy	1 (4.16)	0	
Tissue plasminogen activator + thrombectomy	1 (4.16)	0	
Carotid stent	1 (4.16)	0	
Other	17 (70.83)	22 (91.66)	
Surgery admission (decompression), n (%)	2 (8.33)	4(16.66)	0.66**
Reason of ICU† admission, n (%)			0.73**
Cardiac	2 (8.33)	1 (4.16)	
Respiratory	2 (8.33)	3 (12.5)	
Complication or procedure requiring mechanical ventilation	17 (70.83)	19 (79.16)	
Complication or procedure requiring intensive hemodynamic	3 (12.5)	1 (4.16)	
Comorbid conditions, n (%)			
Type 2 diabetes	4 (16.66)	3 (12.5)	0.68**
Hypertension	4 (16.66)	8 (33.33)	0.31**
Cardiovascular diseases	10 (41.66)	13 (58.33)	0.38**
Prior stroke/transient ischemic attack†	5 (20.83)	6 (25)	0.73**
Other (malignancy, renal disease, Alzheimer)	3 (12.50)	2 (8.33)	1.00**
Number of comorbid conditions, n (%)			.31**
None	11 (45.83)	6 (25)	
One	6 (25)	8 (33.33)	
Two or more	7 (29.16)	10 (41.66)	
Severity of illness			
APACHE II score, mean ± SD†	12.80 ± 4.53	15.30 ± 6.31	0.16***
SOFA score, mean ± SD	3.90 ±1.97	5.85 ± 2.92	0.02***
GCS score, mean ± SD	11.75 ± 2.66	8.91±3.26	0.01***
Mechanical ventilation, n (%)	12 (50)	16 (66.66)	0.24**
Time of first sampling, median (IQR)			
From index stroke, days	4.5 (3-11.25)	6 (4-19)	0.34*
From ICU admission, days	2 (1-3)	2 (2-3)	0.15*
CRP (mg/L), mean ± SD	65.25 ± 32.69	64.4 ± 32.71	0.93***
Glycemic parameters			
FBS (mg/dL), mean ± SD	129.25 ± 21.75	114 ± 21.45	0.03***
Plasma insulin level, µU/mL, median (IQR)	6.75 (4.25-15.09)	6.65 (4.26-10.83)	0.24*
HOMA-IR† score, median (IQR)	1.81 (1.19-4.09)	1.39 (0.89-2.58)	0.16*
Insulin resistant, n (%)			
Based on HOMA-IR	11 (45.83)	8 (33.33)	0.37**
Based on inulin serum level	9 (37.5)	3 (12.5)	0.09**
Hyperglycemic, n (%)	18 (75)	13 (54.16)	0.13**
L-carnitine (nmol/mL), mean ± SD	72.16 ± 11.51	59.40 ± 17.78	0.03***

**P*-values are based on Mann-Whitney test; ***P*-values are based on Chi-square test or Exact-Fisher test; ****P*-values are based on independent t-test; APACHE, acute physiology and chronic health evaluation; BMI, body mass index; CRP, C-reactive protein; FBS, fasting blood sugar; GCS, Glasgow coma scale; HOMA-IR, homeostatic model of assessment-insulin resistance; IQR, interquartile range; SOFA, sequential organ function assessment.

Table 2. Other clinical and laboratory data at baseline.

Laboratory parameters	L-carnitine group (n = 24)	Placebo group (n = 24)	*P*-value
Systolic blood pressure, mean ± SD (mmHg)	128 ± 13.19	130.10 ± 17.94	0.78*
Diastolic blood pressure, mean ± SD (mmHg)	78.70 ± 9.81	75.50 ± 13.24	0.39*
White blood cell, median (IQR) (×10³/µL)	10.05 (7.96-12.30)	8.87 (7.10-12.57)	0.69**
Hemoglobin, mean ± SD (g/dL)	11.40 ± 2.45	10.30 ± 1.77	0.23*
Hematocrit, mean ± SD (%)	35.08 ± 6.41	31.35 ± 4.91	0.07*
Platelets, mean ± SD (×10³/µL)	211.75 ± 105.95	217.00 ± 84.92	0.86*
Blood urea nitrogen, median (IQR) (mg/dL)	17.50 (12.50-25.50)	13.50 (11.12-22.5)	0.25**
Creatinine, median (IQR) (mg/dL)	1.00 (0.90-1.30)	1.05 (0.90-1.17)	0.49**
Sodium, median (IQR) (mEq/L)	133.30 (142.00-146.00)	141.50 (137.00-143.75)	0.96**
Potassium, median (IQR) (mEq/L)	4.20 (4.02- 4.30)	4.00 (3.65-143.75)	0.06**
Magnesium, median (IQR) (mEq/L)	2.00 (1.90-2.10)	1.85 (1.60-2.00)	0.06**
Calcium, mean ± SD (mg/dL)	8.80 ± 0.70	9.08 ± 0.71	0.35*
Phosphor, median (IQR) (mg/dL)	2.60 (2.35-3.22)	2.95 (2.52-3.52)	0.30**
Aspartate transaminase, median (IQR) (unit/L)	35.00 (28.50-52.00)	36.50 (33.00-53.75)	0.42**
Alanine transaminase, median (IQR) (unit/L)	37.50 (27.75-57.50)	39.50 (29.00-60.50)	0.73**
Alkaline phosphatase, median (IQR) (unit/L)	181.50 (150.75-285.50)	189.00 (165.25-206.50)	0.88**
Total bilirubin, median (IQR) (mg/dL)	0.80 (0.60-1.00)	0.80 (0.60-1.00)	0.78**
International normalized ratio, median (IQR)	1.31 (1.13-1.59)	1.40 (1.30-1.59)	0.17**

**P*-values are based on independent t-test; ***P*-values are based on Mann-Whitney test; IQR, interquartile range.

Table 3. Concomitant drugs

Drugs	L-carnitine group (n = 24)	Placebo group (n = 24)	*P*-value
Hydrocortisone equivalent, n (%)	5 (20.83)	4 (16.66)	1.00*
Cumulative hydrocortisone equivalent dose, gram, median (IQR)	0.74 (0.12-1.44)	0.41 (0.28-4.12)	0.90†
Insulin, n (%)	6 (25)	2 (8.33)	0.24*
Cumulative Insulin dose, IU, mean ±SD	66.33 ± 65.85	138.00 ± 132.93	0.32‡
Dextrose, n (%)	2 (8.33)	7 (29.16)	0.13*
Cumulative dextrose dose, gram, mean ±SD	42.85 ± 13.51	151.24 ± 117.29	0.25‡
Antioxidants, n (%)			0.14*
None	19 (79.16)	13 (54.16)	
n-acetyl cysteine	3 (12.5)	8 (29.16)	
Multivitamin	1 (4.16)	2 (8.33)	
Melatonin	0 (0)	1 (4.16)	
Norepinephrine, n (%)	2 (8.33)	4 (16.66)	0.66*
Levofloxacin, n (%)	7 (29.16)	4 (16.66)	0.49*
Cefepime, n (%)	0	1 (4.16)	1.00*
Valproate sodium, n (%)	2 (8.33)	5 (20.83)	0.41*

**P*-values are based on the Fisher-Exact test; †*P*-value is based on Mann Whitney test; ‡*P*-values are based on the Independent t-test.

Assessment of IR and other glycemic indices between groups

The preliminary analyses revealed no difference in the level of FBS, insulin, and HOMA-IR in the LC group compared to the placebo group on day 7 (P = 0.32, 0.65, and 0.14, respectively). However, more analyses with the ANCOVA tests showed a significant decrease for HOMA-IR and insulin levels after adjusted with covariates (baseline levels of FBS, LC, SOFA, and GCS score) (P = 0.01 and 0.04, respectively). Nevertheless, FBS levels remained with no differences between groups (P = 0.23). Moreover, the mean of HOMA-IR and insulin values changes were different in the LC group than placebo in favor of decreasing from baseline (P = 0.01 and 0.03, respectively). The mean changes for FBS levels did not show any significant difference (P = 0.18) (Table 4).

Assessment of plasma LC level between and within groups

The paired t-test displayed; LC concentration did not differ during follow-up in LC and placebo groups (P = 0.06, 0.55, respectively).

Table 4. Post-intervention glycemic and clinical outcomes in between and within-group analysis

Variable	L-carnitine group	Placebo group	*P*-value*	*P*-value†
Fasting blood sugar mg/dL, mean ± SD	117.85±44.83	132.25 ± 46.17	.32	.23
P-value‡	.32	.03		
Difference§ , mean ± SD	-11.40 ± 50.34	18.25 ± 35.70	.04	.18
Plasma insulin, µU/mL, median (IQR)	5.35 (2.46-12.77)	7.59 (2.74-11.47)	0.65	0.033
P-value‡	0.10	0.77		
Difference§, mean ± SD	-2.26 ± 6.81	0.88 ± 4.95	0.10	0.03
HOMA-IR score, median (IQR)	1.29 (0.57-2.72)	1.96 (0.63-2.70)	0.14	0.01
P-value‡	.05	.19		
Difference§, mean ± SD	-0.94 ± 1.92	0.87 ± 2.24	0.009	0.01
C-reactive protein, mg/L, mean ± SD	49.00 ±35.06	64.20 ± 32.15	0.16	0.66
P-value‡	0.05	0.98		
Difference§, mean ± SD	-16.25 ± 35.29	-0.2 ± 40.14	0.18	0.71
Plasma L-carnitine, nmol/mL, mean ± SD	77.07 ± 8.60	61.72 ± 15.27	0.000	0.02
P-value‡	0.06	0.55		
Difference§, mean ± SD	5.81 ± 10.35	2.31 ± 17.23	0.51	0.13
Glasgow coma scale score, mean ± SD	11.94 ± 3.1	8.50 ± 3.56	0.03	.16
P-value‡	0.63	0.43		
Difference§, mean ± SD	0.19 ± 1.76	-0.41 ± 3.26	.47	.14
SOFA score, mean ± SD	4.10 ± 2.44	5.35 ± 2.87	0.14	0.43
P-value‡	0.51	0.34		
Difference§, mean ± SD	0.20 ± 1.70	-0.50 ± 2.06	0.25	0.62
Insulin resistant, n (%)				
Based on inulin serum level	5 (25)	4 (20)	1.00#	
P-value‡	0.50	0.50		
Based on HOMA-IR	7 (35)	8 (40)	0.74#	
P-value‡	0.75	0.25		
Hyperglycemic, n (%)	8 (40)	13 (65)	0.11#	
P-value‡	0.04	0.51		
Mechanical ventilation, n (%)	9 (45)	11 (55)	0.20#	
28-Day mechanical ventilation, days, median (IQR)	15.00 (10-20)	15.00 (11-28)	0.57	
Sepsis events during study, n (%)	10 (41.66)	9 (37.5)	1.00#	
Total ICU stays, days, median (IQR)	21.5 (10.5- 38)	21 (12-34)	0.85	
Hospital stay, days, median (IQR)	24 (12-43)	25 (16-50)	0.74	
28-Day death events, n (%)	6 (25)	7 (29.16)	0.81#	

HOMA-IR, Homeostasis model assessment for insulin resistance; ICU, intensive care unit; SOFA, sequential organ function assessment; **P*-value ≤ 0.05 was considered as significant using an independent t-test or Mann-Whitney test at post-intervention; †*P*-value ≤ 0.05 was considered as significant using analysis of covariance (ANCOVA); ‡*P*-value ≤ 0.05 was considered significant using paired t-test for continuous variable or McNemar test for the dichotomous dependent variable; § mean of changes was measured by subtraction of values after intervention from baseline; #*P*-value ≤ 0.05 was considered significant using the Chi-square test or exact-Fisher test.

On day seven, however, the ANCOVA test revealed that the LC levels of patients who received LC were significantly higher than placebo when the baseline level of LC was considered a confounding factor ($P = 0.02$; Table 4). In the LC group, there was no difference in LC plasma levels at day seven between diabetics and non-diabetics patients ($P = 0.29$).

ANCOVA analysis showed no difference in LC concentrations among patients with and without IR (71.21 ± 13.20 versus 66.67 ± 16.31, $P = 0.20$). Moreover, LC plasma levels' mean changes were not different between groups ($P = 0.13$; Table 4).

Assessment of inflammatory biomarker

Furthermore, we observed a decrease in the CRP level within the LC group ($P = 0.05$) but not in the placebo group ($P = 0.98$). Moreover, the CRP level did not differ between the groups on day 7 ($P = 0.68$), and the mean of changes for CRP levels was not different between the two groups ($P = 0.71$) (Table 4).

Assessment of the other clinical outcomes

Neither SOFA nor GCS score changes were detected during the study period in both groups (P = 0.51 and 0.63 in the LC group, and P = 0.34 and 0.43 in the placebo group, respectively). Also, on day 7, SOFA and GCS scores did not differ between groups (P = 0.43 and 0.16, respectively), and the mean of changes analyses for GCS and SOFA scores between groups did not show any differences (Table 4).

There was no difference in length of mechanical ventilation, ICU, hospital stay, and sepsis rate between the LC and placebo groups (P = 0.57, 0.85, 0.74, and 1.00, respectively). Additionally, patients' 28-day mortality rates were not different between groups (6 patients in the LC group and 7 patients in the placebo group, P = 0.81).

DISCUSSION

Our findings showed that administering the oral LC supplement in acute IS patients is associated with lower IR estimated by HOMA-IR in the subacute stage. However, in contrast to the previous studies, our results could not show better clinical improvement in line with HOMA-IR attenuation; which might be related to the short duration of intervention and follow-up and a low number of included patients.

Nevertheless, the significantly lower CRP concentration within the LC group on day seven of the study could be a positive forecaster for controlling inflammation by LC in acute IS patients at early ICU admission. Additionally, it could be possible to relate this anti-inflammatory effect to the IR improvement shown by LC supplementation.

It is worthy to remind that applying an intervention for these patients is more valuable, especially in a critical care setting, where more risk existed to develop IR.

The most available reports of IR's role in patients with IS are not in a critical care setting (8-10), but IR's harmful effects on clinical and functional outcomes can also be extended to the ICU. On the other hand, since different underlying diseases of critically ill patients could affect metabolic profile, select a homogenous group of these patients can be more precise to evaluate IR interventions (32). Therefore, we try to choose the subgroup of critically ill patients who can benefit the most from glycemic control.

Rising prothrombotic and inflammatory reactions after IS in patients with IR can intensify the brain's ischemic injury (33). Accordingly, LC's anti-inflammatory and anti-hyperglycemic effect could alleviate inflammation and subsequently deteriorate ischemic injury progression. These beneficial effects could place LC as a potential appropriate intervention to improve IS patients' outcomes at risk for IR.

Our results indicated these positive effects of LC in those without any LC deficiency, which revealed the LC supplementation was beneficial to reduce the IR rate even in those with a sufficient level of LC.

The harmful effect of hypoglycemia caused by routinely performed interventions to control hyperglycemia and IR did not occur with LC administration and subsequently put it as an exciting intervention.

We used HOMA as an alternative to the invasive and time-consuming insulin clamp technique, the gold standard for measuring IR. HOMA-IR is a simple formula and established for measuring IR and is the most proximate to the standard method (27).

Different cutoff points reported for HOMA-IR and various IS recruits in previous studies make it difficult to compare our outcomes with former results (4).

The prevalence of hyperglycemia in our study (65%) was higher than antecedent reports which declared that up to 60% of acute IS patients experienced hyperglycemia (4). A higher rate of hyperglycemia was probably related to our population's critical condition, which might endure higher stress than the general IS population. However, it should be mentioned that these values were reported in the subacute stage of IS (at the mean of 9.77 ± 9.18 days after index stroke), whereas most previous data were obtained from the acute phase.

Calleja *et al.* stated 34.8% of acute IS patients who received thrombolysis had HOMA-IR > 1.71 within 24 to 48 h after IS, which were significantly associated with poor

functional outcomes (8). In our critical IS patients, the prevalence of IR compatible with HOMA-IR > 2.17 in men and 1.85 in women, was 37.5% in the subacute stage. Another research exhibited a prevalence of 39.7% for IR (based on HOMA-IR > 2) in the subacute phase of IS (at 8.3 ± 7.8 days after the onset of stroke) (10).

Most researchers assessed the effects of different modalities on IR in the general population of critically ill without defining the specific reason for admission or sole in the surgical population (13, 16). Only one study in critically ill patients, with 78.5% of the neurologic basis for ICU admission, exhibited their intervention, α-lipoic acid, prevented an increase in HOMA-IR in these patients (15).

There have been no reports introducing efficient intervention to control IR in acute IS patients admitted to the ICU to the best of our knowledge. Moreover, our results supported the LC dose lower than 2 g (1.5 g daily LC) for its impact on glucose tolerance, which has not been introduced until now (21).

Regarding free LC < 36 nmol/mL, LC deficiency was reported in 23.4% of patients on ICU entry in a recent study (24); but we did not observe any LC deficiency with the exact definition. It may be explained by delayed ICU admission in the mentioned study since 39% of this population were transferred from other hospitals, which in contrast to our study all patients were assessed during the early time of first hospital admission.

It is important to mention that despite the absence of carnitine deficiency, LC supplementation showed significant beneficial effects on lowering HOMA-IR score and insulin levels in comparison to the placebo group. Therefore, in the absence of contraindications, supplementing LC at the time of ICU admission would be an option to lower IR and probably prevents its harmful consequences in this population. We followed patients for one week, so despite a decline in LC concentration in patients who received placebo compared to the intervention group, LC levels were still above the defined threshold for deficiency at the end of the study, similar to recent results after 14 days of follow-up (24). It seems LC loss is expected among prolonged ICU stay patients, and early supplementation, possibly with a higher dose and longer duration, might avoid this deficiency and related complications (23).

Limitations of the study

It should also be considered that the baseline imbalance of some variables between study groups limited our results. However, we performed further analyses to evaluate these confounding factors' effect on the study endpoints, but the multivariable evaluation was not applicable due to the low number of enrolled patients. This study aimed to evaluate acute outcomes, although stroke severity and functional outcome response are the other valuable endpoints proposed to be assessed in future studies. Moreover, we recommended a more extended period of intervention for the assessment of primary and secondary outcomes.

CONCLUSION

Although better IR has been shown with oral LC supplementation in the subacute stage of critical IS patients; further studies may be warranted to investigate whether a longer duration of LC supplementation could have a potential advantage to improve clinical outcomes and glycemic indices in these patients.

Acknowledgments

This study was financially supported by the Anesthesiology and Critical Care Research Center of Isfahan University of Medical Sciences, Isfahan, I.R. Iran through Grant No. 297137.

Conflict of interest statement

All authors declared no conflict of interest in this study.

Authors' contribution

Sh. Farsaei contributed to the concept, design, and definition of the intellectual concept. M. Nejati, S. Abbasi, and F. Shafiee collected the data. Sh. Farsaei and M. Nejati performed the statistical analysis. Sh. Farsaei, M. Nejati, F. Shafiee, and S. Abbasi interpreted

the data. All authors contributed to preparing the manuscript and approved the final version of it. Literature search was done by M. Nejati, S. Farsaei.

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