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Original Article

Effects of L-carnitine on Serum Lactate and Cardiac Complications in Patients With Heart Failure Undergoing Coronary Artery Bypass Grafting: A Randomized Clinical Trial

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ABSTRACT

Background: The effects of L-carnitine on serum lactate and its metabolism remain uncertain, particularly in candidates for revascularization with a high likelihood of a postoperative rise in lactate levels. The present study aimed to assess the effects of L-carnitine on lactate levels after coronary artery bypass graft surgery (CABG) in patients with grade I heart failure.

Methods: in this randomized clinical trial, 64 consecutive patients suffering from mild heart failure (grade I) who were candidated for coronary revascularization were randomly divided into 2 groups (32 patients in each group) receiving L-carnitine (3 g orally 2 hours before surgery) or a placebo for the same duration before surgery. Postoperative adverse events, as well as the trend of the change in the levels of serum lactate, creatinine, and hemoglobin, within 24 hours after surgery were assessed.

Results: No difference was revealed between the 2 groups in terms of serum lactate levels before surgery (1.51 ± 0.79 in the intervention group vs 1.35 ± 0.43 in the control group; P = 0.33), during intra-aortic balloon pumping (2.27 ± 1.28 in the intervention group vs 2.70 ± 1.42 in the control group; P = 0.20), and also after separating the pump (2.96 ± 1.61 in the intervention group vs 2.56 ± 0.87 in the control group; P = 0.22). No difference was also observed concerning postoperative complications, including atrial fibrillation (P = 0.42), delirium (P = 0.99), agitation (P = 0.88), intra-aortic balloon pump insertion (P = 0.99), atelectasis (P = 0.98), and respiratory distress (P = 0.99).

Conclusions: Administrating L-carnitine had no protective effects on the rise in postoperative serum lactate levels following CABG in our patients with low-grade heart failure. ***(Iranian Heart Journal 2020; 21(4): 14-24)***

KEYWORDS: L-carnitine, Serum lactate, Heart failure, Coronary artery bypass grafting

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Cardiovascular diseases are some of the most common causes of death the world over. According to a report by the World Health Organization (WHO) in 2018, about 56.4 million people died worldwide, and 17.9 million of this total died of cardiovascular diseases. [1] These deaths happen because of both acute ischemic cardiovascular events and progressing heart failure. Heart failure is a clinical syndrome that occurs due to abnormalities in the structure or function of the heart. [2] Any condition that leads to a change in the structure or function of the left ventricle, including coronary artery disease, hypertension, and rheumatic heart disease, renders individuals prone to heart failure. [3,4] Many patients who suffer from ischemic heart diseases require cardiovascular revascularization procedures such as coronary artery bypass grafting surgery (CABG), but patients with heart failure have a poorer postoperative outcome than patients without heart failure. [5] These patients are susceptible to a higher level of lactate and acidosis, as well as difficulty in separation from the left ventricular assist device. [6,7] Several problems force this group of patients to be placed on cardiac supportive devices, separation from which requires appropriate preventive strategies.

Carnitine is a natural protein that plays an important role in cellular metabolism and energy supply. [8] L-carnitine is an organic molecule with a short water-soluble chain; it is a critical component in the transportation of activated fatty acids from the mitochondrial membrane and facilitates the oxidation of long-chain fatty acids, which is the main substrate in metabolism and energy production in the myocardium. [9] Carnitine is also thought to be an antioxidant in the body, and it appears to be involved in controlling duplication in DNAs in the cell nucleus. [10]

Recent has demonstrated that patients with heart failure have L-carnitine deficiency and that the use of L-carnitine in these patients not only increases their endurance in rehabilitation exercises but also reduces their disabilities. [11] Carnitine and its derivatives also increase the coronary flow and protect the myocardium against ischemia in patients with heart failure. [12] Nonetheless, the benefits of using L-carnitine before coronary revascularization in terms of improvements in the postoperative outcome, especially in patients with low ventricular functional status, have not been previously assessed. This issue gains even greater significance when considering the close association between the use of L-carnitine and the reduction in the level of serum lactate, which could prove valuable in the management of patients with heart failure who are susceptible to lactate accumulation. [13, 14]

Accordingly, in the present study, we aimed to assess the effects of L-carnitine on lactate levels after CABG in patients with mild heart failure.

METHODS

This randomized double-blinded clinical trial was performed on 64 consecutive patients suffering from mild heart failure (grade I) who were candidated for coronary revascularization in Masih-e-Daneshvari Hospital in Tehran in 2018. The inclusion criteria were comprised of mild heart failure (grade I), left ventricular ejection fractions ranging from 40% to 55%, being candidated for elective CABG, having no kidney or liver failure, having no allergy to L-carnitine, having no brain problems, and signing a written informed consent form for participation in the study. Those with the following criteria were all excluded from the study: any evidence of postoperative infection, surgery due to severe bleeding, needing the insertion of intra-aortic balloon pumps postoperatively, unwillingness to continue the study at any step, and showing any hypersensitivity to L-carnitine or the

placebo. The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences.

The baseline characteristics, including demographics, medical history, medication history, and previous medical interventions, were all collected by interviewing the patients on admission. After the researchers obtained the necessary information and provided full explanations to the patients who met the inclusion criteria and granted written informed consent for inclusion in the study, the study population was randomly divided through the use of a random number generator into 2 groups (32 patients in each group): the L-carnitine group, who received 3 g of L-carnitine orally 2 hours before surgery, and the placebo group, who received a placebo made in same shape and color for the same dose and duration as the intervention group before surgery. The patients and the physicians ordering the drugs were kept blinded to the study protocol. The study endpoint was to assess the serum levels of lactate, troponin, and creatinine before and 24 hours after coronary revascularization. Additionally, the left ventricular ejection fraction, the duration of mechanical ventilation, the need for cardiopulmonary bypass, the need for intra-aortic balloon pumps, the cross-clamp time, the total time of surgery, the use of inotropes, the need for the transfusion of blood or fresh frozen plasma, and urinary output were assessed. Postoperative complications, including delirium, brain strokes, myocardial infarctions, agitation, sepsis, atelectasis, acute respiratory syndromes, and in-hospital deaths, were also determined postoperatively.

The results were presented as the mean ± the standard deviation (SD) for the quantitative variables and were summarized by absolute frequencies and percentages for the categorical variables. The normality of the data was analyzed using the Kolmogorov–Smirnoff test. The categorical variables were compared using the χ^2 test or the Fisher exact test when more than 20% of cells with an expected count of less than 5 were observed. The quantitative variables were also compared using the *t*-test, the Mann–Whitney *U* test, the ANOVA test, or the Kruskal–Wallis *H* test. The trend of the change in the study parameters was tested using the repeated measure ANOVA test. For the statistical analyses, the SPSS software, version 16.0, for Windows (SPSS Inc, Chicago, IL) was used. A *P*-value of 0.05 or less was considered statistically significant.

RESULTS

Sixty-four patients were included in the study: 32 in the L-carnitine group and 32 in the placebo group. The flowchart of the study design is depicted in Figure 1.

As is shown in Table 1, there were no differences between the 2 groups as regards the baseline characteristics, including gender distribution, average age, anthropometric indices, cardiovascular risk factors (ie, cigarette smoking, opium use, diabetes mellitus, hypertension, hyperlipidemia, and previous myocardial infarctions), previous brain strokes, chronic kidney diseases, gout, and the mean left ventricular ejection fraction. Intraoperative and postoperative assessments showed that except for urinary output, which was significantly higher in the L-carnitine group, the other studied indices such as the duration of mechanical ventilation, the duration of anesthesia, the duration of surgery, the intra-aortic balloon pump time, the cross-clamp time, hemo-filtering during cardiopulmonary bypass, the mean intensive care unit (ICU) length of stay, blood or fresh frozen plasma transfusions during surgery or in the ICU, and the need for diuretic use. As is demonstrated in Table 3, the level of serum creatinine was 1.14 ± 0.26 in the L-carnitine group and 1.03 ± 0.34 in the control group (*P* = 0.16) before surgery and also 1.26 ± 0.54 in the L-carnitine group and 1.11 ± 0.30 in the control group (*P* = 0.16) 24 hours after surgery. The level of serum hemoglobin was

13.99 ± 1.87 in the L-carnitine group and 13.69 ± 1.67 in the control group (P = 0.51) before surgery and 10.30 ± 2.39 in the L-carnitine group and 10.13 ± 1.38 in the control group (P = 0.72) 24 hours after surgery.

Additionally, no difference was revealed between the 2 groups concerning the serum lactate level before surgery (1.51 ± 0.79 in the intervention group vs 1.35 ± 0.43 in the control group; P = 0.33), during intra-aortic balloon pumping (2.27 ± 1.28 in the intervention group vs 2.70 ± 1.42 in the control group; P = 0.20), and also after separating the pump (2.96 ± 1.61, in the intervention group vs 2.56 ± 0.87 in the control group; P = 0.22). Regarding postoperative adverse events (Table 4), no differences were observed in postoperative complications, including atrial fibrillation (P = 0.48), delirium (P = 0.99), agitation (P = 0.99), intra-aortic balloon pump insertion (P = 0.98), atelectasis (P = 0.99), and respiratory distress (P = 0.99). The assessment of the trend of the change in the values of pH and the central vein pressure showed no differences between the L-carnitine and control groups (Fig. 2 & 3); nevertheless, receiving L-carnitine led to a decrease in the mean arterial pressure within 24 of surgery (P = 0.03) (Fig. 4). Further, the use of L-carnitine did not result in a change in the serum lactate level in the L-carnitine group as compared with the control group at the different time points after surgery (Fig. 5).

Table 1: Baseline characteristics of the study population

Item	L-carnitine Group (n = 32)	Placebo Group (n = 32)	*P*-value
Mean age, y	58.61 ± 11.54	60.76 ± 11.54	0.435
Male gender, %	26 (81.2)	20 (64.5)	0.122
Mean weight, kg	71.81 ± 15.62	68.19 ± 14.23	0.336
Mean height, cm	168.16 ± 8.09	164.13 ± 9.89	0.081
Cigarette smoking, %	7 (21.8)	1 (3.2)	0.088
Opium use, %	8 (25.0)	14 (45.2)	0.104
Diabetes mellitus, %	13 (40.6)	15 (48.4)	0.081
Systolic hypertension, %	17 (53.1)	23 (74.2)	0.196
Hyperlipidemia, %	10 (31.2)	10 (32.3)	0.881
Myocardial infarction, %	6 (18.7)	1 (3.2)	0.104
Brain stroke, %	1 (3.1)	0 (0.0)	0.998
Chronic kidney disease, %	1 (3.1)	0 (0.0)	0.998
Gout, %	1 (3.1)	0 (0.0)	0.998
Mean left ventricular ejection fraction, %	47.65 ± 6.59	44.83 ± 6.12	0.084

Table 2: Intraoperative and postoperative outcomes

Item	L-carnitine Group (n = 32)	Placebo Group (n = 32)	*P*-value
Duration of ventilation, h	12.93 ± 5.52	14.47 ± 9.19`	0.442
Duration of anesthesia, h	5.24 ± 1.06	4.82 ± 1.01	0.121
Duration of surgery, h	4.08 ± 0.97	3.94 ± 1.07	0.603
Intra-aortic balloon pump time, min	85.42 ± 41.36	73.49 ± 31.56	0.200
Cross-clamp time, min	46.00 ± 22.61	40.56 ± 12.18	0.236
Hemo-filtering during cardiopulmonary bypass	833.33 ± 361.48	760.00 ± 454.69	0.772
Mean of the ICU length of stay, d	5.00 ± 4.39	3.70 ± 1.02	0.120

Packed cells infusion during surgery, unit	1.45 ± 0.67	1.50 ± 0.60	0.814
Packed cells infusion in the ICU, unit	1.33 ± 0.59	1.24 ± 0.54	0.603
Fresh frozen plasma infusion in surgery, unit	2.00 ± 0.82	2.67 ± 0.58	0.286
Fresh frozen plasma infusion in the ICU, unit	2.67 ± 0.66	3.00 ± 0.10	0.774
Urinary output during surgery, mL	1032.07 ± 660.27	546.77 ± 324.53	< 0.001
Urinary output in the ICU, mL	4596.77 ± 828.66	3737.50 ± 838.68	0.011
Lasix use in surgery, mg	21.07 ± 9.23	23.23 ± 8.16	0.611
Lasix use in the ICU, mg	60.00 ± 86.60	20.00 ± 10.00	0.597

Table 3: Changes in laboratory parameters after surgery

Item	L-carnitine Group (n = 32)	Placebo Group (n = 32)	*P*-value
Serum creatinine, mg/dL			
Before surgery	1.14 ± 0.26	1.03 ± 0.34	0.162
24 hours after surgery	1.26 ± 0.54	1.11 ± 0.30	0.165
Serum hemoglobin, g/dL			
Before surgery	13.99 ± 1.87	13.69 ± 1.67	0.510
24 hours after surgery	10.30 ± 2.39	10.13 ± 1.38	0.728
Serum lactate, mg/dL			
Before surgery	1.51 ± 0.79	1.35 ± 0.43	0.331
During pumping	2.27 ± 1.28	2.70 ± 1.42	0.209
After separating the pump	2.96 ± 1.61	2.56 ± 0.87	0.223

The level of serum hemoglobin was 13.99 ± 1.87 in the L-carnitine group and 13.69 ± 1.67 in the control group (*P* = 0.51) before surgery and 10.30 ± 2.39 in the L-carnitine group and 10.13 ± 1.38 in the control group (*P* = 0.72) 24 hours after surgery.

Table 4: Postoperative complications in the 2 study groups

Item	L-carnitine Group (n = 32)	Placebo Group (n = 32)	*P*-value
Atrial fibrillation	2 (6.2)	5 (16.1)	0.426
Delirium	1 (3.1)	1 (3.2)	0.999
Agitation	3 (9.3)	3 (9.6)	0.884
Intra-aortic balloon pump insertion	2 (6.2)	2 (6.4)	0.999
Renal replacement therapy	1 (3.1)	1 (3.2)	0.999
Atelectasis	1 (3.1)	1 (3.2)	0.999
Respiratory distress	1 (3.1)	1 (3.2)	0.999

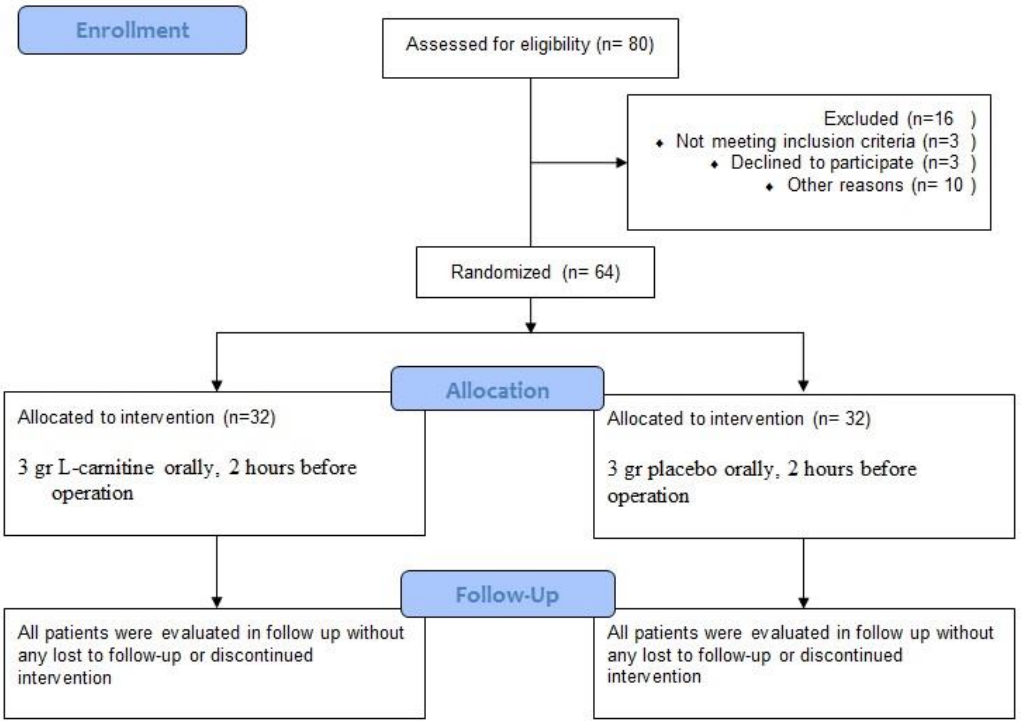

Figure 1: Flowchart of the study design is illustrated herein.

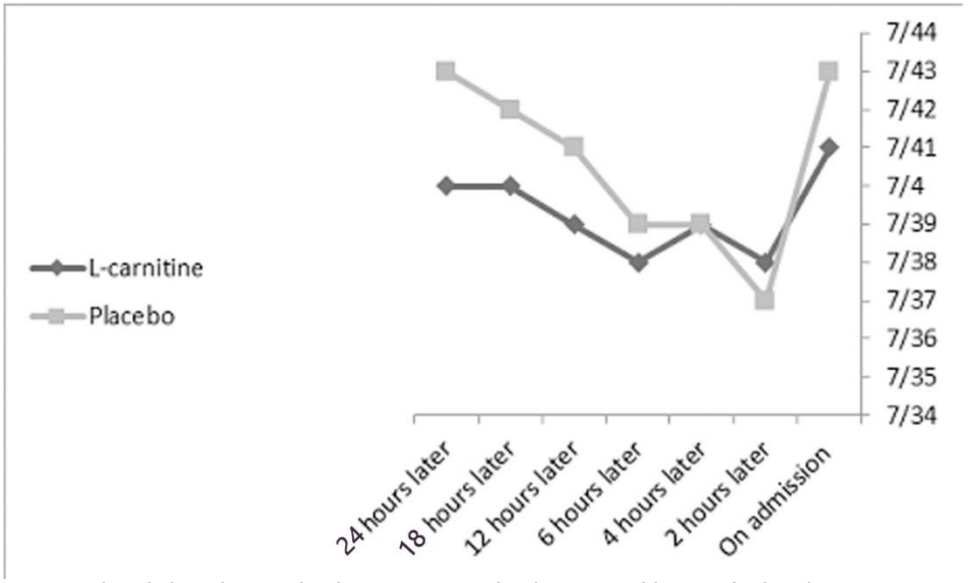

Figure 2: Trends of the change in the serum pH in the L-carnitine and placebo groups are depicted herein.

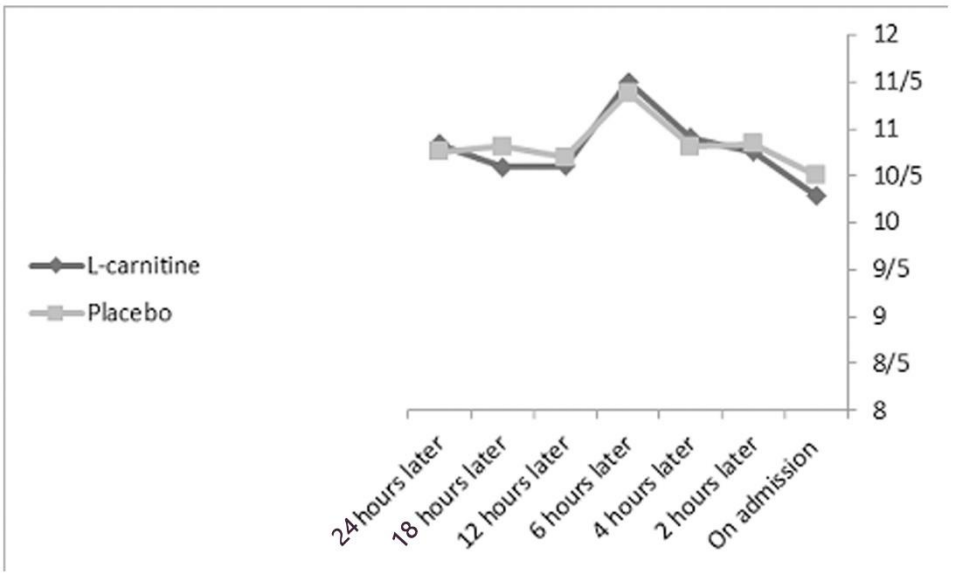

Figure 3: Trends of the change in the serum central vein pressure in the L-carnitine and placebo groups are demonstrated herein.

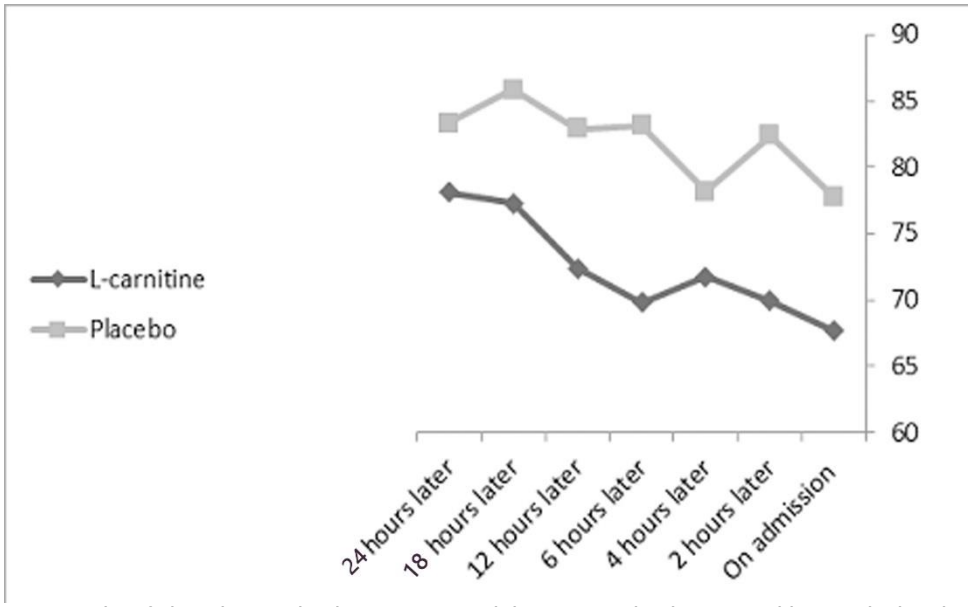

Figure 4: Trends of the change in the mean arterial pressure in the L-carnitine and placebo groups are illustrated herein.

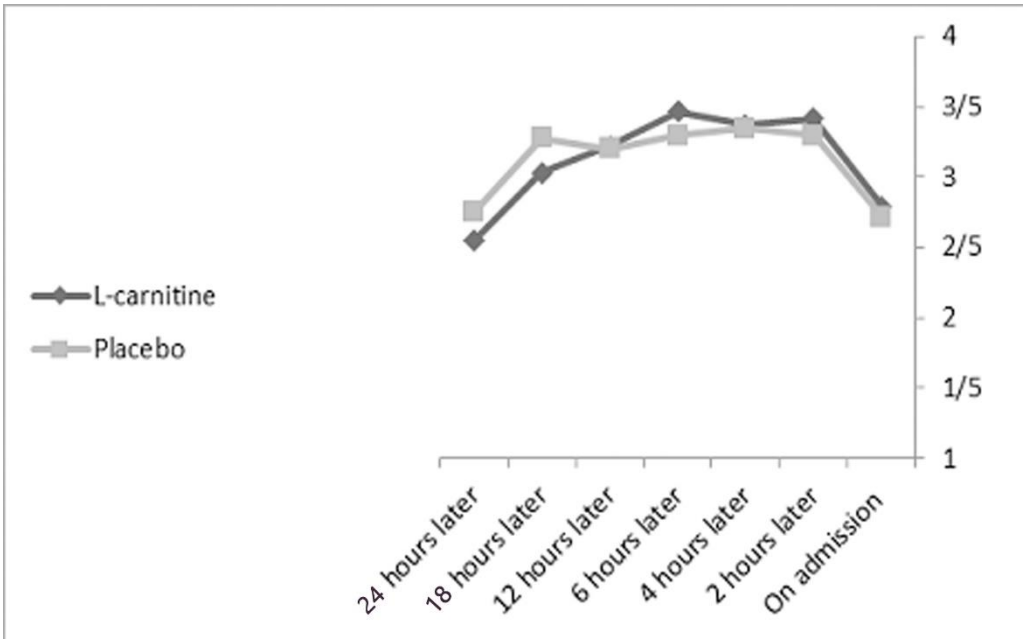

Figure 5: Tends of the change in the serum lactate in the L-carnitine and placebo groups are depicted herein.

DISCUSSION

The effects of L-carnitine on serum lactate and its metabolism have yet to be fully elucidated. This issue is vitally important in the clinical setting, especially among patients with cardiovascular diseases and heart failure because of the high levels of lactate in such patients. As was shown in our trial, the use of L-carnitine did not change the serum level of lactate postoperatively; however, as an adverse event, L-carnitine induced hypotension in the heart failure group scheduled for coronary revascularization. In other words, the use of L-carnitine failed to reduce the risk of lactate rising in our patients with heart failure. Although some studies have demonstrated the therapeutic effects of L-carnitine on increasing lactate, some others have not reported such causality. In an investigation by Claessens et al, [15] the intravenous use of L-carnitine helped the treatment of severe lactic acidosis induced by nucleoside analogs. In this regard, L-carnitine might be used as a specific treatment in severe acidosis secondary to nucleoside analog-induced mitochondriopathy. In a study by Gönen et al, [16] the plasma level of lactic acid was reduced following L-carnitine treatment, which might have been in consequence of both improved insulin resistance and increased oxidative glucose. In a study by Kashef et al, [17] L-carnitine supplementation before exercise decreased lactate. Kashef and colleagues concluded that L-carnitine could increase the consumption of oxygen and the oxidation of lipids by stimulating the pyruvate dehydrogenase complex and pyruvate entry into the beta-oxidation pathway. Some authors have been able to demonstrate that L-carnitine pharmacologically preconditions the heart against ischemic and reperfusion injury in part via the recovery of post-ischemic ventricular hemodynamic functions, the depletion of glycogen, and, thus, the reduction of lactate accumulation. [18] Be that as it may, similar to our study, some authors have not been able to demonstrate significant changes in serum lactate following the administration of L-carnitine. Eroğlu et al [19] reported that L-carnitine intake 1 hour prior to exercise had no effect on the metabolic and blood lactate

values of professional players. Barnett et al [20] also concluded that L-carnitine supplementation had no significant effect on muscle carnitine content and thus could not alter lactate accumulation during exercise. These paradoxical results may be explained by the different methodologies in the investigations such as the type of study and the study power, as well as the time and dosages of the drug used. The influence of L-carnitine on serum lactate in patients with heart failure (as the novelty of our trial) has not been assessed previously. Our results indicated that the use of this drug with its routine dose (9 g/d intravenously for 5 days) might not alter the lactate serum level; thus, it may not play a major role in protecting the myocardium against a rise in the lactate level postoperatively. Perhaps, bioavailability studies are able to determine an optimal dose for L-carnitine to achieve the efficacy required to decrease the risk for rising lactate.

The use of L-carnitine as a therapeutic supplement could not prevent adverse postoperative cardiac events in our study. Otherwise speaking, the preoperative use of L-carnitine did not prevent procedural morbidity and mortality in our patients with heart failure. A few studies have assessed the effective impact of L-carnitine on the cardiovascular postoperative outcome. Dastan et al [21] showed that L-carnitine administration before CABG might inhibit and reduce the incidence of postoperative atrial fibrillation, which could be due to the inhibition of inflammatory pathways. We, however, did not observe this effect in our study. In a similar study by da Silva Guimarães et al, [22] L-carnitine supplementation at a dose of 50 mg/kg (significantly higher than that considered in our study) combined with CABG did not demonstrate any additional benefit in reverse remodeling and failed to improve the postoperative outcome. According to our findings, given the drop in the postoperative blood pressure in patients undergoing CABG, the use of L-carnitine cannot be recommended despite its anti-oxidative or anti-inflammatory effects. The hypotensive effect of L-carnitine has been described previously. [23] The effects of L-carnitine on postoperative blood pressure should be investigated further because of the importance of blood pressure changes after cardiac surgery.

CONCLUSIONS

In the present study, the use of intravenous L-carnitine before CABG in patients suffering from mild heart failure did not influence the postoperative outcome except for inducing hypotension after surgery. The intraoperative and postoperative serum levels of lactate may not be affected by the preoperative use of L-carnitine; consequently, it may not be beneficial in reducing the risk for a postoperative rise in the lactate level in such patients.

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