





Original Article

Effect of L-carnitine on Troponin, IL-6 and HS-CRP levels after Coronary Artery Bypass Graft Surgery

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Abstract

Background: L-carnitine seems to be able to prevent complications after heart surgery using Cardiopulmonary bypass (CPB) and the adverse effects of pump usage. This study aimed to evaluate the effects of L-carnitine on cardiac biomarkers and operation characteristics after coronary artery bypass graft (CABG) surgery.

Methods and materials: In this randomized triple-blinded, sixty patients undergoing elective CABG surgery were divided into three equal groups to receive 2gr oral L-carnitine (group A), 5gr oral L-carnitine (group B) and placebo (group C) 2 hours before surgery. IL-6, creatinine, and high sensitivity C-reactive protein (HS-CRP) levels, CK-MB, cardiac troponin and inotrope administration in ICU or after CPB were recorded for all patients at baseline levels and at 8 or 24 hours postoperatively.

Results: There was an evidence of a significant difference in CPK-MB level and number of red blood cell packed used in group A was lower than group C ($p < 0.05$). The cardiac troponin level 8 hours after surgery significantly decreased in two treatment groups in comparison to group C ($p < 0.05$). The need for inotropic support after weaning from CPB, in B group was statistically higher than C group ($p = 0.021$).

Conclusion: Although L-carnitine adjunct therapy appears not to be associated with IL-6 and HS-CRP levels, it had beneficial effects on cardiac troponin and CPK-MB levels.

Keywords: Coronary artery bypass graft surgery, IL-6, HS-CRP levels, L-carnitine, Troponin

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Introduction

Cardiovascular disease (CVD) is the main cause

of death in the world (1). It is also one of the most important chronic illnesses, which its growing trend has direct connection to the development of urban

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communities, changing dietary patterns and reducing physical activity (2). Ischemic heart disease (IHD) refers to a partial to complete narrowing or obstruction of the coronary arteries following the atherosclerosis, spasm or the presence of a clot. In this disease, the affected artery cannot supply the requirements of myocardial muscle, which results in angina pectoris and myocardial infarction (3).

Coronary artery bypass grafting (CABG) is an effective way to reduce or eliminate IHD symptoms. In other words, surgical treatment is one of the methods for improving the quality of treatment that leads to reduced morbidity and mortality (4). Cardiopulmonary bypass (CPB) is a safe and effective technique in coronary artery bypass surgery, but the harmful effects on brain, lungs and heart should not be ignored (5, 6). Development of systemic inflammatory response and organ dysfunction are the untoward effects of CPB, which leads to increased morbidity or even mortality after surgery (7).

Many assessments have shown that interleukin 6 (IL-6) is one of the most well-described cytokines which acts as a pro-inflammatory factor and also plays an important role in ischemia-reperfusion injury (8). In addition, this multifunctional anti-inflammatory cytokine regulates synthesis of acute phase proteins such as fibrinogen, C reactive protein and albumin in liver (9-13). The assessment and measuring of C-reactive protein (CRP) using both standard and high-sensitivity CRP (HS-CRP) assays is becoming popular in clinical practice. The recent medical investigations also emphasize on the role of HS-CRP in cardiovascular disease (CVD) risk stratification and treatment decisions (14, 15). In addition, the cardiac troponin T is an known diagnostic tool for pathologies including myocardial cell necrosis such as acute myocardial infarction, unstable angina pectoris myocarditis, and the monitoring of reperfusion interventions (16, 17).

L-carnitine is involved in the transport of fatty acids to mitochondria and the consequent oxidation. In addition, it participates in the removal of mitochondrial metabolism products. The lack of L-carnitine or the Carnitine-acylcarnitine carrier has a particular adverse effect on cardiomyocytes resulting in cardiomyopathy, cardiac arrhythmias, or heart failure (18-20). On the other hand, investigations have shown that L-carnitine

can reduce inflammation in patients (21-23). It facilitates transfer of fatty acids to the mitochondrial matrix and has protective effects on heart(24). Therefore, L-carnitine seems to be able to prevent complications after heart surgery using CPB and the adverse effects of pump usage.

Despite the technological advancement in cardiopulmonary bypass equipment and using much anti-inflammatory or immunological therapy, there is no specific treatment to eliminate pump complications. The aim of this study was evaluation of L-carnitine on preventing inflammation after CABG surgery.

Methods

Through this randomized triple-blinded clinical trial study, 60 CABG surgery patients divided into three groups. Two interventions and a control, each containing 20 patients. Patients were assigned to each group using a table of random numbers. The entry criteria were candidates for elective on-pump CABG, aged 18-70 years old and known case of mild heart failure (EF: 40-50%).

Patients with history of seizures, epilepsy, cerebrovascular disease, liver failure (elevation of liver enzymes more than two times of normal), renal failure (serum creatinine higher than two times normal), receiving non-steroidal anti-inflammatory or corticosteroid drugs were excluded.

Background information such as demographic characteristics, history of diseases and any medication were basically recorded for all the participants. This study was approved by the ethics committee institutional review board of the National Research Institute of Tuberculosis and Lung disease (NRITLD) and Shahid Beheshti University of Medical Sciences. The study conducted according to the declaration of Helsinki. All participants signed the informed consent term. The study was registered in the Iranian registry of clinical trials (IRCT2016060528260N1).

Group A, patients received 2gr oral solution of L-carnitine while B group received 5gr of the same medication 2 hours before surgery, in addition to standard therapy. For control group, placebo was administered in liquid form in the same time. All patients received the same premedication and anesthetic drugs and the surgery was performed by the standard on-pump method. After CPB removal,

patients received epinephrine if the hemodynamic was not acceptable they transferred to the ICU while intubated and passed the standard weaning processes. To determine the effectiveness of L-carnitine, IL-6 and HS-CRP levels were recorded before and 24 hours after surgery beside some other clinical parameters. In addition, for all patients the elevation of blood creatinine kinase-muscle/brain (CK-MB) and cardiac troponin were measured 8 hours after surgery.

Data were analyzed using SPSS software V.24 (SPSS Inc.), and Microsoft excel. The normality of data was verified by the Shapiro-Wilk and Kolmogorov-Smirnov tests. The groups were compared in the study periods using Student's t-test and Mann-Whitney, if applicable. The differences between variables before and after the intervention were compared by paired t test or nonparametric Wilcoxon signed rank test. Continuous nonparametric distributed variables were compared by using the Kruskal-Wallis analysis of variance on ranks. Post hoc comparisons were performed with the Dunn method for all pairwise multiple comparisons (25). Normally distributed variables were displayed as mean \pm standard deviation and non-normally distributed variables were presented as frequency (percentage). The differences were considered significant at $p < 0.05$.

Results

Totally, sixty CABG candidates enrolled in this study, 20 in each group (Group A: 2gr L-carnitine, Group B: 5gr L-carnitine and Group C: control group). There was no significant difference between the groups in demographic and clinical characteristics of the participants, prior to surgery but aspirin usage (ASA) in A group and MI in B group were significantly higher ($p < 0.05$; Table 1).

Our result showed that there was no statistically difference between groups regarding surgery and anesthesia characteristics. Although the pump time and clamp time were lower in C and B groups than other two group but these differences were not significant ($p > 0.05$).

The need for inotropic support after weaning from CPB in B group was statistically higher than C group ($p = 0.021$). In contrast, the number of patients receiving inotropes in ICU were the same in all groups ($p = 0.979$).

The number of packed red blood cell units which were transfused during surgery in C group was significantly higher than A group ($p = 0.036$). However, we did not find any significant difference between studied groups regarding usage of fresh frozen plasma (FFP) and platelet (Plt) unites during and after that in ICU.

The results of these comparisons can be found in Table 2. The cardiac troponin level 8 hours after surgery was significantly decreased in two treatment groups in comparison to C group. Similarly, the level of CPK-MB in A group was significantly lower than the C group as well as CPK-MB level in A group was less than B group ($p = 0.032$ and 0.032 , respectively).

In all participants, although the both duration of mechanical ventilation and ICU stay were decreased in treatment groups but these reductions did not show any statistical evidence of correlation regarding the clinical interventions with group C ($p > 0.05$).

Further analysis showed that changes in creatinine, IL-6, HS-CRP and serum creatinine level before and after surgery were not statistically different between groups ($p = 0.493$).

Some complications such as atrial fibrillation (AF), myocardial infarction (MI), agitation and atelectasis were registered during first 24 hours after surgery. The results demonstrated no statistical difference between groups in this view ($p > 0.05$). The detail of biomarkers level and ICU characteristics are described in table 3.

Discussion

During the last decades, the mortality associated with isolated CABG surgery has been decreased (26-28). However, myocardial injury is still a significant issue in patients undergoing CABG (29). Carnitine deficiency is one of the most important causes of impaired metabolism, which mainly results in cardiomyopathy. Hence, carnitine administration as a treatment factor for the deficiency is supported (29-32). This investigation was designed to assess possible beneficial effects of two doses of oral solution of carnitine supplementation (2gr, 5gr and control groups) on postoperative cardiac function and metabolism in patients undergoing CABG.

Recent findings have revealed that possible mechanisms responsible for the observed influence of

Table 1: Baseline and demographic characteristics.

	Total	Group A, n=20	Group B, n=20	Control, n=20	P value#
Age-years	60.2 ± 11.2	59.7 ± 11.9	58 ± 13.8	63 ± 6.4	0.88
Gender (Male)	50 (83.3%)	16 (80%)	18 (90%)	16 (80%)	0.64
BMI (kg/m ²)	26.6 ± 3.5	26.7 ± 3.9	26 ± 3.7	26.9 ± 3.6	0.84
EF-%	47.4 ± 11.2	50.9 ± 67	46 ± 13.1	45.2 ± 12.6	0.54
Body Surface Area (m ²)	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.1	1.8 ± 0.2	0.38
CVA-no (%)	1 (5%)	0	0	1	0.88
Diabetes mellitus-no (%)	34 (56.6%)	8 (40%)	12 (60%)	14 (70%)	0.31
Hypertension-no (%)	41 (68.3%)	10 (50%)	16 (80%)	15 (75%)	0.13
Hyperlipidemia-no (%)	30 (50%)	6 (30%)	12 (60%)	12 (60%)	0.11
Opium abuse rate (%)	13 (21.6%)	3 (15%)	4 (20%)	6 (30%)	0.66
MI (%)	6 (10%)	2 (10%)	4 (20%)	0	0.02
Aspirin (%)	66 ± 9	65 ± 11	71 ± 12 **	64 ± 8	0.002
Cigarette Smoking-no (%)	27 (45%)	11 (55%)	8 (40%)	8 (40%)	0.7

Table 2: Operation characteristics and blood products consumption.

	Group A, n=20	Group B, n=20	Group C, n=20	P value#
Anesthesia duration-hour	4.85 ± 1.22	4.77 ± 0.84	5.44 ± 1.34	0.374
Pump time- minute	117.87 ± 45.1	121.33 ± 34.7	116 ± 28.93	0.981
Clamp time- minute	71.73 ± 26.08	62.62 ± 21.73	64.8 ± 18.23	0.374
Inotrope after CPB -no (%)	17 (86.7)	19 (93.3)**	15 (73.3)	0.024
Inotrope in ICU -no (%)	11 (55)	11 (55)	11 (55)	0.979
OR Packed Cell -unit	0.73 ± 1.2*	0.8 ± 0.86	1.6 ± 0.91	0.028
O.R.FFP-unit	0.2 ± 0.56	0.33 ± 0.72	0.67 ± 0.9	0.208
ICU Packed Cell-unit	0.93 ± 1.33	1.13 ± 1.59	0.33 ± 1.047	0.053
ICU.FFP-unit	0.4 ± 1.12	0.6 ± 1.18	0.7 ± 1.2	0.586
OR Plt-unit	0	0	0	-
ICU Plt-unit	0	0.2 ± 0.77	0	0.38

*P<0.05 Group A vs. Group C; **P<0.05 Group B vs. Group C; ***P<0.05 Group A vs. Group B; P value # Kruskal-Wallis between-group

L-carnitine in MI are multifactorial. L-carnitine may improve mitochondrial energy metabolism in heart by facilitating the transport of long-chain fatty acids from cytosol to mitochondrial matrix, reducing ischemia induced by long-chain fatty acid concentrations, and replenishing depleted carnitine concentrations seen in ischemic, infarcted, and failing myocardium (33-39).

Therewith, L-carnitine have beneficial effects on left ventricular remodeling which accompanied by a significant reduction in left ventricular volumes after MI (30). Multiple clinical trials showed that L-carnitine reduced infarct size leading to a greater degree of myocardial salvage (40-42). Lack of carnitine is the main cause of impaired metabolism,

which commonly results in cardiomyopathy (30).

operative complications. Indeed, L-carnitine groups

Table 3: Biomarkers level and other ICU characteristics.

	Group A, n=20	Group B, n=20	Control, n=20	P value
Mechanical ventilation duration-hour	15.7 ± 15.2	13.7 ± 6.7	14.2 ± 6.8	0.051
Cardiac Troponin	0.56 ± 0.83*	0.41 ± 0.92**	1.94 ± 2.63	0.049
Serum creatine phosphokinase (CPK_MB)	55.13 ± 33.5*	67.8 ± 32.4***	64.87 ± 26.7	0.002
HS- CRP – before- mg/l	6.58 ± 7.14	6.38 ± 6	7.9 ± 6.4	0.247
HS- CRP-after - mg/l	18.9 ± 0.0001	16.4 ± 5.2	18.5 ± 1.5	0.138
IL 6 –before- pg/ml	1.76 ± 2.83	4.24 ± 6.07	1.02 ± 0.077	0.648
IL 6 –after- pg/ml	33.7 ± 22.7	34.7 ± 30.4	30.4 ± 20.57	0.789
Serum Creatinine level-before Mg/dl	1.17 ± 0.4	1.13 ± 0.53	1.19 ± 0.17	0.999
Serum Creatinine level-after- Mg/dl	1.6 ± 0.8	1.6 ± 0.7	1.6 ± 0.3	0.493
Atrial fibrillation (AF)	3 (15)	2 (10)	2 (10)	0.848
Post Op. MI	-	1 (5)	-	0.368
Agitation	-	2 (10)	-	0.129
Atelectasis	-	-	1 (5)	0.368
ICU stay-day	3.1 ± 1.1	3.3 ± 0.8	4.2 ± 1.1	0.051

Plus-minus values are means ± SD. CPB cardiopulmonary bypass. HS- CRP

*P<0.05 Group A vs. Group C; **P<0.05 Group B vs. Group C; ***P<0.05 Group A vs. Group B; P value # Kruskal-Wallis between-group

L-carnitine has been investigated as one of the several agents which is effective in prevention of the clinical complications associated with ischemia-reperfusion injury during cardiac surgery (43). The results of our study revealed that treatment with L-carnitine had significant effects on the levels of CK-MB, use of inotrope after CPB, cardiac troponin and intraoperative packed cell transfusion in patients undergoing CABG surgery ($p < 0.05$). Although there was a reduction in mechanical ventilation time and ICU stay in treatment groups, this decline was not significant ($p > 0.05$), which could partly be explained by the small sample size in our study. On the other hand, L-carnitine did not have any effect on inflammatory markers levels (IL-6 and HS-CRP). Similarity, inotrope in ICU did not change by taking L-carnitine. By comparison, neither creatinine level ($p = 0.49$) nor mechanical ventilation and ICU duration ($p = 0.051$) were significantly associated with receiving treatment. Although the reduction of length of ICU stay and mechanical ventilation time was not statistically significant, but they are clinically important which play a vital role in the survival or post-

had shorter ICU stay and mechanical ventilation time than control group which are the utmost important indicators for cost estimation in ICU setting (44).

According to the investigations, pharmacological therapy in combination with reperfusion can attenuate myocardial dysfunction associated with acute coronary syndrome (45, 46). It seems that, in patients who suspected to acute myocardial infarction, oral L-carnitine supplementation could decrease the infarct size and cardiac biomarkers. In fact, L-carnitine supplementation prevents ventricular enlargement and ventricular dysfunction, and even diminished total cardiac events including cardiac deaths and nonfatal infarction (42). The present study has demonstrated that the addition of L-carnitine to standard therapy in CABG patients before surgery has beneficial effects, which the troponin level in treatment groups, verified this result. In addition, the packed red blood cell usage that transfused during surgery in C group was significantly higher than B group ($p = 0.036$) which may be related to higher clamp time in this group. In the other words, the present study has demonstrated that

the addition of oral L-carnitine to standard treatment before intervention reduces the levels of troponin and packed red blood cell usage, indicating diminished myocardial injuries which these findings supported by previous findings in the literature (47).

Myocardial ischemia as a metabolic phenomenon in CABG patients leads to stress imposed during CPB, obligatory interruption of coronary blood flow during aortic cross clamp and reperfusion after aortic cross clamp release. These side effects affect patients in the form of hemodynamic instability, arrhythmias and even greater use of inotropes. In fact, the lack of oxygen which imposed during CPB induce some serious side effects such as increased need of inotropes, prolonged mechanical ventilation, prolonged ICU stay and even increase in the morbidity and mortality rate of patients. According to this study, the two treated groups with L-carnitine had higher usage of inotrope but there was a significant difference between the B and C groups in terms of receiving inotropes following surgery ($p=0.021$). In fact, patients with a higher pump time showed more needs for taking inotropes and higher inotrope use following the surgery.

In another view, supplementation with oral L-carnitine reduces superoxide production (48) and the function of endothelial nitric oxide-synthase (NO) (49). Indeed, L-carnitine enters the NO production cycle and increase the rate of NO. Therefore, the dilated vessels cause a drop in blood pressure (47). In our patients, this reduction was temporary because the blood pressure reduction was not observed in ICU patients. Since, the pulse pressure and thereby blood pressure can be used for decision about early treatment strategy especially associated with usage of inotropic agents, Therefore blood pressure reduction leads to more inotrope administration in CABG patients (50).

Randomized trials have revealed that patients with acute coronary syndrome who received L-carnitine as an adjunct therapy had improved outcomes comparing to patients who were not treated (51-53). Treatment with L-carnitine leads to a significant reduction of these enzymes that is attributable to a decrease in oxidative stress and stabilization of cardiomyocyte cell membranes. The infarct size, cardiac mortality rates and in-hospital events would decrease if the occluded coronary arteries were rapidly

reperfused. However, other degrees of reperfusion injuries have been stated following the intervention. These injuries result in an increase in plasma CK-MB and troponin levels which this increment in myocardial markers is strongly related to adverse clinical outcomes after intervention (54). The pharmacological treatment in addition to reperfusion therapy can attenuate myocardial dysfunction associated with acute coronary syndrome (45-47, 54). The current study has represented that the addition of L-carnitine (dosage 2gr) two hours before surgery can reduce the levels of CK-MB and troponin which indicate a reduction in myocardial injuries. The above data are consistent with previous findings (47, 55). Current studies confirmed that the cardiac troponins are considered as offering the highest diagnostic and prognostic value (56). On the other hand, these markers can be used for the prediction of future left ventricular dysfunction. They can be used for early detection of necrosis, even prior to significant increase in the levels of CK-MB (57, 58).

The limitation of this assessment is related to the small sample size in each group which seems has a significant impact on the results. Therefore, larger samples need to be further investigated to confirm our preliminary results. We would recommend conducting similar trials with larger sample sizes and different dosage of L-carnitine to investigate cardiac and inflammation biomarkers.

Conclusion

Our results demonstrated that among mild heart failure patients undergoing CABG surgery, oral L-carnitine 2 hours before surgery reduced cardiac troponin and CK-MB as biomarkers of cardiac injury, whereas it did not have any impact on clinical parameters.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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