

Randomized Trial of Carnitine for the Prevention of Perioperative Atrial Fibrillation

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Atrial fibrillation (AF) is one of the most common complications in patients who undergo coronary artery bypass graft surgery (CABG). The aim of this study was to evaluate the effect of L-carnitine administration on postoperative AF and the levels of C-reactive protein (CRP) following CABG. The effects of L-carnitine on the incidence of acute kidney injury after CABG were also assessed. One hundred thirty-four patients undergoing elective CABG, without a history of AF or previous L-carnitine treatment, were randomly assigned to an L-carnitine group (3000 mg/d L-carnitine) or a control group. CRP levels, as a biomarker of inflammation, were assessed in all the patients before surgery as baseline levels and 48 hours postoperatively. Neutrophil gelatinase-associated lipocalin, as a kidney biomarker, was also measured in the patients before surgery and 2 hours thereafter. The incidence of AF was 13.4% in our population. The incidence of AF was decreased in the L-carnitine group (7.5% in the L-carnitine group vs 19.4% in the control group; $P = 0.043$) and the postoperative CRP level (8.79 ± 6.9 in the L-carnitine group, and 10.83 ± 5.7 in the control group; $P = 0.021$). The postoperative neutrophil gelatinase-associated lipocalin concentration demonstrated no significant rise after surgery compared with the preoperative concentration (72.54 ± 20.30 in the L-carnitine group vs 67.68 ± 22.71 in the placebo group; $P = 0.19$). Our study showed that L-carnitine administration before CABG might inhibit and reduce the incidence of AF after CABG. It seems that a rise in the CRP level, as an inflammation marker, may be associated with the incidence of AF. Inflammation as measured by CRP was also reduced in the carnitine group, compared with the control group.

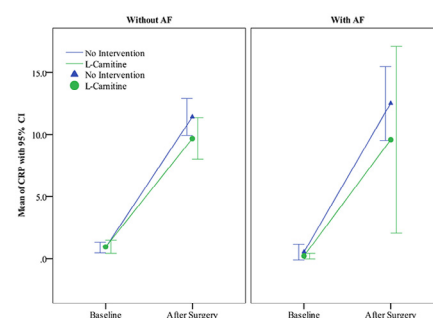
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INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia following coronary artery bypass graft (CABG) surgery.¹ The reported incidence of postoperative AF ranges from 25% to 40% post CABG, and up to 62% after a combined CABG and valve procedure.^{1,2} The occurrence of postoperative AF has been associated with a

prolonged length of hospital stay, intensive care unit readmission, and a greater need for reintubation.^{3,4} AF can also cause atrial pump dysfunction and ventricular filling impairment with an increase in the incidence of heart failure and development of stroke, contributing to a rise in post-CABG disability and mortality.^{5,6} Thus, it is crucial to prevent the occurrence of AF following CABG. Carnitine (3-hydroxy-4-N-trimethylaminobutyric acid) is an essential amino acid that is necessary for the transport of long-chain fatty acids from the cytoplasm of cells to the mitochondrial matrix facilitating energy production. Carnitine deficiency is associated with the accumulation of excess acyl-CoA esters and the disruption of intermediary metabolism. Its supplementation increases carnitine plasma concentrations. The use of carnitine reduced ischemia or reperfusion-induced injury in the myocardium in a number of experimental models. There are also no reports of toxicity from



The changes in hs-CRP levels and incidence of AF between groups.

Central Message

L-Carnitine administration before coronary artery bypass graft surgery reduces the incidence of postoperative atrial fibrillation.

Perspective Statement

Atrial fibrillation is one of the most common complications in patients who undergo coronary artery bypass graft surgery and has been associated with a prolonged length of hospital stay, intensive care unit readmission, and a greater need for reintubation. The aim of this study was to evaluate the effect of L-carnitine administration on postoperative AF following CABG.

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an overdose of L-carnitine.⁷ Recent studies have claimed that AF after CABG may be related to the inflammatory response, and that L-carnitine, as an inflammatory inhibitor, may diminish the incidence of AF after CABG.⁸ However, because AF has significant interpatient differences and the efficacy of the drugs can be diverse among patients, investigating the effects of L-carnitine on post-CABG AF is of great clinical significance. Some studies have revealed that the time-dependent C-reactive protein (CRP) level, as a biomarker of inflammation, tends to significantly rise after surgery as a biomarker of inflammation.⁶

Acute kidney injury (AKI) is another serious complication of CABG that causes a postoperative increase in serum creatinine; it is detected in 5%-20% of patients.⁹ Moreover, AKI necessitates dialysis in 1% of patients and is associated with extreme in-hospital morbidity and mortality.⁹ Postsurgery AKI has been shown to be associated with the systemic inflammatory response during surgery and ischemia or reperfusion injury. L-Carnitine, as an antiinflammatory agent, may reduce the systemic inflammatory response and consequently improve the kidney function.⁷

In this randomized controlled trial, we assessed whether the administration of L-carnitine (3 g/d), commenced 2 days before selective CABG and continued for 2 days postoperatively, could prevent postoperative AF as compared with a control group. We also evaluated the effects of L-carnitine on the prevention of AKI following CABG as another end point by using neutrophil gelatinase-associated lipocalin (NGAL) as a kidney biomarker.

METHODS

This study was registered at the Iranian Registry of Clinical Trials (registration # 201301028698N7) and was approved by the Ethics Committee of Tehran Heart Center, a referral hospital. From April to December 2013, a total of 195 consecutive patients, who were scheduled to undergo CABG at Tehran Heart Center, were enrolled. The exclusion criteria comprised history of any preoperative supraventricular arrhythmias, concomitant valve surgery, history of the use of antiarrhythmic drugs except for beta-blockers and calcium-channel blockers, history of seizure or epilepsy, history of hypersensitivity to L-carnitine, chronic liver insufficiency (liver enzyme levels > 3 times the upper limit of normal), chronic kidney disease (stages IV and V), history of the use of antiinflammatory medications except for aspirin for at least 2 weeks before admission, hypothyroidism, and consumption of magnesium before CABG. To detect an effect size of at least 0.51 (30 mg/L difference of C_{max} [CRP kinetic parameter] levels) between groups with standard deviation of 58.5 mg/L,¹⁰ with 80% power and 5% type I error, we needed 61 samples in each group. Considering 10% probability of sample loss increased the sample size to 67 in each group). Thus, 180 patients were included in the study population and randomly assigned to an L-carnitine group (3000 mg/d of L-carnitine, $n = 90$) or a control group ($n = 90$) via the permuted block randomization method, as is described in the Consolidated Standards of Reporting Trials (CONSORT) flowchart (Figure). The whole study population underwent on-pump cardiopulmonary bypass surgery.

All the patients underwent preoperative electrocardiography (ECG), chest X-ray, echocardiography, and selective coronary angiography. They also signed a consent form before surgery. Finally, 134 patients met the selection criteria for the randomized trial, with 67 patients assigned to receive L-carnitine and 67 to be included in the control group. An oral solution (1 g, 3 times a day) of L-carnitine (So.Se.PHARM, Italy) was administered to the 67 patients in the L-carnitine group from 2 days before the scheduled surgery to 2 days afterward, whereas those in the control group did not receive L-carnitine or a placebo. The assessors were blinded to the intervention groups. Continuous ECG monitoring was carried out for at least 7 days for all the patients. Optimization of magnesium serum levels and beta-blockers are considered for all patients undergoing CABG without contraindication. We continued b-blockers for those patients taking these medications preoperatively to avoid b-blockade withdrawal. Atorvastatin was also considered by some cardiologists to prevent POAF for statin-naïve patients. AF was defined as the occurrence of at least 1 episode of AF (with or without symptoms) lasting for over 5 minutes and confirmed by ECG. The time of the onset of AF and its duration were observed and recorded. The adverse reactions associated with L-carnitine, as well as the complications, were followed up in both groups. The primary end point of the trial was the occurrence of postoperative AF.

As some other studies have revealed that the time-dependent CRP level tends to significantly rise after surgery and reach a peak within 48-72 hours ($P < 0.001$),^{6,11} we assessed the CRP levels in all the selected patients before surgery and 48 hours postoperatively. High-sensitivity C-reactive protein (hs-CRP) was measured via the KRIPTOR ultrasensitive immunofluorescent assay (Brahms, Hennigsdorf/Berlin, Germany) with a detection limit of 0.06 mg/mL. Additionally, NGAL, as an emerging kidney biomarker, was measured in the patients before surgery as baseline levels and 2 hours after surgery to evaluate the effects of L-carnitine on the incidence of post-CABG AKI (defined as $\geq 50\%$ or 0.3 mg/dL increase in serum creatinine during a 48-hour period according to the Acute Kidney Injury Network criteria) based on preclinical studies in animal models. In these studies, NGAL was identified as one of the most upregulated genes and proteins in the kidney very early in the course of AKI, especially within 2 hours of CABG.¹² The patients' serum creatinine levels before and then after surgery were also evaluated in the 2 groups until discharge from the hospital. Twenty-four hours' urine specimens were collected, and creatinine clearance was estimated using both Cockcroft-Gault and Modification of Diet in Renal Disease-7 formulas.

Statistical Analysis

The continuous data are described as means and standard deviations or medians with 25th and 75th percentiles when the data had a skewed distribution, and they were compared between the intervention and the control groups using the Student *t* or the Mann-Whitney *U* tests. The categorical variables are expressed as frequencies and percentages, and they were compared between the treatment and the control groups using the chi-square or the Fisher exact test. To adjust the effect of intervention on AF for sex, we

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