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L-Carnitine Supplementation Reduces Short-Term Neutrophil-Lymphocyte Ratio in Patients Undergoing Coronary Artery Bypass Grafting

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This study aims to investigate whether preoperative L-carnitine supplementation affects the neutrophil-to-lymphocyte ratio (NLR) in patients undergoing coronary artery bypass grafting surgery. The neutrophil-to-lymphocyte ratio is an inflammatory marker that has proven usefulness for predicting postoperative complications in coronary artery bypass surgery. A lot of studies concerning the role of L-carnitine in the immune system have been performed, contradictory results have been reported on its effects on absolute numbers of WBC subtypes. This randomized, double-blinded, placebo-controlled study was conducted among patients scheduled for coronary artery bypass grafting surgery between June 2012 and December 2013 in our cardiovascular surgery clinic. A total of 60 consecutive patients were randomized and divided into 2 groups. The first group received 2 g of L-carnitine in 1000 mL of 0.9% saline solution infused over 24 hours for each of the 3 preoperative days (L-carnitine group, n = 30), or only 1000 mL of 0.9% saline solution for the same time period (placebo group, n = 30). The basal values of leukocyte,

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neutrophil, lymphocyte counts, and neutrophil to lymphocyte ratio were similar in the 2 groups. After L-carnitine supplementation (just before surgery), leukocyte and neutrophil counts of the L-carnitine group were significantly lower than those of the placebo group (7.7 ± 1.5 versus 9.7 ± 2.6, $P < 0.001$ and 4.6 ± 1.3 versus 6.5 ± 2.2, $P < 0.001$). On postoperative day 1, lymphocyte counts were significantly higher in the L-carnitine group (1.1 ± 0.6 versus 0.8 ± 0.9, $P < 0.001$). Moreover, the increase in NLR was significantly lower in the L-carnitine group at postoperative day 1 (20.7 ± 13.8 versus 10.8 ± 4.1, $P < 0.001$). Preoperative L-carnitine supplementation may reduce neutrophil-lymphocyte ratio during the early postoperative period of coronary artery bypass grafting surgery.

Key words: L-carnitine – Neutrophil-to-lymphocyte ratio – Coronary artery bypass grafting

Coronary artery bypass grafting (CABG) is the most common procedure in cardiovascular surgery. But the procedure itself is associated with significant morbidity and mortality. Preoperative renal impairment (increased serum creatinine); heart failure (reduced ejection fraction); diabetes mellitus; and duration of cardiopulmonary bypass (CPB) might be considered as independent risk factors leading to increased morbidity and mortality after CABG.[1] The definition of prognostic risk predictors for CABG is very important for taking effective preventive measures. Some predictors are available for the risk assessment of CABG. There are a number of studies related to biomarkers of inflammation for predicting cardiovascular risk.[2] Total white blood cell (WBC) count has been extensively studied as a prognostic risk predictor for CABG.[3] However, specific subtypes of WBCs and their ratios to each other have been shown to be more valuable measurements than WBC count alone.[4,5] A well-known marker, the neutrophil to lymphocyte ratio (NLR) has been recently accepted as an independent risk predictor for CABG.[6]

L-carnitine is a natural amino acid that plays an important role in fatty acid metabolism. Its major function is the transport of long-chain fatty acids into mitochondria for oxidation, particularly in the heart and skeletal muscles.[7] L-carnitine is an endogenous cofactor that enhances carbohydrate metabolism and reduces the intracellular buildup of toxic metabolites in ischemic conditions.[8] The protective effect of L-carnitine against cell killing by oxygen radicals is well known.[9] It also protects against myocardial ischemia, improves cardiac performance, and restores high-energy phosphate sources in myocardial cells.[10] Furthermore, Mast *et al*[11] demonstrated improved effects of L-carnitine supplementation on protective immunity. L-carnitine is also known to enhance neutrophil and macrophage functions in rats at lower concentrations.[12] However, the effect of L-carnitine on NLR still needs to be clarified. Hence, in this double-blinded, randomized, and placebo-controlled study, we aimed to evaluate whether preoperative intravenous (IV) L-carnitine supplementation has effects on WBCs, total leukocytes, neutrophils, lymphocytes, and especially NLR in patients undergoing CABG.

Materials and Methods

This randomized, double-blinded, placebo-controlled study was performed after approval of the local ethics committee. Written informed consent was obtained from the 60 patients included in the study. The patients were evaluated between June 2012 and December 2013 in our cardiovascular surgery clinic. Eighty-five eligible adult patients were scheduled for CABG with CPB. Twenty-five of them were excluded from the study for the following reasons: CABG surgery associated with valvular replacement or any other procedure, an ejection fraction less than 30%, emergent coronary revascularization, patients with unstable angina pectoris, circulatory support with intra-aortic balloon pump before surgery, hepatic failure, autoimmune disease, connective tissue disease, systemic inflammatory disease, re-operation, tumor, acute or chronic renal failure (preoperative renal insufficiency was defined as a serum creatinine level ≥ 1.5 mg/dL), respiratory impairment, peripheral vascular disease, coagulopathy and a history of cerebrovascular disease within the last 6 months. Because of the possible interrelation between blood cell counts and postoperative wound infection and re-explora-

tion for bleeding, such patients were also excluded from the study.

Patients were randomly assigned to 2 groups to receive either 2 g of L-carnitine (MEDICE Arzneimittel Pütter GmbH & Co KG, Iserlohn, Germany) in 1000 mL of 0.9% saline solution infused over 24 hours for each of the 3 preoperative days[13] (L-carnitine group, n = 30), or only 1000 mL of 0.9% saline solution for the same time period (placebo group, n = 30). Randomization assignment of patients to the groups was performed by opening an envelope. The preparation of the study drug was performed by a person unrelated to this study. Study personnel, patients, and individual participating in the data collection and data analysis were blinded to the treatment assignment. All patients had coronary artery disease with a varying degree of stenosis of the left anterior descending coronary artery. Patients having left main or left main equivalent coronary artery disease were also included in the study.

Preoperatively, all patients received their standard cardiac medications. Acetylsalicylic acid and nonsteroidal anti-inflammatory drugs were stopped 5 and 1 days before surgery. They were premedicated with oral midazolam before arrival to the operating room. The patients were monitored (Datex-Ohmeda Avance, GE Healthcare, Helsinki, Finland) by continuous electrocardiography, pulseoximetry, capnography, entropy (state and response), central venous pressure (CVP), and invasive blood pressure. Anesthesia was induced by etomidate 0.2 to 0.5 mg/kg and fentanyl 3 μg/kg in addition to rocuronium 0.9 mg/kg for tracheal intubation. For the maintenance anesthesia, remifentanil was infused at 0.25 μg/kg/min and rocuronium 0.1 mg/kg hourly following induction.

Median sternotomy was performed. All patients underwent conventional CABG using cardiopulmonary bypass by the same surgical team. The patients were anticoagulated with 300 U/kg of heparin to provide an activated clotting time (ACT) higher than 400 seconds. Cardiopulmonary bypass was started following the cannulation of the aorta and the right atrium. Membrane oxygenators (Hilite 7000, Medos, Stolberg Germany) were primed with 1000 mL of Ringer's Lactate and 100 mL of 20% mannitol to maintain a hematocrit level of 26%. None of the patients received aprotinin. An additional 100 mL of 20 % mannitol was given just before declamping of the aorta. A nonpulsatile pump flow was set at with 2.4 L/min/m^2 to maintain mean arterial pressure between 50 and 70 mmHg. Cardiopulmonary bypass was performed at mild hypothermia with a core temperature of 32°C. Intermittent antegrade crystalloid cardioplegia with blood in a ratio of 4:1 or 8:1 was used for myocardial protection. Protamine sulfate was used to antagonize the heparin. The patients were rewarmed to a temperature of 37°C. When the heart was paced as the atrioventricular sequential mode at a rate of approximately 90 beats/min (BPM), the patients were weaned from CPB. During CPB, when required, Isolyte-S was added to the CPB circuit to keep volume above the minimal level of the venous reservoir.

Prior to the transfer from the operating room to the intensive care unit (ICU), a remifentanil infusion was continued in all patients. Sedation was stopped when the patients were hemodynamically stable, normothermic (core temperature >36.5°C), and had acceptable ventilatory parameters (FiO_2 < 50 %, PaO_2 > 60 mmHg). Extubation was performed as soon as the following criteria were met: hemodynamic stability with no significant arrhythmia, chest tube drainage <100 mL/h, patient awake and responding to the commands, and adequate respiratory parameters (FiO_2 < 45 %, peak end-expiratory pressure < 7.5 cm H_2O, respiratory rate >10 BPM, and minute ventilation >100 mL/kg/min).

Intraoperative hemodynamic variables, mean arterial pressure (MAP), heart rate (HR), and CVP were recorded to analyze statistically. Each of them was recorded before CPB, during CPB, and at the end of surgery. Any hypotension (MAP < 60 mmHg) or bradycardia (HR < 60 BPM) episode longer than 10 minutes in the ICU follow-up period, inotropic drug need, or intra-aortic balloon pump (IABP) support were also recorded. Any dysrhythmia (any rhythm other than sinus) that appeared during the ICU follow-up period was recorded for analysis.

After CPB and in the ICU, additional fluid (Isolyte-S or fresh frozen plasma) was administered according to routine postoperative care. Red blood cells were transfused when hemoglobin concentration fell below 6 mg/dL during extracorporeal circulation or below 8.5 mg/dL after operation.

Blood was sampled from a peripheral vein for total leukocyte count, differential count (neutrophils and lymphocytes), and NLR. The time points for sampling blood were as follows: just before L-carnitine infusion (for basal values); just before surgery (after 3 days of L-carnitine supplementation or placebo administration); and on postoperative days 1 and 5. Neutrophil and lymphocyte counts

Table 1 Demographic features and perioperative variables of the two groups

Variables	L-carnitine (group 1, n = 30)	Placebo (group 2, n = 30)	*P*
Age (y), mean ± SD	64.6 ± 11.2	67.0 ± 9.4	0.381
Male, n (%)	20 (66.7)	17 (56.7)	0.426
Preoperative MI, n (%)	5 (16.7)	3 (10.0)	0.706
DM, n (%)	14 (46.7)	9 (30.0)	0.184
HT, n (%)	11 (36.7)	18 (60.0)	0.071
Smoking, n (%)	16 (53.3)	15 (50.0)	0.796
Previous PCI, n (%)	3 (10.0)	5 (16.7)	0.448
CPB time (min), mean ± SD	90.4 ± 27.7	81.7 ± 25.5	0.212
Cross-clamp time (min), mean ± SD	47.0 ± 17.9	44.7 ± 15.4	0.590
Bleeding (mL),[a] mean ± SD	630.3 ± 214.5	673.2 ± 278.3	0.498
Red Blood Cell (Unit),[b] mean ± SD	1.82 ± 0.89	1.39 ± 1.08	0.069
Mechanical ventilation (hours), mean ± SD	6.0 ± 2.4	6.5 ± 3.6	0.834
Dysrhythmia,[c] n (%)	3 (10)	5 (16.67)	0.456
ICU stay (d), mean ± SD	1.6 ± 0.7	1.9 ± 0.7	0.079
PO inotropic drug need, n (%)	5 (16.6)	8 (26.7)	0.068
PO IABP, n (%)	1 (3.33)	2 (6.67)	0.561
Hospital stay (d), mean ± SD	5.7 ± 1.7	7.2 ± 1.6	**<0.001**
Increased plasma creatinine ≥1.5 mg/dL or >25%, n (%)	2 (6.67)	5 (16.67)	0.235

DM, diabetes mellitus; HT, hypertension; IABP, intra-aortic balloon pump; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PO, postoperative.

[a]Total bleeding during the postoperative first 24 hours.

[b]Total unit of packed red blood cell transfusion during ICU follow-up.

[c]Any rhythm other than sinus during postoperative day 1.

were derived from differential percentages of leukocytes measured by automatic cell counters (Sysmex KX-21, Sysmex International Reagents Co, Ltd, Kobe, Japan). The determination of NLR was entrusted to one of our authors who was blinded to the samples collected from the groups. Serum creatinine levels were measured from different blood samples at the same time points with the NLR measurement. Serum creatinine was analyzed with an enzymatic assay method (CREA Plus, BEN Biochemical Enterprise, Milano, Italy) on a chemistry analyzer (ChemWell 2910, Awareness Technology, Inc, Palm City, Florida). Mortality in 30 days after surgery and renal replacement therapy were also recorded.

Statistical Analysis

Collected data were analyzed by a statistical software program (SPSS, version 15.0, SPSS, Inc, Chicago, Illinois) in computerized media. Continuous variables were expressed as mean ± SD and categorical data were denoted as numbers (%) where appropriate. The variables were investigated using visual (histogram, probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether or not they were normally distributed. Statistical evaluation was performed by χ^2 or Fisher's exact test, independent sample *t* test and Mann-Whitney *U* test for data with abnormal distribution. Values of $P < 0.05$ were considered to be statistically significant.

Results

A total of 60 patients were studied: 30 in the L-carnitine group and 30 in the placebo group. All demographic features were similar in the 2 study groups (Table 1). There were no statistically significant differences between the 2 groups with respect to CPB time and aortic cross-clamp time. Statistical values of those variables are also shown in Table 1. During the postoperative period, 5 (16.6%) patients in the L-carnitine group and 8 (26.7%) patients in the placebo group needed inotropic drug support. This difference between the 2 groups was not statistically significant ($P = 0.068$). With respect to the amount of bleeding (630.3 ± 214.5 mL in the L-carnitine group and 673.2 ± 278.3 mL in the placebo group), during the first 24 hours, there was no statistical difference between the 2 groups ($P = 0.498$). The incidence of postoperative hypotension, defined as MAP below 60 mmHg over 10 minutes (10% in each group) and bradycardia, defined as below 60 BPM over 10

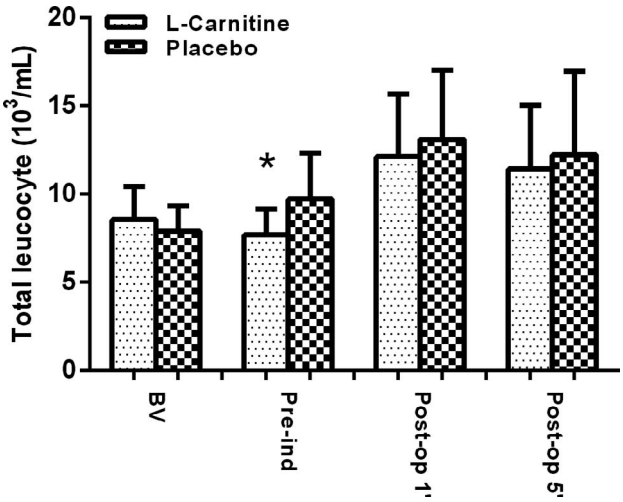

Fig. 1 Values of total leukocytes in different time points. Each bar represents 30 patients. Data were expressed as mean ± SD. *$P < 0.001$, significantly different from placebo. BV, basal values; pre-ind, pre-induction time; post-op 1′, postoperative day 1; post-op 5′, postoperative day 5.

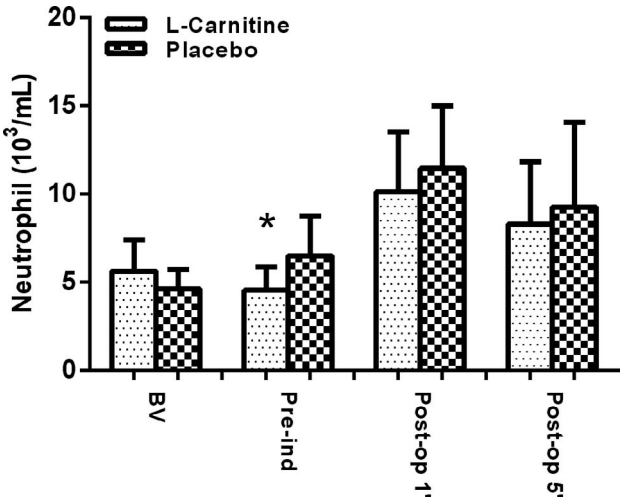

Fig. 2 Values of neutrophils in different time points. Each bar represents 30 patients. Data were expressed as mean ± SD. *$P < 0.001$, significantly different from placebo.

minutes (10% in the L-carnitine group and 6.67% in the placebo group) were similar between the 2 groups. One patient in the L-carnitine group and 2 patients in the placebo group suffered from low-output syndrome requiring an IABP. While mean hospital stay was 5.7 ± 1.7 in the L-carnitine group, it was 7.2 ± 1.6 in the placebo group. This difference was statistically significant ($P < 0.001$).

There were no significant differences between the 2 groups with respect to basal values of total leukocyte, neutrophil, lymphocyte counts and NLR (Figs. 1–4). After L-carnitine infusion for 72 hours (just before surgery), total leukocyte count and neutrophil count of the L-carnitine group were significantly lower than those of the placebo group (7.7 ± 1.5 versus 9.7 ± 2.6, $P < 0.001$ and 4.6 ± 1.3 versus 6.5 ± 2.2, $P < 0.001$; Figs. 1 and 2). On the first postoperative day, total leukocyte and neutrophil counts of the L-carnitine and placebo groups were statistically similar, but the lymphocyte count was significantly higher (1.1 ± 0.6 versus 0.8 ± 0.9, $P < 0.001$) and NLR was significantly lower in the L-carnitine group (10.8 ± 4.1 versus 20.7 ± 13.8, $P < 0.001$; Figs. 3 and 4). L-carnitine and placebo groups were statistically similar with respect to leukocyte count, neutrophil count, lymphocyte count, and NLR at postoperative day 5 (Figs. 1–4).

When we looked at the intraoperative hemodynamic parameters, MAP, HR, and CVP were similar between the groups, except MAP measured at the end of surgery. MAP measured at the end of surgery was significantly higher in the L-carnitine group ($P < 0.001$).

One of the patients in the placebo group died on postoperative day 7 because of acute kidney injury needing hemodialysis. Three patients of the placebo group and 1 patient of the L-carnitine group were excluded from the study because of development of intractable unstable angina pectoris during the supplementation period, requiring urgent operation. There was no mortality in the L-carnitine

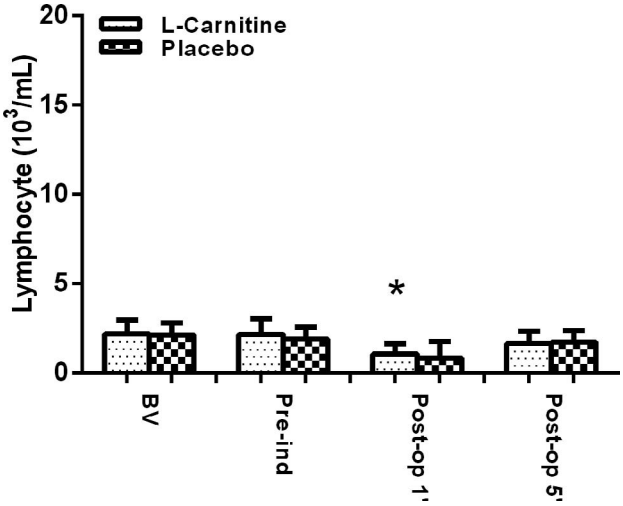

Fig. 3 Values of lymphocytes in different time points. Each bar represents 30 patients. Data were expressed as mean ± SD. *$P <$ 0.001 significantly different from placebo.

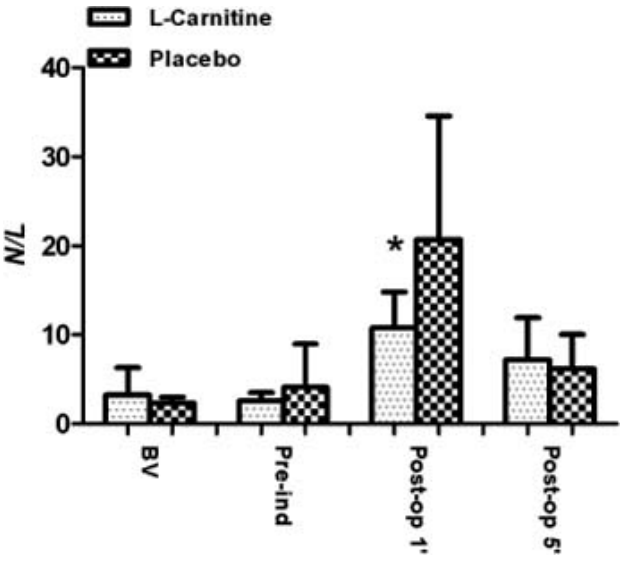

Fig. 4 Values of neutrophil/lymphocyte ratios in different time points. Each bar represents 30 patients. Data were expressed as mean ± SD. *$P < 0.001$, significantly different from placebo.

group. No sternal wound infection developed in any study patient. One patient in the L-carnitine group and 2 patients in the placebo group required revision for major postoperative bleeding. We added 7 new eligible patients to the study for fulfilling the number to the total of 60. The number of patients with increased plasma creatinine ≥1.5 mg/dL or >25% of baseline value at any time of study period was 2 (6.67%) in the L-carnitine group and 5 (16.67%) in the placebo group being statistically insignificant ($P = 0.235$). Only 1 patient in the placebo group required renal replacement therapy and, as mentioned before, this patient died at postoperative day 7.

Discussion

This double-blinded, randomized, and placebo-controlled study aims to examine the effects of L-carnitine on the NLR of the patients undergoing CABG. Thus, the alterations in total leukocyte, neutrophil, and lymphocyte counts just after 3 days of L-carnitine infusion were considered with respect to the baseline values. As a result, total leukocyte and neutrophil counts were significantly decreased and the NLR tended to decrease in the L-carnitine when compared with the placebo group. It appears that the decrease in NLR of the L-carnitine group was related to both the reduced neutrophil count and the increased lymphocyte count. The effects of L-carnitine on lymphocyte and neutrophil counts are compatible with the findings of previously published studies.[12] Whenever prominent neutrophilia develops or cellular immunity is suppressed, NLR increases. So a smaller activation of inflammatory response evaluated by neutrophil count and a lesser deterioration of cellular immunity measured by lymphocytic count can be defined as a favorable pattern of systemic leukocytic alteration. Therefore, a smaller value of the NLR may be diagnosed as a favorable pattern of systemic leukocytic alteration.[14] In a study designed by Ünal *et al*[15], it was demonstrated that increased neutrophil/lymphocyte ratio can be accepted as an independent risk factor for early mortality after CABG surgery.

L-carnitine is a small essential molecule for long-chain fatty acid transformation.[16] It is endogenously synthesized in the human body and also found in our diet, acting as a scavenger of oxygen free radicals.[17] L-carnitine enabling long-chain fatty acid β-oxidation, plays a major role in the branched chain amino acid metabolism and in the cellular membrane stabilization process.[18] L-carnitine, as a carnitine palmitoyltransferase 1 cofactor, facilitates fatty acid transport into mitochondria. It also allows long chain fatty acid incorporation into β-oxidation cycle to obtain acetyl-CoA.[19] The accumulations of mitochondrial long-chain acyl-CoA and long-chain acyl-carnitine have been shown to be reduced by L-carnitine in ischemic hearts.[20] In a study designed by DiNicolantonio *et al*,[21] it was demonstrated that L-carnitine compared with placebo was associated with the reduction in all-cause mortality and ventricular arrhythmias (27% and 65%, respectively). Recently, NLR has been reported as a prognostic marker for atrial fibrillation after CABG.[22] Among our study patients, there was 1 mortality on postoperative day 7. This was a patient in the placebo group who developed acute kidney injury needing hemodialysis. However, the size of our study population was not sufficient to determine whether the difference between the 2 groups was related to L-carnitine. L-carnitine has a protective effect against reperfusion arrhythmias and this protective action of L-carnitine is due to its mitochondrial action, but cannot be solely attributed to increased fatty acid oxidation.[23] In this present study, dysrhythmias were more common in the placebo group, although we did not classify dysrhythmias into subgroups. Our results were similar to previous studies.

Deufel[24] suggested that immune networks might be regulated by L-carnitine–enriching leukocytes,

including lymphocytes. Although a certain number of studies concerning the role of L-carnitine in the immune system have been performed, contradictory results have been reported on its effects on absolute numbers of WBC subtypes, due in most cases to the known complexity of the immune system.

In experimental studies, it has been noted that L-carnitine may modulate unbalanced immune responses associated with aging.[25] Structural and functional refreshment of mitochondria by L-carnitine supplementation have been demonstrated in old animals.[26] Famularo *et al*[27] demonstrated *in vitro* anti-apoptotic effects of L-carnitine whereas Franceschi *et al*[28] showed increased lymphocyte proliferation in L-carnitine preloaded lymphocytes from old human subjects, suggesting that L-carnitine improved the defective proliferative ability of lymphocytes. Moreover, in AIDS patients treated with zidovudine, L-carnitine supplementation contributed to lymphocyte proliferation.[29]

Cardiac surgery, especially with CPB, is a well-known cause of an inflammatory host response with suppression of cellular immunity.[30] Increasing neutrophils and decreasing lymphocytes are 2 strong predictors of postoperative infection.[31] Previous studies have showed that an increased NLR is associated with morbidity and mortality in cardiovascular diseases.[6] During CPB, because of hemodilution, leukocyte counts decrease, but increase markedly postoperatively.[32] The contact and complement systems, producing kallikrein and C5a, strongly activate the neutrophils during CPB and the release of interleukin (IL)-6 and IL-8 may partially inhibit the apoptosis of neutrophils so that neutrophil activity is prolonged.[33] Cardiopulmonary bypass causes lymphopenia, representing an immunodepressive status, which is an indicator of susceptibility to infection.[30] It has been reported that neutrophils may inhibit the immune system. Neutrophilia caused by CPB could suppress the cytolytic activity of lymphocytes, and the degree of suppression is proportional to the number of neutrophils.[34] Therefore, lower neutrophil count can be anticipated in subjects who received preoperative L-carnitine supplementation.[32] To the best of our knowledge, there is no published study concerning the preventive effects of L-carnitine supplementation on infection. In our study population, we did not encounter any infection. However, it is not possible to make any inference because of the small size of our study population.

In patients awaiting CABG, L-carnitine usefully overcomes the negative effects of myocardial injury by neutralizing the toxic effects of high levels of free fatty acids that are released in ischemic conditions.[35] Several animal models and human studies demonstrated that L-carnitine administration treats the ischemia-related injury within the heart muscles and improves exercise tolerance in patients with angina pectoris.[36] In this present study, during L-carnitine or placebo infusion, unstable angina pectoris developed in 1 patient in the L-carnitine group compared with 3 patients in the placebo group. This might be an indication of a preventive effect of L-carnitine against ischemia-related injury. It was also reported that L-carnitine treatment during cardioplegia had a positive influence on the stroke volume immediately after weaning from CPB.[34] But in another study designed by Demeyere *et al*,[37] it was concluded that pretreatment with carnitine neither facilitated weaning from cardiopulmonary bypass in patients undergoing aortocoronary bypass surgery nor favorably affected hemodynamic function during the first 24 hours. In our present study, intraoperative MAP after weaning from CPB was higher in the L-carnitine group. Although Nakagawa *et al*[34] used L-carnitine in a different way than we did, we think that higher MAP after weaning from CPB was evidence of myocardial protection with preoperative L-carnitine supplementation. After L-carnitine supplementation for 3 days, the NLR of the L-carnitine group was lower than basal levels. Although the difference between the 2 groups was not statistically significant, considering the prognostic role of NLR, this finding is meaningful.

In patients undergoing CABG, the rehabilitation of unbalanced immunity may be beneficial to improve postoperative adverse outcomes. Although L-carnitine has become popular, no studies have been performed to investigate its effects on the N/L ratio in patients undergoing CABG.

In this study, the group supplemented with L-carnitine infusion for 3 preoperative days had a lower NLR on postoperative day 1. It seems that the tendency toward increasing lymphocyte count is more influential in the favorable NLR of the L-carnitine group. On the other hand, the influence of L-carnitine supplementation on leukocytic alterations after CABG was shown to be transient.

Study Limitations

One limitation of our study is the relatively small number of patients. Further research including NLR with other inflammatory markers such as C-reactive

protein, IL-6, and IL-8 is warranted to clarify the effects of L-carnitine treatment in patients undergoing cardiovascular surgery.

Conclusions

Preoperative L-carnitine supplementation can favorably modify leukocytic alterations, including the neutrophil-to-lymphocyte ratio in peripheral blood during the early postoperative period of CABG.

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