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SHORT COMMUNICATION

L-carnitine as an Adjunct Therapy to Percutaneous Coronary Intervention for Non-ST Elevation Myocardial Infarction

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Abstract
Objectives To evaluate the effects of L-carnitine as an adjunct therapy to percutanenous coronary intervention (PCI) for non-ST elevation acute coronary syndrome (NSTEMI).
Materials and methods Ninety-six consecutive patients with NSTEMI were randomized into treatment group (L-carnitine 5 g IV bolus followed by 10 g/day IV infusion for 3 days), and control group. All patients also underwent PCI within 24 h from the onset of chest pain. The peak values of creatine kinase-MB and troponin-I before and after PCI were observed.
Results In the treatment group, the peak values of creatine kinase-MB were significantly lower than the control group at 12 h and 24 h after PCI ($P<0.01$). The peak values of troponin-I in the treatment group were also lower than the control group at 8 h after PCI ($P<0.01$). Multivariate regression analysis showed that L-carnitine therapy was an independent predictor for the reduction of creatine kinase-MB ($r=0.596$, $P<0.001$) or troponin-I ($r=0.633$, $P<0.001$).
Conclusion L-carnitine adjunct therapy appears to be associated with a reduced level of cardiac markers in patients with NSTEMI. These results support a larger clinical trial to investigate the effect of L-carnitine on cardiac events following PCI.

Key words L-carnitine · myocardial infarction · percutaneous coronary intervention · mortality

Introduction

L-carnitine, a quaternary amine responsible for the transport of long-chain fatty acids into the mitochondria for energy production, has been shown to have favourable effects in patients with several cardiovascular disorders, such as coronary heart disease, chronic heart failure and peripheral vascular disease [1, 2]. In patients with acute myocardial infarction, L-carnitine treatment for up to 12 months attenuates left ventricular dilatation and prevents ventricular remodelling [3]. It also reduces combined incidence of death and chronic heart failure in these patients [3]. L-carnitine diminishes myocardial injury after ischemia mainly by counteracting the toxic effect of high levels of free fatty acids and by improving carbohydrate metabolism [2].

Percutaneous coronary intervention (PCI) does not appear to reduce the risk of death, myocardial infarction or other major cardiovascular events in patients with stable coronary artery disease receiving optimal medical therapy [4]. However, PCI offers significant clinical benefits in patients with acute coronary syndrome (ACS) [5]. In the last decade, the percentage of patients with non-ST elevation myocardial infarction (NSTEMI) managed with *PCI* has steadily increased, and now stands at approximately 50% [6]. Even with optimal adjunctive drug therapy, there is still a

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relatively high incidence of death after PCI in patients with NSTEMI [7]. The primary purpose of this study is to investigate the addition of L-carnitine to other standard adjunctive drug therapies would reduces post-PCI cardiac markers in patients with NSTEMI.

Patients and methods

Patient selection

The study was approved by the institutional review board of Liaocheng People's Hospital. Informed consent was obtained from all participants. Patients who met the following diagnostic criteria for NSTEMI were selected for the study: anginal chest pain within 24 h of hospitalization, and one of the following ECG changes: transient or persistent ST depression ≥1 mm, or newly developed T wave inversion ≥3 mm. All patients had elevation of blood creatine kinase-MB, (CK-MB), and/or troponin I.

Patients who met one or more the following criteria were excluded from the study: (1) coronary artery stenosis <70%; (2) ST elevation myocardial infarction; (3) plasma creatinine >2.5 mg/dl; (4) stroke within 3 months; (5) terminal illnesses such as advanced cancer.

Between November 2005, and December 2006, 96 patients who met the selection criteria were enrolled into the study. They were randomized into two study groups according to the order of hospitalization dates.

PCI and administration of L-carnitine

The study was performed according to an open-label, single-blind design. All patients underwent PCI within 48 h of hospital admission. The PCI operators were unaware of patient's groupings. Coronary angiogram and *bare-metal* stenting was performed through the femoral artery. Target-lesion revascularization was always attempted and complete revascularization was performed as clinically appropriate. The standard pre-PCI pharmacological therapy included oral aspirin 300 mg, and clopidogrel 300 mg. Post-PCI medications included clopidogrel 75 mg once daily, and subcutaneous administration of enoxaparin every 12 h for 3 days. Long term maintenance therapies included aspirin 100 mg, and clopidogrel 75 mg daily for up to 12 months. Patients were also prescribed with a beta-blocker, a statin and an angiotensin-converting enzyme inhibitor during the follow up.

In the treatment group, 30 min before PCI, 5.0 g of L-carnitine (Lanling Pharmaceuticals, Changzhou, China) was intravenously administered in a bolus injection. This was followed by 10 g intravenous infusion daily for 3 days. The manufacturer's recommendation of intravenous L-carnitine is 50 mg/kg (no more than 300 mg/kg). Since only one dose of the drug was tested, a higher dose (approximately 160 mg/kg) was chosen for a short-maintenance therapy. Half of the maintenance dose (approximately 80 mg/kg) was tried on day one to make sure there were no adverse effects following the administration.

The same volume of normal saline was administered in the control group patients.

Assessment of outcomes

Success after PCI as seen on angiography was defined as normal coronary-artery flow (TIMI 3) and less than 50% stenosis in the luminal diameter after balloon angioplasty, or less than 20% after coronary stent implantation. Slow coronary-artery flow after PCI was defined as TIMI 2 whereas extremely slow or no flow was defined as TIMI 1 or TIMI 0, respectively.

Plasma levels of creatine kinase-MB and troponin-I were measured immediately before and 8, 12 and 24 h after PCI.

The composite end-point was recurrent ischemia, myocardial infarction and death during hospitalization and within 30 days of hospital discharge.

Statistical analysis

Data were expressed as means±SD. Data analysis was performed with SPSS10.0 software. Student *t* test was used to analyze the difference in the average age of patients in the treatment and the control group. Comparison of the composite end-point between the treatment and control group was performed with *Fisher's* exact test. Other categorical data between the two groups was compared by *Chi-square* test. Multivariate regression analysis was used to assess the predicting factors for the reduction of CK-MB or tropoinin-I following L-carnitine therapy. $P<0.05$ was considered to be statistically significant.

Results

General findings

There was no significant difference in age, sex, and other baseline clinical data between the two groups (Table 1, $P>0.05$). None of the patients had clinical symptoms of peripheral artery disease. The number of coronary arteries involved and the TIMI flow were also similar between the two groups (Table 1, $P>0.05$).

Revascularization was successful in all patients. All patients in the treatment group achieved TIMI 3 coronary

Table 1 Comparison of baseline and coronary angiography characteristics

	Treatment group (n=48)	Control group (n=48)	P value
Age (years)	63.8±12.9	56.9±13.1	>0.05
Male	32 (66.7%)	25 (52.1%)	>0.05
SBP on admission	142±10.9	146±13.6	>0.05
Hypertension	17 (35.4%)	12 (25.0%)	>0.05
Type 2 diabetes	13 (27.1%)	9 (18.9%)	>0.05
Dislipidemia	20 (41.7%)	14 (29.2%)	>0.05
Previous MI	7 (14.6%)	5 (10.5%)	>0.05
Currently smoking	23 (47.9%)	17 (35.4%)	>0.05
Coronary artery lesions			
Single vessel	12 (25.0%)	11 (22.9%)	>0.05
Two vessels	14 (29.2%)	13 (27.1%)	>0.05
Three vessels	22 (45.8%)	24 (50.0%)	>0.05

SBP systolic blood pressure

flow. In the control group, TIMI 3 was achieved in 45 and TIMI 2 achieved in 1.

Plasma levels of CK-MB and troponin-I

There was no significant difference in CK-MB and troponin-I before PCI (Table 2, P>0.05). CK-MB in the treatment group was lower than the control group at 12 and 24 h after PCI (Table 2). Troponin-I in the treatment group was also lower than the control group 8 h after PCI (Table 2). During the multivariate regression analysis, patient's age, sex, presence of hypertension or diabetes, previous myocardial infarction, admission systolic blood pressure and number of diseased coronary arteries were taken into consideration. For the CK-MB levels at 24 h following PCI, L-carnitine therapy (r=0.596, P<0.01) was an independent predictor. L-carnitine was also an independent predictor for the troponin-I levels at 24 h following PCI (r=0.633, P<0.001).

End-point

At 48 h after PCI, composite end-point in the treatment and control group was recorded in 1 (2.1%) and 2 (4.2%) of the patients, respectively (P>0.05). These included one nonfatal myocardial infarction in the treatment group, one nonfatal myocardial infarction and one acute heart failure leading to cardiogenic shock and death in the control group. After hospital discharge, no further cardiac events were observed in the treatment group. However, one patient from the control group experienced nonfatal myocardial infarction. Therefore the 30 day composite end-point in the treatment and the control group was 2.1% and 6.3%, respectively (P>0.05).

There were no significant adverse effects, such as nausea, vomiting or diarrhea, from L-carnitine administration.

Discussion

Several randomized trials have demonstrated that patients presenting with an ACS and who subsequently undergo routine angiography and revascularization by PCI have improved outcomes compared with patients who were not treated with PCI [5, 8, 9]. Early reperfusion of totally occluded coronary arteries reduces the infarct size, cardiac mortality rates and in-hospital events. However, a various degree of reperfusion injuries has been reported following PCI. These injuries lead to an increase in plasma CK-MB and troponin I [10]. The elevation in myocardial markers has a strong positive relationship with the adverse clinical outcomes after PCI [10].

In combination with reperfusion therapy, pharmacological treatment can attenuate myocardial dysfunction associated with ACS [11, 12]. The present study has demonstrated that the addition of L-carnitine before and immediately following PCI reduces the post-PCI levels of CK-MB and troponin-I, indicating diminished myocardial injuries.

The protective effect of L-carnitine on ST-elevation myocardial infarction has been documented in several clinical trials. Prompt administration of L-carnitine followed by maintenance therapy attenuates progressive left ventricular dilatation immediately following an acute anterior myocardial infarction [13]. There is a significant reduction in end-diastolic volume and end-systolic volume in patients who received L-carnitine compared with placebo [14]. In patients with anterior acute myocardial infarction, L-carnitine therapy leads to a reduction in early mortality but did not affect the risk of death and heart failure at 6 months [14]. In patients with suspected acute myocardial infarction, oral L-carnitine supplementation for up to 28 days reduces the infarct size and cardiac biomarkers. L-carnitine supplementation also prevents ventricular enlargement and ventricular dysfunction, and diminishes total cardiac events including cardiac deaths and nonfatal infarction [15].

Table 2 Changes in creatine-MB (CK-MB) and troponin-I (TnI) after percutaneous coronary intervention

	Treatment group (n=48)	Control group (n=48)
CK-MB (ng/ml)		
Before	1.12±1.66	1.03±1.55
8 h	4.34±9.01	5.58±11.2
12 h	1.98±4.15	3.21±5.23**
24 h	0.66±1.04	1.59±2.72*
TnI (ng/ml)		
Before	0.21±0.11	0.19±0.33
8 h	0.44±1.05	1.78±5.11**
12 h	0.86±2.45	1.35±3.36
24 h	0.41±1.34	0.89±1.35

Compared with treatment group * P<0.05, ** P<0.01

The most likely explanation for the beneficial effects of L-carnitine appears to be the resumption of normal oxidative metabolism and the restoration of myocardial energy reserves. L-carnitine is known to increase the rate of toxic fatty acid transport into mitochondria in the ischemic myocardium [2]. It also reduces the intramitochondrial ratio of acetyl-CoA to free CoA, thus stimulating the activity of pyruvate dehydrogenase and increasing the oxidation of pyruvate [2]. An increase in tissue carnitine content prevents the loss of high-energy phosphate stores, ischemic injury and improves ventricular recovery on reperfusion [2]. L-carnitine also prevents the accumulation of long chain acyl-CoA in the ischemic myocardium and thus the life-threatening ventricular arrhythmia [16]. Furthermore, L-carnitine improves repair mechanisms for oxidative-induced damages to membrane phospholipids, and reduces ischemia-induced apoptosis and the subsequent remodeling of the left ventricle [16].

One limitation of this study is that the number of patients is relatively small. The patient sample seems sufficient to show the significant reduction in cardiac markers following L-carnitine treatment. However, the difference in the 30-day composite end-point in the treatment (2.1%) and control group (6.3%) was not statistically significant. The insignificant difference between the two groups may be due to the inadequate number of patients. The other potential limitation is that the data on the left ventricular ejection fraction was incomplete in this study. Therefore, the impact of ventricular dysfunction on the composite endpoints could not be determined. However, the results from this study do indicate that a larger clinical trial may be warranted to investigate the impact of L-carnitine on the clinical outcomes of patients with NSTEMI.

In summary, this relatively small clinical trial has demonstrated that intravenous administration of L-carnitine is associated with reduced plasma levels of CK-MB and troponin-I in patients with NSTEMI treated with PCI. The effect of L-carnitine on the clinical outcomes of NSTEMI remains unknown. These preliminary results support a larger clinical trial to investigate the effect of L-carnitine on mortality, recurrent ischemia and other cardiac events following PCI.

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