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Prevention of Contrast-Induced Nephropathy with L-Carnitine Injection in Coronary Heart Disease Patients with Diabetes Mellitus Undergoing Percutaneous Coronary Intervention

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Abstract

Purpose: Contrast-Induced Nephropathy (CIN) is an important complication in the use of iodinated contrast media. The present study aimed to assess the safety and efficacy of L- carnitine in prevention of CIN in patients with Diabetes Mellitus undergoing percutaneous coronary intervention.

Methods: The study group consisted of 145 patients with Diabetes Mellitus who had undergone a coronary intervention procedure. These patients were randomly divided into the L- carnitine group (72 patients) and the control group (73 patients). The control group received 0.9% sodium chloride solution for routine hydration only; The L- carnitine group received routine hydration and L- carnitine intravenous infusion at 3.0 g /d for 3 d before and 3 d after the administration of contrast media. A nonionic, low osmolality contrast agent was used in our laboratory at this time. Serum creatinine values were measured before and within 24h, 48h after the administration of contrast agents. Urine samples were collected before and 24h, 48h after coronary interventional procedure and urinary Kidney Injury Molecules 1(KIM-1) levels were measured by using an ELISA kit. CIN was defined as an increase in serum creatinine level of $\geq$ 0.5 mg/dL or $\geq$ a 25% above baseline within 48 h after contrast administration.

Results: The incidence of CIN was lower in the L- carnitine group than in the control group (6.9% vs 19.2%, $P < 0.05$). There was not a significant difference between the Scr levels 24 h before and after the procedure, There was a significant difference ($P < 0.05$) between the urinary KIM-1 levels of 24h, 48h after the procedure and before the procedure, The area under the ROC curve of urinary Kim-1 24 h after the procedure was 0.856, confidence interval of AUC 95% was (0.782,0.929). If the critical point of the diagnosis of CIN was 6327.755 pg/ml, the sensitivity was 73.7% and the specificity was 85.7%. It was found in univariate analysis that urinary Kim-1 was positively correlated with Serum creatinine in pre-procedure and post-procedure. No serious adverse effects were observed.

Conclusions: In patients undergoing percutaneous coronary intervention, the use of L- carnitine for prevention of CIN is safe and efficacious. Urinary Kim-1 could be a better indicator of early prediction of CIN.

Keywords: Contrast-Induced Nephropathy; Kidney Injury Molecules 1; L- Carnitine; Prevention

Introduction

Contrast-Induced Nephropathy (CIN) may be a severe complication to the administration of iodine-based contrast media for diagnostic or interventional procedure. The incidence of CIN is 2% for the general population. However, patients undergoing percutaneous coronary intervention(PCI) are at greater risk, and patients with diabetes mellitus or previous renal impairment have a risk of almost 50% [1]. CIN is associated with increased morbidity and mortality, particularly in high-risk patients who have undergone percutaneous coronary intervention [2]. The effective prevention of CIN is an important goal. Many investigators have undertaken clinical trials of clinical procedures and pharmacological agents intended to reduce the risk for CIN. For the incidence of contrast induced nephropathy, now that the production of oxygen free radicals is an important mechanism [3].

L-carnitine is a special amino acid exist widely in the body tissues, organs, tissue energy metabolism in the body, recent studies have shown that L-carnitine can reduce ischemia, hypoxia, inflammatory mediators and oxygen free radical to the damage of kidney tissues and cells [4,5]. This study aimed to assess the safety and efficacy of L-carnitine injection in the prevention of CIN in Coronary Heart Disease (CHD) patients with Diabetes Mellitus (DM) undergoing percutaneous coronary intervention, so as to provide a kind of economical and practical for clinical prevention strategies.

Patients and Methods

In this single-institution, single-blind, superiority trial, a total of 145 patients undergoing PCI were randomly assigned to undergo the L- carnitine group (72 patients) and the control group (73 patients) in a 1:1 ratio. Among them, 91 were men and 54 were women, and the mean age was 64.8±10.0 years. Exclusion criteria were (1) Iodine allergy test positive patients (2) patients who used drugs with renal toxicity at the preoperative period, (3) severe hepatic and renal dysfunction, severe renal dysfunction was defined as the eGFR less than 30 ml min-1· 1.73 m-2, (4) tumor patients, (5) New York Heart Association class IV congestive heart failure or Left Ventricular Ejection Fraction (LVEF) of <35%. (6) thyroid or adrenal dysfunction, and (7) acute or chronic infectious diseases, or hyperpyrexia. (8) l-carnitine injection was used in patients with preoperative one week. A nonionic, low-osmolar iodinated contrast agent iohexol (Omnipaque; GE Healthcare, Shanghai, China) was used in our hospital. The patients in the L-carnitine group which based on control group and received L-carnitine intravenous infusion (Carnitene 1 g/5 ml injectable ampoule, Sigma-Tau Industrie Farmaceutiche Riunite S.p.A, Italy.), 3.0 g per day, 3 d before operation and 3 d after operation. The control group was routinely offered antiplatelet, anticoagulation, antianginal agents, lipids, glucose. All patients receive pre-or post procedural hydration with normal saline. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the Affiliated Hospital of Xuzhou Medical College. Written informed consent was obtained from all participants.

According to the study design, all entrants checked Serum Creatinine (Scr), urine Kidney Injury Molecules 1(KIM-1), estimated Glomerular Filter Rate (eGFR) before and 24 h ,48 h after operation. KIM-1 levels were measured by ELISA. Renal function was assessed by the estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula for Chinese patients [6]: GFR (mL/min/1.73 m2) = 175 × Scr (mg/dL)-1.1549 × age-0.2039 × (0.79 if female). The incidence rate of CIN and occurrence of adverse cardiac events were observed. CIN was defined as an elevation in Scr by ≥ 0.5 mg/dL or ≥ 25% occurring within 3 days after the intravascular administration of contrast medium, without an alternative etiology [7].

Statistical analysis

Statistical analysis was performed by a professional statistics researcher. Continuous variables are expressed as mean±Standard Deviation (SD), and categorical data were presented as absolute values and percentages. The t-test and one-way analysis of variance followed by the Scheffe-type multiple comparison test were used for parametric comparison. The Mann–Whitney U test and the Kruskal-Wallis test were used for nonparametric comparison. The Chi-square or the Fisher's exact test was used for comparison of categorical variables as required. Multivariate predictors of CIN were identified by logistic regression using stepwise selection. A two-sided 95% Confidence Interval (CI) was constructed around the point estimate of the Odds Ratio (OR). All hypothesis testing was two tailed. A P value < 0.05 was considered as statistically significant. SPSS 19.0 (SPSS, Inc., Chicago, IL, USA) was used to perform the statistical analyses.

Results

Baseline Clinical and Procedural Characteristics

A total of 145 patients with Coronary Heart Disease (CHD) complicated with Diabetes Mellitus (DM) undergoing selected PCI were eligible for the study. A total of 91 (62.6%) patients were men with a mean age of 64.8±10.0 years. Baseline clinical characteristics are shown in (Table 1).

Characteristic	Control group n=73	L-carnitine group n=72	P value
age (years)	63.7±9.9	66.0±10.0	0.17
Male gender	42（57.5）	42（57.5）	0.19
Hypertension 〔n (%)〕	37（50.7）	27（37.5）	0.11
Total cholesterol	4.5±1.1	4.8±1.1	0.11
LVEF（%）	57.8±9.5	59.6±9.1	0.26
Contrast agents dosage(ml)	140.1±50.0	134.4±46.5	0.49
Scr (μmol/L)	66.3±15.8	62.9±11.3	0.15
eGFR（ml/min/1.73m2）	104.2±23.1	111.5±23.0	0.06
LDL-C (mmol/L,)	2.7±1. 0	2.9±1.1	0.12
FBG（mmol/L）	7.2±2.2	7.1±2.7	0.87
Glycated hemoglobin	7.0±0.8	7.1±0.9	0.83
Hemoglobin（g/L）	132.6±14.7	135.3±14.7	0.27
Drug〔n (%)〕			
Aspirin〔n (%)〕	71（97.3）	71（98.6）	1
Low molecular heparin〔n (%)〕	70（95. 9）	70（97.2）	1
βBlockers〔n (%)〕	65（89.0）	62（86.1）	0.59
ACEI/ARB〔n (%)〕	20（27.4）	15（20.8）	0.36
Calcium channel blockers〔n (%)〕	30（41.1）	26（36.1）	0.54
Diuretic〔n (%)〕	8（11.0）	13（18.1）	0.25
Statin drug〔n (%)〕	72（98.6）	70（97.2）	1

Data are expressed as the mean±SD or number (%).
LVEF: Left Ventricular Ejection Fraction
Scr: Serum Creatinine
eGFR: Estimated Glomerular Filtration Rate
LDL: Low-Density Lipoprotein
FBG: Fasting Blood-Glucose
ACEI: Angiotensin-Converting Enzyme Inhibitor
ARB: Angiotensin-Receptor Blocker

Table 1: Baseline clinical characteristics of the patients in the two groups.

The two groups had no significant differences in age, sex, body mass index, hemoglobin, left ventricular ejection fraction, SCr, eGFR, the incidence of hypertension, etc. The medications and hydration volumes used at the time of hospitalization were also not significantly different between the groups. Changes in Scr, GFR, and urine KIM-1 values before and after PCI are shown in (Table 2).

Group	Scr(μmol/L)	GFR(ml·min-1·1.73-2)	Urine KIM-1(pg/ml)
Control group			
pre-procedure	66.5±15.8	104.2±23.1	3938.3±1192.1
post-procedure			
24h	70.5±18.1	98.7±24.2	5608.9±1766.0a
48h	74.1±21.1a	95.1±27.3a	5266.4±1642.8a
l-carnitine group			
pre-procedure	63.1±11.1	111.5±23.0	3695.2±920.5
post-procedure			
24h	65.1±12.6b	108.6±25.5b	4658.7±1365.9ab
48h	65.7±14.9b	108.8±27.3b	4425.7±1209.2ab
Data are expressed as the mean ± SD [a]P < 0.05 Compared with the pre-procedure; [b]P < 0.05 Compared with the same period of the l-carnitine group Incidence of CIN and the correlation analysis between Scr and KIM - 1 CIN occurred in 19 (13.1%) patients. There was a significantly higher incidence of CIN in the control group (14, 19.2%) compared with the l-carnitine group (5, 6.9%, P < 0.05). Bivariate showed that the level of KIM-1 before and 24h, 48h after operation positively correlated with Scr at the same time (P < 0.01).			

Table 2: Changes in Scr, GFR, and urine KIM-1 values before and after PCI.

There were no significant differences in Scr and GFR before and after the PCI procedure in the control and PGE1 groups (P > 0.05). Urine KIM-1 levels 24 h, 48h after the procedure were significantly higher than those before the procedure in both groups.

Multivariate Logistic Regression Analysis

Multivariate logistic regression analysis showed that low eGFR and low left ventricular ejection fraction before PCI were independent predictors of CIN (Table 3).

Variables	OR	95% CI	P values
Age > 70 years	3.42	(1.157, 10.094)	0.025*
LVEF< 35%	6.95	(1.144, 42.193)	0.035*
eGFR, ml/min/1.73m^2)	2.45	(0.953, 11.593)	0.039*
Contrast agents dosage (200ml)	5.20	(1.437, 18.795)	0.012*
*P < 0.05 Observe clinical adverse events			

Table 3: Multivariate logistic regression analysis.

During the entire study, all patients who did not appear with iodine allergy phenomenon, had not been observed in severe cardiac adverse events (revascularization, myocardial infarction, pulmonary edema, sudden death, etc.)

Discussion

CIN is defined as renal impairment occurring after the administration of contrast materials. For the pathogenesis of CIN study, contrast medium caused renal hemodynamic changes, kidney ischemia hypoxia, and renal tubular cell injury, during this period produce the energy metabolism disorders, as well as the generation of oxygen, which can lead to acute renal injury [8]. L-carnitine palys a role as the inhibitor of free radical production processes and oxidative stress. The most important finding of this study is the demonstration of a significant decrease in the incidence of CIN by means of L-carnitine administration in patients with Diabetes Mellitus undergoing percutaneous coronary intervention. This study indicated that the antioxidant properties of L-carnitine might have contributed to the positive finding. On 48 h after the procedure, there was statistically significant difference compared with preoperative in serum creatinine and eGFR in control group, while not, in L-carnitine group (P < 0.05).

Diabetes is one of the high-risk factors for CIN, but also is the common complication of CHD. The total incidence of CIN in diabetic population is approximately 5.7% ~ 29.4%, and when combined with renal insufficiency, the risk factors such as age, PCI, the incidence of CIN will be higher [9]. Diabetes affects the function of the vascular system. Endothelial dysfunction can be found in diabetes [10], it will reduce the ability of vessels to vasodilate in response to ischemia. Patients with diabetes are also at increased risk for coronary artery disease, hypertension, and congestive heart failure which may contribute to an increased risk of CIN by renal blood flow. This study suggests that the total incidence is not high, considering the possible reason of all the selected patients with normal renal function, conventional hydration, and without postoperative follow-up Scr 72 h.

Currently, the only effective prevention measure for CIN is hydration therapy [11]. Hydration therapy, through correcting subclinical dehydration, reduces the viscosity of contrast agents and the resulting hyperosmolar state. It reduces tubulo-glomerular feedback, decreases renal vasoconstriction, increases urine volume to control renal tubular obstruction, reduces vasoconstrictor substances produced, reduces renal medullary ischemia, and can directly decrease tubular renal epithelial toxicity caused by contrast agents. L-carnitine is in 1905 by two Russian scientists first discovered in muscle extract [12]. L-carnitine is an important medium of human body lipid metabolism, plays a role of carrier in the process of the oxidation of fatty acid used. It has been used as clinical medicine in the treatment of primary and secondary l-carnitine lack, especially for the late kidney dialysis patients. The present study showed that the L-carnitine can promote fatty acid oxidation, or a kind of effective oxygen free radical scavenger which has obvious protective effect in reducing oxidative stress and lipid peroxidation [13]. L-carnitine can effectively improve

the drug caused by renal tubular necrosis, protect renal function [14]. Animal model, and find that the L-carnitine has a good effect in preventing of contrast-induced Nephropathy [5].

In our study, CIN occurred in fourteen (19.2%) patients in the control group and three (6.9%) patients in the L-carnitine group. 24 hours ,48 hours after the procedure, the increase in urine KIM-1 levels in the L-carnitine group was significantly lower than that in the control group. Recent studies have suggested that KIM-1 is an early molecular marker, which reflects acute kidney injury, and its sensitivity is better than Scr [15,16] We conclude that L-carnitine is likely to decrease the incidence of CIN in patients with high-risk factors undergoing PCI. However, the mechanisms and efficacy of L-carnitine on the prevention of CIN after PCI need to be determined by a further multicenter, randomized, double-blind, large-scale, clinical prospective study.

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