Efficacy of Nicorandil in Preventing Contrast-Induced Nephropathy in Patients with ST-segment Elevation Myocardial Infarction undergoing Primary Percutaneous Coronary Intervention

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Efficacy of Nicorandil in Preventing Contrast-Induced Nephropathy in Patients with ST-segment Elevation Myocardial Infarction undergoing Primary Percutaneous Coronary Intervention

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criteria with the following roles. Qian Geng: Data collection, analysis and manuscript drafting. Chen Si: Data analysis and revision of the manuscript. Jiang Xiaosi and Ying Zhang: Data analysis and data collection. Xin A: Statistical analysis and revision of the manuscript. Ping Li: Data collection. Yun-dai Chen: guarantor of the clinical trial and study design.

Ethics approval：The trial was registered on www.clinicaltrials.gov (registration number: NCT03445728). The trial protocol was approved by the Ethics Committee of Chinese PLA General Hospital.

Consent to participate：All participants provided written informed consent.

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Abstract

Objective: It is widely reported that nicorandil could reduce contrast-induced nephropathy (CIN) after selective percutaneous coronary intervention (PCI) or coronary angiography. The aim of this multi-center prospective randomized controlled trial is to evaluate the efficacy of nicorandil for the prevention of CIN after primary PCI in patients with ST-segment elevation myocardial infarction (STEMI).

Methods: Patients with STEMI received primary PCI were enrolled, and they were randomly assigned into nicorandil group and placebo group, receiving intravenous nicorandil or placebo before PCI, respectively. The endpoint was the incidence of CIN, defined as an absolute increase in serum creatinine (SCr) > 0.5 mg/dl or a relative increase > 25% compared with baseline SCr. The secondary endpoints were major adverse cardiovascular events (MACEs) within a year.

Results: The final study population comprised 238 randomized patients, and 226 of them (n=113 for each group) were included in the primary analysis. Compared with the placebo group, the final TIMI grade in the nicorandil group was significantly better (P = 0.001), and the incidence of CIN in nicorandil group was significantly lower (9.7% (11/113) vs. 24.8% (28/113), P = 0.003). The logistic regression analysis revealed that nicorandil was significantly associated with the decreased odds of CIN (OR: 0.379, 95% CI: 0.166-0.861, P=0.021). Nicorandil is an independent protective factor for the development of CIN in STEMI patients undergoing primary PCI.

Conclusions: Our study indicated that intravenous nicorandil could prevent CIN in patients with STEMI undergoing primary PCI.

Keywords: contrast-induced nephropathy; nicorandil; primary percutaneous coronary intervention; ST-elevation myocardial infarction

1. Introduction

Contrast-induced nephropathy (CIN) has become the important cause of hospital-acquired renal failure, which is a recognized complication of percutaneous coronary intervention (PCI). CIN is associated with prolonged hospitalization, increased risk of adverse cardiovascular events, as well as short- and long-term mortality[1-2]. Some studies are exploring effective prevention for CIN[3-5]. To assess the efficacy of nicorandil for CIN prevention in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI, we analyzed a multi-center prospective randomized controlled trial, which explored the effects of nicorandil administration on infarct size in patients with STEMI treated with PPCI (primary PCI)[6]. We analyzed the effect of pre-procedural treatment with intravenous nicorandil for renal protection for STEMI patients undergoing primary PCI.

2. Methods

2.1 Study Design

This multi-center prospective randomized controlled trial study was approved by the Ethics Committee of Chinese PLA General Hospital and other research centers. This trial was registered in clinicalTrials.gov (NCT03445728). The results of the the trial have been published, which have showed administration of nicorandil before PPCI reduced infarct size in STEMI. The study protocol also has been previously published[7]. All study patients were followed up by routine clinical visit for one year. The inclusion criteria were the patients with STEMI within 12 hours of the onset, who were admitted to hospitals and were plan to perform primary PCI and provided informed consent. The exclusion criteria included: 1) low systolic blood pressure; 2) left main artery as culprit artery; 3)

aortic dissection; 4) myocardial infarction or previous PCI or CABG (coronary artery bypass grafting) within 6 months; 5) active treatment with nicorandil; 6) any known contraindication for nicorandil; 7) involving in other clinical trial; 8) other clinical disorders not suitable for the clinical trial. We monitored the changes in renal function before and after the PPCI procedure, and we monitored the serum creatinine before PPCI, 24 h, 48 h, and 72 h after PPCI, and checked the maximum value of serum creatinine post infarction. Contrast volume was recorded after PCI procedure.

2.2 Definitions and Dosage of Administration

STEMI was diagnosed as persistent chest pain or other symptoms suggestive of ischemia and ST-segment elevation in at least two contiguous leads[8]. CIN was defined by a relative increase in the level of serum creatinine (Scr) > 25% compared to the baseline and/or an absolute increase in the Scr level > 0.5 mg/dl that occurs within 48 to 72 hours after the PCI[9]. Nicorandil dissolved in saline was administrated as 6 mg bolus *i.v.* before the first balloon expansion or stent implantation and 6 mg/h *i.v.* for 24 hours.

2.3 Study endpoints

We have explored the effect of nicorandil on incidence of CIN. Other secondary endpoint was the incidence of slow/no-reflow duiring PPCI, and major adverse cardiovascular events (MACEs) within a year, including all-cause death, cardiovascular death, re-hospitalization for acute heart failure, and unplanned PCI after primary PCI.

2.4 Statistical analysis

The quantitative data were described as mean ± standard deviation (SD) or median with inter-quartile ranges, and the Student’s t-test or Mann-Whitney U test was used for the comparison between the nicorandil group and placebo group. The categorical indicators

were described as numbers and ratio, and the Pearson's Chi-square or Fisher exact tests were performed between two groups. We also used the logistic regression model to explore relationship between the use of nicorandil and CIN. Odds ratio (OR) was reported with 95% confidence interval (CI). SPSS statistics 23.0 was used for all data analysis, and *P*-value < 0.05 (2-tailed) was considered being statistically significant.

3. Results

3.1 Patient Characteristics

A total of 613 patients with STEMI who underwent primary PCI were considerate to enroll in our study. Among the patients, 375 did not meet the inclusion criteria or were excluded from this trial. The study population included 238 randomized patients, but 12 patients didn't have perioperative serum creatinine data, so 226 of 238 STEMI patients were included in the final analysis (Figure 1). The clinical characteristics of the patients in nicorandil group and placebo group are showed in Table 1. There was no significant difference between the two groups in relation to demographic information, past medical history, clinical manifestation, laboratory tests and medication on admission (all P > 0.05). The baseline serum creatinines between the two groups were not statistically difference [(80 ± 22) μmol/L vs. (82 ± 23) μmol/L ; P=0.644].

3.2 Angiographic results of Primary PCI

The results of primary PCI of the patients in nicorandil and placebo groups are showed in Table 2. There were no significant difference between the two groups with respect to TIMI grade flow before PCI, volume of contrast and number of stents implanted (all P > 0.05). Postoperative TIMI grade in nicorandil group was significantly better than that in placebo group (P=0.001). Nicorandil could improve the final perfusion for STEMI patients in this trial.

3.3 CIN incidence and MACEs between the groups

The incidence of CIN in nicorandil group and placebo group are summarized in Table 3. The incidence of CIN in nicorandil group was significantly lower than that in placebo group [9.7% (11/113) vs. 24.8% (28/113), P=0.003]. There was no significant difference between the two groups with respect to MACEs (P > 0.05). In addition, no patients needed renal replacement therapy.

3.4 Association between Nicorandil and CIN

The logistic regression analysis is used to explore the independent risk factors and protective factors or CIN. Results showed that nicorandil was still an independent protective factor for CIN adjusted by gender, age, hemoglobin, cardiac function, baseline serum creatinine, diabetes mellitus and contrast volume (OR: 0.379, 95% CI: 0.166-0.861, P =0.021).

4. Discussion

The cardio protective effects of nicorandil have been widely reported[10-12]. However, the renal protective potential for nicorandil has often been studied in selective PCI, and retrospective study explored effects of nicorandil for emergency PCI on preventing CIN in STEMI patients[13]. Patients receiving primary PCI have an increased risk of CIN compared with those after selective PCI[14], but CIN prevention are less frequently applied in primary PCI than in elective PCI. In this prospective trial study, we aimed to investigate the potential effect of intravenous nicorandil on CIN in STEMI patients undergoing PPCI, and found nicorandil was protective factor for CIN for STEMI patients undergoing PPCI. These findings would suggest a new strategy for the prevention of CIN after primary PCI in patients with STEMI.

The negative results (nicorandil is ineffective in preventing CIN)

were showed in the PRINCIPLE study. The study enrolling 149 patients with renal insufficiency undergoing elective PCI used a smaller dose of nicorandil with a relative smaller sample size[15]. Some acute coronary syndrome patients may benefit from nicorandil administration before PCI. Previous studies have demonstrated that the incidence of CIN fluctuates from 6% to 20% in patients undergoing primary PCI[1,2], and in our study, the incidence of CIN in the placebo group was more than 20%. Although the mechanism of CIN is not fully understood, it is believed that this complication is closely related to renal ischemic injury and the direct renal tubular cytotoxicity of contrast medium[16]. These two processes are possibly mediated by the release of reactive oxygen species, intracellular calcium overload and the imbalance of vasoconstrictors and vasodilators such as adenosine, endothelin-1, angiotensin II, serotonin, nitric oxide and prostaglandins[17]. Nicorandil have both nitrate and K channel effects. On the one hand, nitrate helps to increase the production of nitric oxide in blood vessels and to decrease the generation of intracellular reactive oxygen species. On the other hand, the opening of intracellular K_{ATP} channel improves the intracellular calcium overload [18]. The activation of the KATP channel can reduce renal injury due to ischemia and reperfusion by limiting the accumulation of reactive oxygen radicals.

The purpose of primary PCI is to open culprit arteries as quickly as possible to protect more myocardium in STEMIs. However, even without residual stenosis, it is not always possible to achieve the recovery of blood flow and complete myocardial reperfusion, which is known as no-reflow phenomenon. In our study, postoperative TIMI grade in nicorandil group was significantly better than that in placebo group, demonstrating the effect of nicorandil, which is

consistent with previous researches[19]. These STEMI patients with nicorandil had more successful PPCI outcome and smaller infarcts, which also ensured renal effective perfusion and protection.

There were several limitations in our study. Firstly, the definition of CIN is based on the changes in serum creatinine. However, studies have reported that serum creatinine levels are susceptible to a number of factors, including food, age and weight[20]. Therefore, another biomarker, Cystatin C, which is cleared only in the kidney and would not be affected by age, sex, dietary, medications or inflammation[21], could be used in future studies to evaluate CIN in early renal damage. Secondly, as a multi-center study, the number of patients was relatively small. Larger sample study and long follow-up time should be performed in future studies.

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Figure 1. Study Flowchart.

STEMI, ST-elevation myocardial infarction; pPCI, primary percutaneous coronary intervention;

Figures

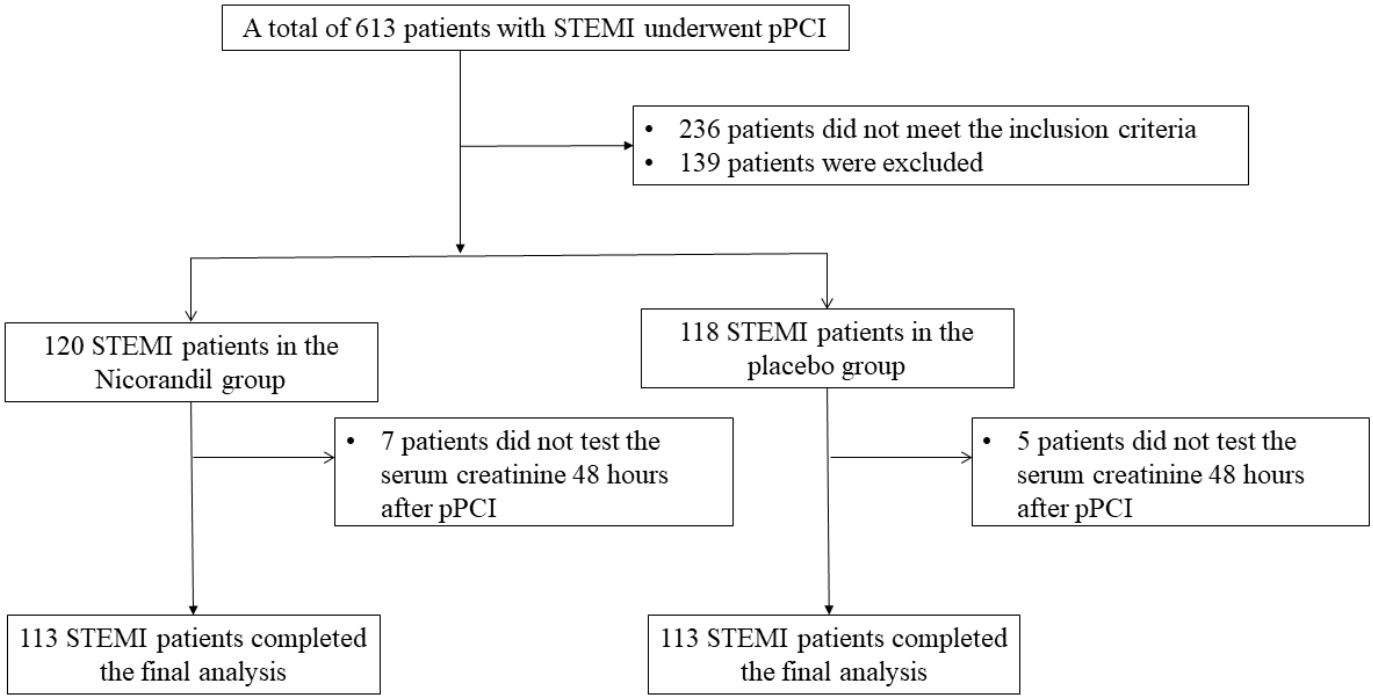

Figure 1

Study Flowchart.

STEMI, ST-elevation myocardial infarction; pPCI, primary percutaneous coronary intervention;

Supplementary Files

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