Original paper

Effect of nicorandil administration on myocardial microcirculation during primary percutaneous coronary intervention in patients with acute myocardial infarction

Chunguang Feng, Bing Han, Yi Liu, Lulu Wang, Dongdong Niu, Ming Lou, Cunzhi Lu

Institute of Cardiovascular Disease, Xuzhou Central Hospital, Xuzhou, China

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Abstract

Introduction: Prevention of the no-reflow phenomenon has a crucial role in primary percutaneous coronary intervention (P-PCI) procedures.

Aim: To assess the effects of early intracoronary administration of nicorandil (NIC) during P-PCI on myocardial microcirculation in patients with acute myocardial infarction (AMI).

Material and methods: A total of 120 patients with first acute anterior wall ST segment elevation myocardial infarction who underwent P-PCI were randomly divided into two groups: the NIC group (A, $n = 60$) and the placebo group (B, $n = 60$). Before stent placement, NIC or normal saline was injected using a guiding catheter. The thrombolysis in myocardial infarction (TIMI) grade, TIMI myocardial perfusion grade (TMPG), resolution of ST segment elevation (defined as > 50% decrease in ST elevation) 1 h after surgery, and $^{99}Tc^{m}$-methoxyisobutyl isocyanide (MIBI) rest myocardial perfusion imaging (MPI) *via* single-photon emission computed tomography ($^{99}Tc^{m}$-MIBI SPECT) findings 10 days after surgery were compared between the two groups.

Results: The number of patients who achieved TIMI grade 3 (96.67% vs. 86.67%; $p = 0.047$) and TMPG 3 (95% vs. 83.33%; $p = 0.040$) was higher in the NIC group than in the placebo group. Resolution of ST segment elevation occurred in 95% and 81.67% of the patients in the NIC and placebo groups, respectively ($p = 0.023$); the MPI score of the two groups was 4.1 ±1.89 and 7.3 ±2.65, respectively ($p = 0.014$).

Conclusions: Early coronary administration of NIC can significantly reduce the damage in the myocardial microcirculation caused by P-PCI and the myocardial infarct size in patients with AMI.

Key words: primary percutaneous coronary intervention, nicorandil, no-reflow.

Introduction

Primary percutaneous coronary intervention (P-PCI) is currently the most effective method of treating acute myocardial infarction (AMI). However, intraoperative reperfusion injury is not rare, appearing as the no-reflow phenomenon, reperfusion-induced arrhythmia, or recurrence of chest pain [1]. The no-reflow phenomenon is an independent risk factor that affects the short-term prognosis in PCI and long-term cardiac death and events, and patients with this condition may experience increased myocardial infarct size, left ventricular enlargement, decreased cardiac function, malignant arrhythmia, or even death; thus, the clinical outcomes are poor [2, 3].

Nicorandil (NIC) is a K^{+}-ATP channel opener with a unique dual mechanism of action. Nicorandil can play nitric acid ester-like roles to expand the coronary artery; conversely, it can open the K^{+}-ATP channel on the vascular smooth muscles, thus increasing the outflow of K^{+} from cells, inhibiting the inflow of Ca^{2+}, reducing the Ca^{2+} overload, and consequently reducing the incidence of arrhythmia; at the same time, it can expand the small coronary arteries and increase the coronary blood flow [4, 5]. Several studies have confirmed that the administration of verapamil [6, 7] or sodium nitroprusside [8, 9] in P-PCI can improve the no-reflow phenomenon. Compared with calcium antagonists and sodium nitroprusside, NIC has no significant adverse reactions, such as significant blood pressure decline, heart rate decline, or atrioventricular block inducement [10, 11].

In the current guidelines, there is no recommendation regarding preventive medication against the no-re-

Corresponding author:
Chunguang Feng, Institute of Cardiovascular Disease, Xuzhou Central Hospital, 199 Jiefang South Road, 221009 Xuzhou, China, phone: +86 516 83985081, e-mail: cnchunguangfeng@163.com
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flow phenomenon, and no previous relevant research on NIC injection has been conducted yet on the Chinese mainland. Compared with position emission computed tomography (PET), $^{99}Tc^{m}$- methoxyisobutyl isocyanide single-photon emission computed tomography (MIBI SPECT) has very high accuracy and specificity in assessment of viable myocardium; therefore, it is a very important noninvasive method of evaluating myocardial ischemia in and the prognosis of patients with coronary heart disease (CHD) [12–15].

Aim

In this study, we selected patients with acute anterior wall ST segment elevation myocardial infarction (AASTMI) as the study subjects, examined the effect of coronary infusion of NIC on myocardial microcirculation before the occurrence of the no-reflow phenomenon, and investigated its safety and whether it can reduce the occurrence of reperfusion injury and myocardial infarct size.

Material and methods

General information

A total of 120 patients, who were hospitalized at Xuzhou Central Hospital and underwent P-PCI for initial AASTMI from June 2014 to March 2016, were selected, including 86 men and 34 women aged 67.20 ±5.04 years (range: 32–79 years). The inclusion criteria were as follows: (1) chest pain of > 30 min and unresponsiveness to nitroglycerin administration; (2) lead ST segment elevation in V1 to V4–V6 segments of ≥ 0.1 mV (acute anterior wall or extensive anterior wall myocardial infarction); (3) normal or greater than normal troponin level on admission; (4) no cardiogenic shock; (5) occluded infarct-related blood vessels. The exclusion criteria were as follows: (1) history of myocardial infarction; (2) conditions that could affect the assessment of the ST segment in the electrocardiogram (ECG), such as left bundle branch block, ventricular autonomic heart rate, presence of ventricular pacemaker, etc.; (3) inability to achieve satisfactory cardiac ultrasound images; (4) age > 80 years. The physicians obtained written informed consent from each patient, and the study was approved by the hospital ethics committee. The Clinicaltrials.gov registration number is NCT02435797.

Treatment

All the patients were emergently administered 300 mg of aspirin and 180 mg of ticagrelor per meal and underwent trans-radial artery coronary angiography and interventional therapy. When the guide wire passed through the target lesion and reached the distal end of the coronary artery, the balloon was dilated. If the thrombus-induced load was obvious, one suction catheter was used (Thrombuster, Terumo Corporation, Japan) to aspirate the thrombi. When the antegrade blood flow was restored, each patient was classified on the basis of the thrombolysis in myocardial infarction (TIMI) grade. When the TIMI grade reached grades 2–3, tirofiban (platelet membrane glycoprotein IIb/IIIa receptor antagonist, 10 μg/kg, trade name: Lunan Hengkang, Shandong Lunan Pharmaceutical Co., Ltd.) was injected via a coronary incision. The patients were then randomly divided into the nicorandil group (all the patients were administered NIC early, n = 60) and the placebo group (all the patients were administered placebo, n = 60) by the method of a random number table. Patients in the nicorandil group were intravenously injected with 2 mg of NIC via the coronary incision (trade name: Ruikexi, Beijing Sihuan Kebao Pharmaceutical Co., Ltd.) and underwent repeated angiography after 5 min; if the TIMI grade in the coronary artery was less than grade 3, 2 mg of NIC was re-injected to the distal end of the target lesion, and the total amount of NIC injected was never more than 6 mg. Patients in the placebo group were injected with saline (2 ml each time) via the coronary incision and underwent repeated angiography after 5 min; if the TIMI grade in the coronary artery was less than grade 3, 2 ml of saline was re-injected to the distal end of the target lesion, and the total amount of saline injected was never more than 6 ml. After related medication administration, thrombus suctioning was continued when the thrombus-induced load was still obvious; when the patients in the two groups had TIMI grades 0–2 after stent implantation, the suction catheter was re-used, or 100–200 μg of sodium nitroprusside was injected to the distal end of the target lesion. The TIMI grade and TIMI myocardial perfusion grade (TMPG) were determined at the designated time points (immediately after stent implantation (T1) and at the end of surgery (T2)). No reflow after reperfusion was defined as follows [16]: coronary angiography revealing TIMI grades 0–2 (antegrade blood flow) after PCI, without residual stenosis, vascular wall intercalation, thromboembolism, spasm, or other mechanical obstruction. The criteria used for coronary angiography TIMI grade [17] and TMPG were in accordance with the conventional criteria [18]. The flow diagram is as follows (Figure 1).

Each patient preferred the optimized medication if no contraindication occurred, including antiplatelet, anticoagulant, statin, angiotensin-converting enzyme inhibitor, angiotensin II receptor antagonist, β-blocker, nitrate, or blood pressure and blood glucose control medications.

ECG

ECG was performed in each patient immediately on admission and 1 h after PCI; thereafter, the sum of the elevated ST segment (ΣST) and the decline amplitude was calculated. The calculation formula was as follows: [ΣST (on admission) – ΣST (after PCI)]/ΣST (on admission). The patients were divided into two groups: rapid decline group (decline ≥ 50%) and ST segment continuous eleva-

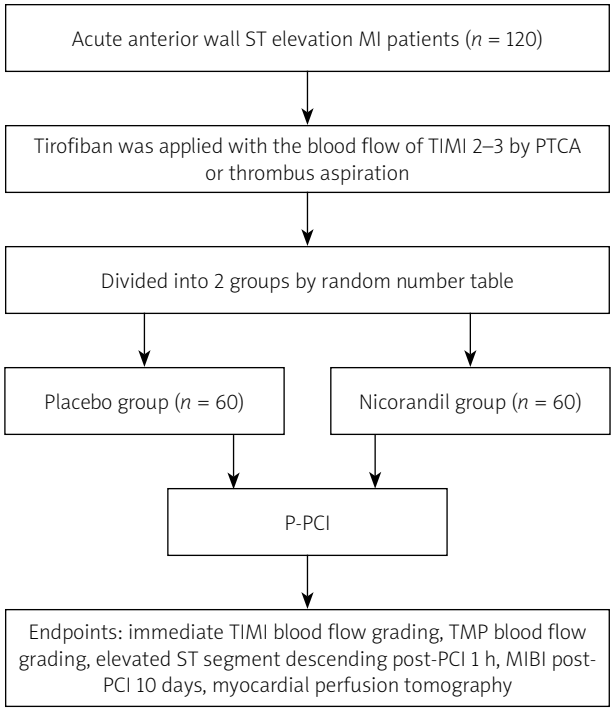

Figure 1. Flow diagram of this trial

tion group (decline < 50%); and a decline of < 50% was considered to indicate poor reperfusion [19].

Myocardial perfusion imaging (MPI)

The two groups underwent MPI 10 days after P-PCI using one Siemens E.cam SPECT instrument, with the imaging agent $^{99}Tc^{m}$-MIBI (radiochemical purity > 95%); MIBI was provided by Jiangyuan Pharmaceutical Factory, Jiangsu Provincial Institute of Atomic Medicine, and ~740 MBq was injected into each patient's elbow vein. Based on the relationship between the distribution of the coronary artery and the anatomy of the myocardium, the left ventricle was divided into the anterior wall, anterior wall base, anterior septum, posterior septum, apex, anterolateral wall, posterior wall, lower wall, and posterior wall, which were scored in accordance with the following criteria: 0 points: normal intake of $^{99}Tc^{m}$-MIBI (the radioactivity count of this area was also set as 100%); 1 point: radioactivity count lower than the normal level by > 25%; 2 points: radioactivity count lower than the normal level by > 50%; and 3 points: radioactivity count lower than the normal level by > 75%. The evaluation and semi-quantitative analysis of the images were conducted independently by two experienced nuclear medicine physicians using the single-blind method.

Statistical analysis

The SPSS 17.0 software was used for the analysis; the sparse or defective segments on $^{99}Tc^{m}$-MIBI SPECT were expressed as $\bar{x} \pm s$. The measurement data between groups A and B were compared using the *t*-test of two independent samples; the count data were compared using the χ^2 test (when the theoretical value was < 5, the corrected value was used), with $p < 0.05$ considered as significant.

Results

Baseline data

There was no significant difference in age, sex, risk factors of CHD (hypertension, diabetes, dyslipidemia, or smoking history), interval from onset to surgery, stent, or medication conditions between the two groups (Table I).

TIMI grade and TMPG

The grades in the nicorandil group at post-stent and post-procedure were significantly better than those in the placebo group ($\chi^2 = 4.62$, $p = 0.032$ and $\chi^2 = 3.93$, $p = 0.047$), suggesting that early intraoperative application of NIC can significantly reduce the occurrence of postoperative no/slow blood flow (Figure 2).

Comparison of TMPG

The number of patients with TMPG 3 in the nicorandil group at post-stent and post-procedure was significantly higher than that in the placebo group ($\chi^2 = 5.07$, $p = 0.024$ and $\chi^2 = 4.23$, $p = 0.040$), indicating that the early intraoperative application of NIC can significantly improve the postoperative coronary microcirculation (Figure 2).

After surgery, the comparison of the ST segment decline between the two groups showed that the nicorandil group had significantly better results than the placebo group. ECG revealed a rapid ST-segment decline in the nicorandil group (95% vs. 81.67%, $p = 0.02$), indicating that the early intraoperative application of NIC can significantly improve this sensitive and specific noninvasive index, which can reflect the level of myocardial microcirculation (Table I).

The changes in the MPI score indicated that the early administration of NIC can reduce the MPI score and myocardial infarct size (Table I).

Comparison of side effects

Ten patients in the nicorandil group exhibited a transient blood pressure decline of < 10 mm Hg after medication administration but self-recovered thereafter.

Discussion

This study found that early P-PCI-intervened administration of NIC in patients with AASTMI can significantly reduce the incidence of reperfusion injury and the myocardial infarct size without obvious side effects.

The most effective method of treating AMI is to open the infarct-related blood vessels as soon as possible to save the dying myocardium at present [20]. Early complete reperfusion against the infarct-related coronary ar-

Table I. Comparison of baseline patient characteristics and outcomes between the two groups

Parameter	Nicorandil (n = 60)	Placebo (n = 60)	P-value
Age [years]	67.53 ±5.11	66.86 ±4.97	0.785
Male	45	41	0.418
Hypertension	28	31	0.584
Dyslipidemia	18	23	0.336
Type 2 diabetes mellitus	25	18	0.182
Smoking (within 1 year)	27	21	0.264
Interval from onset to PCI [h]	4.21 ±2.67	4.33 ±2.12	0.698
3 of suction catheter	5	12	0.067
Stent length [mm]	22.88 ±7.82	23.25 ±8.17	0.726
Number of stents	71	79	0.812
Drug:			
Aspirin	60	60	
Ticagrelor	60	60	
Tirofiban	60	60	
Nitrates	47	50	0.487
Statins	58	60	0.154
ACEI	52	50	0.609
ARB	8	10	0.609
B-receptor blockers	53	54	0.769
Rapid ST-segment decline	57 (95%)	49 (81.67%)	0.023
MPI score	4.1 ±1.89	7.3 ±2.65	0.014

Dyslipidemia: L-LDL > 70 mg/dl. The drug was used during the whole duration of therapy, including admission, in-hospital stay and after discharge.

tery can reduce the myocardial infarct size, cardiac mortality, and incidence of other adverse cardiac events [21]. Owing to various reasons, TIMI grades 0–2 would still be observed even if stenosis or occlusion had been released; although the TIMI grade reaches grade 3 in some cases, the myocardial tissue still may not achieve effective reperfusion, namely, the no-reflow phenomenon. The presence of the no-reflow phenomenon greatly diminishes the clinical benefits of P-PCI; additionally, it is a sign of severe myocardial and microvascular injuries, as well as an important factor for continuous ischemia, infarct extension, ventricular remodeling, and cardiac functional recovery disorder [1–3].

Studies have shown that patients with and without rapid normalization of the ST segment within 1 h of P-PCI (elevated ST segment decline of ≥ 50%) may exhibit significantly different prognoses. The declining amplitude of the elevated ST segment after P-PCI can reflect the level of microcirculatory reperfusion in the related infarcted myocardium, and the more obvious the declining amplitude is, the better is the patient's prognosis [22]. $^{99}Tc^{m}$-MIBI SPECT provides direct manifestations of myocardial activity and is an important noninvasive method of assessing myocardial ischemia in and the prognosis of patients with CHD. In this study, we did not use the gold standard to assess myocardial viability, namely PET. Many studies have suggested that $^{99}Tc^{m}$-MIBI SPECT has

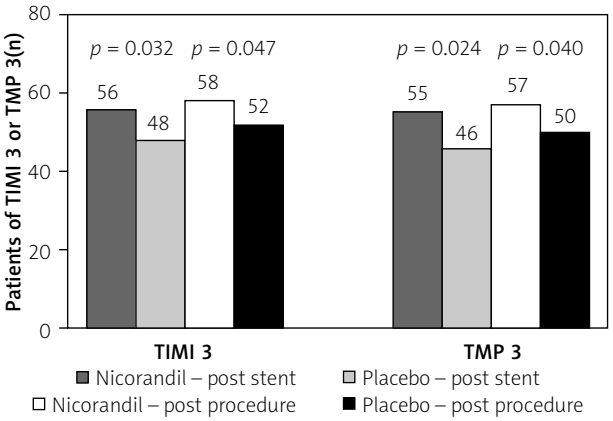

Figure 2. Comparison of target blood vessel TIMI grade 3 blood flow between the two groups. Significant improvement of target blood vessel TIMI grade 3 blood flow occurred in nicorandil group compared with placebo group

a good correlation with PET when used to measure the local myocardial metabolic status; thus, it may have considerable clinical application value [12–15].

Previous studies have confirmed that the administration of verapamil [6, 7], adenosine [23], or sodium nitroprusside [8, 9] can improve the no-reflow phenomenon in percutaneous transluminal coronary angioplasty; however, these medications all yield adverse reactions, such as blood pressure and heart rate decline and atrioventricular block inducement. Moreover, the doses of such medications are limited to a certain extent. Nicorandil is a K^+-ATP channel opener with a unique dual mechanism of action. Nicorandil can also play nitric acid ester-like roles to expand the coronary artery and to reduce the pre- and post-loads. Conversely, the increased outflow of K^+ can cause hyperpolarization of the cell membrane, shorten the duration of action potentials, inhibit the inflow of Ca^{2+}, and reduce Ca^{2+} overload, thus reducing the occurrence of arrhythmia, when the K^+-ATP channel on the vascular smooth muscle is open; it can also relax the vascular smooth muscles, expand the small coronary arteries, and increase coronary blood flow. Nicorandil has the same expansion effect toward the coronary arteries with different diameters, which can be more obvious in the smaller coronary arteries; compared with verapamil, adenosine, and sodium nitroprusside, it has no significant adverse reactions as in the abovementioned examples [10, 11].

Although the use of NIC at the time of PCI did not show any potential benefit on fatal and non-fatal outcomes in western countries [24], to our knowledge, no previous relevant research on NIC injection has been conducted yet on the Chinese mainland; thus, it is necessary to compare NIC with placebo to clarify its efficacy. In this study, high-concentration NIC was intravenously administered before the occurrence of the no-reflow phenomenon and exhibited its effect rapidly, in which the distal blood vessels showed a state of full expansion; NIC also further reduced the possibility of microvascular congestion and microvascular edema and spasm. The TIMI grade and TMPG in the nicorandil group were significantly superior to those in the placebo group, and after slow/no blood flow occurred, the effect of sodium nitroprusside was also significantly better in the nicorandil group than in the placebo group; the ST segment decline and the $^{99}Tc^m$-MIBI SPECT score were both significantly better in the nicorandil group than in the placebo group, without significant side effects, which is consistent with the reports of other researchers [25–27]. Although administration of drugs targeting mitochondrial function, such as NIC, in STEMI patients undergoing primary PCI appear to have no effect on mortality, they may reduce hospital readmission for HF [28].

Campo *et al.* [29] found that C subunit values were higher in AMI patients with poor values of TMPG and fully or partially absent of ST-segment resolution, and C subunit values were higher; left ventricle ejection fraction, wall motion score index and cumulative incidence of death and heart failure were worse in patients with elevated C subunit. It can be concluded that the early application of nicorandil would reduce C subunit values, so C subunit can be used as a new index in future studies.

The limitations of this study were as follows: (1) This study was conducted in a single center and had a relatively small sample size, which make the results less reliable. We will conduct multi-center, large-sample, randomized controlled studies for further confirmation. (2) If SPECT and PET had both been applied to evaluate the viable myocardium, the results would have been more reliable. (3) This study compared NIC with placebo, and a pairwise comparison with active medications can further elucidate its effectiveness.

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Conflict of interest

The authors declare no conflict of interest.

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