Heart, Lung and Circulation (2019) **28,** 858–865
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2018.05.097

ORIGINAL ARTICLE

Effects of Early Intracoronary Administration of Nicorandil During Percutaneous Coronary Intervention in Patients With Acute Myocardial Infarction

Chunguang Feng, PhD [*], **Yi Liu, MSc, Lulu Wang, MSc, Dongdong Niu, MSc, Bing Han, PhD**

Department of Cardiology, Central Hospital of Xuzhou, Xuzhou Institute of Cardiovascular Disease, Xuzhou City 221009, Jiangsu Province, China

Received 23 March 2017; received in revised form 28 April 2018; accepted 7 May 2018; online published-ahead-of-print 22 May 2018

Background To determine whether nicorandil administration distal to the thrombus in the coronary artery during percutaneous coronary intervention (PCI) in acute ST-segment elevation myocardial infarction (STEMI) patients reduced the incidence of no-reflow phenomenon, reperfusion injury, and adverse events.

Methods This randomised controlled trial involved 170 STEMI patients who underwent PCI. All patients underwent thrombectomy and tirofiban injection (10 μg/kg) distal to the vascular lesion via a suction catheter, followed by nicorandil (84 patients; 2 mg) or saline injection (86 patients; 2 mL) at the same site. The primary endpoint (major adverse cardiac events, MACEs) was 6-month cardiovascular mortality or unplanned readmission rate due to worsening congestive heart failure. The secondary endpoints were thrombolysis in myocardial infarction (TIMI) grade, TIMI myocardial perfusion grade (TMPG), resolution of ST-segment elevation (defined as >50% decrease in ST elevation); and ventricular arrhythmias.

Results Upon Kaplan-Meier analysis, freedom from MACEs was 92.9% in the nicorandil group and 81.4% in the placebo ($p = 0.026$). The numbers of patients achieving TIMI grade 3 (95.24% vs. 86.05%; $p = 0.040$) and TMPG 3 (94.05% vs. 83.72%; $p = 0.033$) were greater in the nicorandil group than in the control group. Resolution of ST-segment elevation occurred in 84.52% and 68.60% patients in the nicorandil and control groups, respectively ($p = 0.014$). Ventricular arrhythmias occurred in 5.95% and 16.28% patients in the nicorandil and control groups, respectively ($p = 0.032$).

Conclusions Early administration of nicorandil distal to the vascular lesion during PCI in STEMI patients may reduce the incidence of reperfusion injury, and improve short-term clinical outcomes.
Trial registration number: NCT02435797.

Keywords Acute myocardial infarction • Percutaneous coronary intervention • Reperfusion injury • No-reflow

Abbreviations: PCI, Percutaneous coronary intervention; AMI, Acute myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; TMPG, TIMI myocardial perfusion grade; P-PCI, Primary percutaneous coronary intervention; IRA, Infarct-related artery; ECG, Electrocardiographic; CHF, Congestive heart failure; NRP, No-reflow phenomenon; ΣST, The sum of the ST-segment deviations; SPECT, Single photon emission computed tomography; CMR, Cardiovascular magnetic resonance; PET, Positron emission computed tomography

*Corresponding author at: Department of Cardiology, Central Hospital of Xuzhou, Xuzhou Institute of Cardiovascular Disease, 199 Jiefang South Road, Xuzhou, 221009, Jiangsu Province, PR China. Tel.: +86 18936376559, Fax: +86 021 64085875., Email: fcg999@163.com

Background

Currently, primary percutaneous coronary intervention (P-PCI) is the most effective method for the treatment of acute ST-segment elevation myocardial infarction (STEMI) [1]. However, reperfusion injury commonly occurs during this procedure, and manifests as reperfusion-associated arrhythmias, no-reflow phenomenon, and recurrent chest pain [1]. The no-reflow phenomenon is an independent risk factor that affects the short-term prognosis after PCI as well as the long-term risks of cardiac death and cardiac events. Patients with this condition may develop left ventricular dilation, decreased cardiac function, malignant arrhythmia, and even death [2,3].

Nicorandil is a K^+-ATP channel opener with a unique dual mechanism of action. Nicorandil can act as a vasodilator similar to nitrate esters. In addition, it can activate K^+-ATP channels on vascular smooth muscles. The opening of these channels leads to the outflow of K^+ ions and the inhibition of Ca^{2+} ion inflow. In this way, cellular calcium overload can be reduced, and the incidence of arrhythmias can be decreased. Furthermore, small coronary arteries can be dilated, and coronary blood flow can be increased [4]. Importantly, nicorandil does not cause adverse reactions such as a sudden drop in blood pressure, bradycardia, and atrioventricular block. Therefore, nicorandil is administered in P-PCI patients by some investigators after the development of the no-reflow phenomenon [5–7]. However, few studies have investigated whether nicorandil can be administered before the occurrence of the no-reflow phenomenon as a preventive measure.

This study aimed to determine the safety and efficacy of nicorandil administration distal to the lesion site in the infarct-related artery (IRA) during P-PCI in acute myocardial infarction (AMI) patients in order to prevent the occurrence of the no-reflow phenomenon and reduce the incidence of reperfusion injury and adverse cardiac events, including cardiac death.

Methods

Patient Enrolment and Study Groups

From January 2015 to June 2016, we performed a randomised controlled trial (trial registration number: NCT02435797) at the Department of Cardiology, Central Hospital of Xuzhou to determine whether nicorandil administration into the IRA was safe and efficacious to prevent the incidence of the no-reflow phenomenon after P-PCI in AMI patients with ST-segment elevation.

A total of 180 patients were randomised to a treatment (nicorandil) group (n = 90) or a control (placebo) group (n = 90) by using a random number table. All subjects were blinded to the study groups. The study protocol was approved by the ethics committee of Xuzhou Central Hospital (Approval ID: XZXH1409), and written informed consent was given by each patient.

Selection Criteria

Acute myocardial infarction patients who met the following criteria were enrolled in this study: (1) ST elevation of >0.1 mV in two or more contiguous electrocardiographic (ECG) leads; (2) troponin I level above the upper limit of the normal range; (3) age, 18–80 years; (4) no history of myocardial infarction, PCI, or coronary artery bypass grafting; (5) total occlusion of the IRA; (6) blood pressure >90/60 mmHg; and (7) arrival at the hospital within 12 hours after AMI onset.

The exclusion criteria were as follows: (1) left bundle-branch block; (2) kidney dysfunction (creatinine >2 mg/dL); (3) history of myocardial infarction; and (4) severe hypotension at the time of AMI onset.

Intervention

Prior to P-PCI, all patients were orally administered 300 mg aspirin and 180 mg ticagrelor. In both groups, diagnostic coronary angiography was performed via the radial artery using the Seldinger method after the administration of local anaesthesia. A guidewire (Sion, Asahi Intecc Co., Japan; Runthrough NS, Terumo Corporation, Japan) was passed into the lesion in the coronary artery. A suction catheter (Thrombuster, Terumo, Japan) was used to aspirate the thrombus in the coronary artery. If obvious residual stenosis was present, then balloon expansion was conducted first, followed by repeated suction-catheter aspiration. Tirofiban, an antagonist of the glycoprotein IIb/IIIa receptors on platelet membranes (10 μg/kg; Lunanbeite Co. Ltd., China), was injected into the distal part of the lesion. After this, patients were randomly divided into the nicorandil group and control group.

In the nicorandil group, the thrombus-aspiration catheter was used to administer 2 mg nicorandil distal to the site of the lesion in the coronary artery. The drug was injected distal to the arterial thrombus to avoid low drug concentrations in the affected area, which would diminish its efficacy. At 5 minutes after the administration of nicorandil, angiography was repeated. If the TIMI flow grade of the affected coronary artery was less than 3, nicorandil administration (at the same dose) was repeated. The total dose of nicorandil administered did not exceed 6 mg in any patient. A minimum interval of 5 minutes was maintained between consecutive doses of nicorandil to reduce the incidence of adverse effects.

In the control group, the thrombus-aspiration catheter was used to administer 2 mL saline distal to the thrombus in the coronary artery. After 5 minutes, angiography was repeated. If the TIMI flow grade of the affected coronary artery was less than 3, saline administration was repeated. The total dose did not exceed 6 mL in any patient.

If TIMI grades of 0–2 were found after stent implantation, 100–200 μg sodium nitroprusside was administered via the suction catheter, distal to the site of the vascular lesion. All surgeries were performed by the author, himself.

Main Outcome Measures

The primary endpoint (MACEs) was the rate of cardiovascular death or unplanned readmission due to worsening congestive

heart failure (CHF) at 6 months (180 days) after the P-PCI [8]. Evidence of worsening heart failure included progressive aggravation of dyspnoea during exercise, paroxysmal nocturnal dyspnoea, orthopnoea, and the progression of the radiological signs of CHF. If these signs were detected, the patient was hospitalised and treated with intravenous diuretics.

The secondary endpoints were measured immediately after reperfusion, and were as follows: (1) TIMI flow grade after PCI [9]; (2) TMPG after PCI [10]; (3) resolution of ST-segment elevation on ECG after PCI; and (4) the occurrence of reperfusion arrhythmias, i.e., ventricular tachycardia and ventricular fibrillation.

No-reflow phenomenon (NRP) was defined as follows [3]: TIMI flow grade of 0–2 after PCI, before coronary angiography, after stenting, and at the end of the surgery, in the absence of residual stenosis, coronary artery dissection, thromboembolism, vasoconstriction, or other mechanical obstructions.

ECG

An ECG was performed 1 hour before and after PCI. To evaluate resolution of ST elevation, we calculated the total sum of ST segment elevation from the J point to the point reached 20 ms later on the 12-lead ECG. Evaluation of anterior infarction was based on the total sum of the ST elevation in leads V1–6, I, and aVL. Evaluation of non-anterior infarction was based on the total sum of the ST elevation in leads II, III, and aVF (including I, aVL, V5, and V6, if present). STR was measured by a physician without knowledge of the patient group allocation. The sum of the ST-segment deviations (ΣST) was calculated by adding the sum of ST-segment depressions measured in reciprocal leads to the sum of ST segment elevations. The formula used was as follows[11]: [ΣST (admission) – ΣST (after PCI)]/ΣST (admission). According to the ST segment deviation, the patients were divided into two groups: those who showed a rapid decrease in ST-segment deviation ($\geq$50% decrease) and those who did not (<50% decrease).

The type and frequency of ventricular arrhythmias were evaluated from the ECG monitoring in the cardiac catheterisation unit and the coronary care unit. Malignant ventricular arrhythmia was defined as ventricular tachycardia (a minimum of five consecutive beats of ventricular origin at a rate >100 bpm) or ventricular fibrillation within 24 hours after angioplasty.

Follow-Up

At 1, 3, and 6 months after PCI, both outpatient and telephone follow-up were conducted. The parameters assessed during follow-up mainly included changes in symptoms, drug treatment, and re-hospitalisation for worsening CHF.

Statistical Analysis

SPSS statistical software (SPSS 11.0, Chicago, IL, USA) was used in this study. Quantitative variables were compared between the two groups by using the independent-samples *t*-test. Categorical variables were compared between the two groups by using the four-fold contingency table χ^2 test. $p < 0.05$ was considered statistically significant.

Prior to the commencement of this study, we performed a sample-size calculation. We had planned to enrol one control subject for each case. Prior data indicated that the probability of exposure among the controls was 0.05. If the true probability of exposure among cases was 0.2, we would need to enrol 75 cases and 75 controls to be able to reject the null hypothesis that the exposure rates for cases and controls are equal, with a probability (power) of 0.8. The probability of type I error associated with this test of this null hypothesis is 0.05. We intended to use an uncorrected chi-square test to evaluate this null hypothesis. Considering a drop-out rate of 20%, we determined that the sample size of each group should be 90.

Results

Baseline Characteristics

Four patients in the nicorandil group and six patients in the control group were lost to follow-up. Thus, the nicorandil group consisted of 86 patients, while the control group consisted of 84 patients. The baseline characteristics of the two groups are shown in Table 1. No significant differences were present in any of the baseline characteristics between the two groups.

Primary Endpoint

On the first day of admission, there were no statistical differences between two groups on the values of concentration of brain natriuretic peptide (BNP), left ventricular end diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF). On the 180th day of admission, the values of concentration of BNP in nicorandil group were less than those in control group [(352.77 $\pm$ 108.45) pg/ml vs(542.31 $\pm$ 155.77) pg/ml, $p < 0.05$]. On the 180th day of admission, the values of LVEDD in the nicorandil group were less than those in control group [(55.02 $\pm$ 3.52 mm) vs (59.45 $\pm$ 4.75 mm), $p < 0.05$]; the values of LVEF in nicorandil group and in control group were not statistically different(42.21 $\pm$ 3.65% vs 39.54 $\pm$ 4.56%, $p > 0.05$) (Table 4).

By 6 months (180 days) after the surgery, five patients in the nicorandil group and 11 patients in the control group had been rehospitalised due to worsening CHF. During the same time frame, one patient in the nicorandil group and five patients in the control group died of cardiovascular causes. Figure 1 shows Kaplan-Meier curves of follow-up data for freedom from MACEs. Over 180-day period, the rate at which subjects avoided MACEs was 92.9% in the nicorandil group and 81.4% in the placebo group (Log Rank test, $\chi^2 = 4.929$, $p = 0.026$).

Secondary Endpoints

At the baseline, the TIMI flow grade was 0 in all patients. The flow grades both immediately after stent implantation ($p = 0.025$) and at the end of the operation ($p = 0.04$) were significantly better in the nicorandil group than in the control group (Table 2).

The number of patients who achieved a TMPG of 3 was significantly higher in the nicorandil group than in

Table 1 Baseline characteristics of the two study groups.

	Nicorandil group (n = 84)	Control group (n = 86)	P-value
Age (yr)	69.2 ± 4.2	68.5 ± 5.1	0.895
Male	59 (70%)	62 (72%)	0.789
Hypertension	47 (56%)	51 (59%)	0.659
Abnormal blood lipid profile[1]	28 (33%)	26 (30%)	0.664
Type 2 diabetes	35 (42%)	31 (36%)	0.452
Smoking history (within 1 yr)	38 (45%)	42 (49%)	0.638
Time from onset to PCI (h)	4.67 ± 3.12	4.84 ± 2.98	0.735
IRA			
LAD	38 (45%)	41 (48%)	0.750
LCX	13 (15%)	10 (12%)	0.463
RCA	33 (40%)	35 (40%)	0.851
Stent length (mm)	21.16 ± 7.82	19.89 ± 8.17	0.456
Number of stents	125	118	0.462
DES use	100%	100%	
post-dilatation	100%	100%	
Medications[2]			
Aspirin	84 (100%)	86 (100%)	
Ticagrelor	84 (100%)	86 (100%)	
Tirofiban	84 (100%)	86 (100%)	
Nitrate	75 (89%)	78 (91%)	0.759
Statin	82 (98%)	83 (97%)	0.669
ACEI	43 (51%)	47 (55%)	0.651
ARB	17 (20%)	15 (17%)	0.641
β-Blocker	49 (58%)	47 (55%)	0.628
Sulphonylureas	8/84 (9.52%)	14/86(16.28%)	0.19

Abbreviations: PCI, percutaneous coronary intervention; IRA, infarct-related artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; DES, drug eluting stent.

[1]Abnormal blood lipid profile was defined as a low-density lipoprotein cholesterol level >70 mg/dL.

[2]Aspirin and ticagrelor were administered prior to PCI. Tirofiban was administered during PCI, and the other drugs were administered after PCI. All the drugs were for long-term use.

the control group, both immediately after stenting (p = 0.039) and at the end of the operation (p = 0.033; Table 3).

A rapid decrease in ST-segment deviation occurred after the operation, as compared to the baseline, in 71 (84.52%) patients in the nicorandil group and 59 (68.60%) patients in the control group. The difference in the rate of improvement in ST-segment deviation between the two groups was statistically significant ($\chi^2 = 5.98$, p = 0.014). At 24 hours after PCI, the incidence rate of ventricular arrhythmias was significantly lower in the nicorandil group (five patients, 5.95%) than in the control group (14 patients, 16.28%; $\chi^2 = 4.56$, p = 0.032). After the administration of nicorandil, nine patients experienced a transient drop in blood pressure of 5–10 mmHg, but all of them recovered spontaneously.

Discussion

This study showed that, in AMI patients with ST-segment elevation, nicorandil injection distal to the coronary vascular lesion via a suction catheter before the occurrence of no-reflow phenomenon reduced the incidence of reperfusion injury after P-PCI as well as the rates of cardiovascular mortality and rehospitalisation at 6 months after the operation.

The most effective strategy to treat AMI is to open the IRA as soon as possible in order to salvage the dying myocardium. Early recanalisation of the IRA via P-PCI and the complete restoration of perfusion can reduce infarct size, cardiac mortality, and the incidence of adverse cardiac events [12]. However, this procedure is commonly complicated with reperfusion injury, which manifests as reperfusion-associated arrhythmia with no-reflow phenomenon and the recurrence of chest pain [1]. Reperfusion with no-reflow phenomenon refers to the adverse reperfusion of the myocardium in some patients due to various reasons, even though the IRAs are patent. Many of these patients have TIMI flow grades of 0–2. In some patients, poor myocardial reperfusion is present even after a TIMI flow grade of 3 has been achieved. Therefore, the recanalisation of the affected vessel alone may not always be sufficient to restore perfusion at the tissue level [13–15].

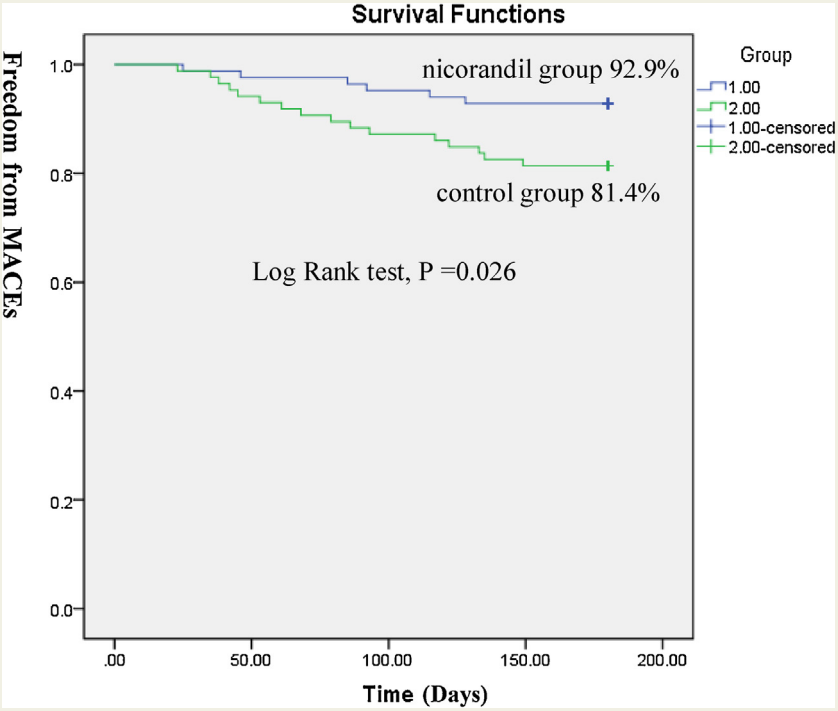

Figure 1 A Kaplan–Meier analysis for the freedom from major adverse cardiac events (MACEs) between two groups.

Table 2 **Comparison of TIMI flow grade of the affected vessel between the two study groups.**

TIMI flow grade	Nicorandil group (n = 84)	Control group (n = 86)	P-value
Immediately after stenting			
Grade 0	2	5	
Grade 1	3	6	
Grade 2	3	8	
Grades 0–2	8 (9.52%)	19 (22.09%)	0.025*
Grade 3	76	67	
End of operation			
Grades 0–2	4 (4.76%)	12 (13.95%)	0.040*
Grade 3	80	74	

*Compared with patients with TIMI grade 3 flow.

Table 3 **TMPG in the study patients.**

TMPG	Nicorandil group (n = 84)	Control group (n = 86)	P-value
Immediately after stenting			
Grade 0	2	4	
Grade 1	3	7	
Grade 2	6	11	
Grades 0–2	11 (13.09%)	22 (25.58%)	0.039*
Grade 3	73	64	
End of operation			
Grades 0–2	5 (5.95%)	14 (16.28%)	0.033*
Grade 3	79	72	

*Compared with patients with grade 3 TMPG.

The no-reflow phenomenon has been attributed to endothelial cell inflammation in the coronary microvasculature, microvascular spasm, platelet activation and aggregation, distal thrombosis or embolisation of atherosclerotic plaque debris, oxygen free radical-mediated endothelial injury, incarceration of activated neutrophils or red blood cells that have lost deformability in the capillaries, intracellular and intercellular oedema or coronary intramural haematoma, increased angiotensin II receptor density, loss of capillary integrity, and inflammatory responses [16]. No-reflow phenomenon is an independent risk factor that affects short-term prognosis after PCI as well as the long-term probability of cardiac death and cardiac events, such as left ventricular dilation, decreased cardiac function, malignant arrhythmia, left ventricular remodelling, hospital death, and revascularisation [2,3,17].

Studies have shown that the prognosis after P-PCI significantly differs between patients with and without rapid normalisation of the ST segment (≥50% decrease in ST elevation) [18,19]. Thus, the decrease in the amplitude of the ST segment immediately after P-PCI can reflect the reperfusion level in the infarct-related myocardium. The more obvious the decrease in the amplitude, the greater is the blood flow to the affected area and the better is the clinical prognosis. Several studies have verified that the application of

Table 4 Comparison of the appearance of echocardiogram and BNP between the two study groups.

	Day 1 after admission				Day 180 after admission			
	Group A	Group B	T value	P-value	Group A	Group B	T value	P-value
BNP (pg/ml)	231.52 ± 59.47	236.21 ± 57.63	0.712	0.591	352.77 ± 108.45	542.31 ± 155.77	2.763	0.039
LVEDD (mm)	49.42 ± 2.71	50.04 ± 2.84	0.581	0.675	55.02 ± 3.52	59.45 ± 4.75	4.412	0.021
LVEF (%)	47.11 ± 2.67	47.72 ± 2.42	1.854	0.342	42.21 ± 3.65	39.54 ± 4.56	1.846	0.245

Group A: Nicorandil group; Group B: Control group.

Abbreviations: BNP, brain natriuretic peptide; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction.

verapamil [20–22], adenosine [23–25], or sodium nitroprusside [26–28] during percutaneous transluminal coronary angioplasty can improve no-reflow phenomenon.

Nicorandil is a K^+-ATP channel opener with a unique dual mechanism of action. On the one hand, nicorandil can act as a nitrate ester and induce vascular smooth muscle relaxation, vasodilation, and reduction of preload and afterload. On the other hand, it can lead to the opening of the K^+-ATP channels on vascular smooth muscles, thereby resulting in K+ ion outflow, membrane hyperpolarisation, shortened action potential duration, decreased Ca^{2+} ion inflow, decreased calcium overload, and reduced arrhythmia incidence. Relaxation of the vascular smooth muscle and dilation of the coronary microvessels increase the blood flow through the coronary arteries. The vasodilatory effects of nicorandil on the coronary arteries differ with the arterial diameter, with finer coronary arteries showing more obvious dilation [4,29–31]. Compared with verapamil, adenosine, and sodium nitroprusside, nicorandil is not associated with adverse reactions such as an obvious drop in blood pressure, bradycardia, and atrioventricular block. Many studies have shown that the application of nicorandil during P-PCI can improve reperfusion injury and left ventricular ejection fraction in AMI patients, including diabetic patients [5–7,32,33]. Chen et al. found that nicorandil was superior to anisodamine in improving the TIMI flow grade after PCI (odds ratio, 2.501), and was associated with a similar incidence of major adverse cardiac events during a 30-day follow-up [34]. Similarly, Yamada et al. showed that the complementary use of intravenous and intracoronary nicorandil during PCI was superior to that of nitrate in limiting damage to the myocardium after MI [35]. Furthermore, the oral administration of nicorandil has also been shown to be useful in reducing myocardial injury during PCI as well as mortality rates after AMI [35,36].

However, few studies have applied nicorandil *before* the occurrence of the no-reflow phenomenon to prevent the incidence of the latter [37], even though early administration is likely associated with better efficacy. At present, the guidelines do not recommend nicorandil administration before the occurrence of the no-reflow phenomenon as a preventive measure. Moreover, few reports have examined the effects of nicorandil administration distal to the lesion in the IRA. Nicorandil injection was not routinely used during P-PCI in the Chinese Mainland in the past, and thus, relevant studies are lacking. In this study, nicorandil was injected distal to the vascular lesion via a suction catheter leading to relatively high local blood concentrations in the distal vasculature and improved dilation of the myocardial microvasculature. Moreover, the drug was injected *before* the occurrence of the no-reflow phenomenon to ensure that the distal vasculature was fully dilated, and further reduce the possibility of microvascular congestion, oedema, and spasm. This injection protocol produced no obvious side effects. Both TIMI grade and TMPG at the time of stenting were significantly better in the nicorandil group than in the control group. Furthermore, the efficacy of sodium nitroprusside when administered after the occurrence of slow/no blood flow was significantly better in the nicorandil group than in the control group. In addition, the incidence of rapid decrease in ST-segment deviation and ventricular arrhythmias, and the 6-month cardiovascular mortality and rehospitalisation rates were all significantly better than in the nicorandil group than in the control group.

There is some evidence for hypercholesterolaemia and sulphonylureas for the treatment of diabetes mellitus being a factor that modifies K_{ATP} channel function in the vasculature [38]. In this study, around 30% of the patient cohort had abnormal blood lipid profile [28/84(33%) vs 26/86(30%), p = 0.664] and 40% of the patient cohort had diabetes mellitus. Sulphonylureas administered in nicorandil group and control group were no statistical difference [8/84(9.52%) vs 14/86 (16.28%), p = 0.19]. Further investigation is necessary to clarify the effects on cardiovascular K_{ATP} channels and interaction with nicorandil in patients with ischaemic heart disease.

Study Limitations

The reliability of the present results may be affected by the relatively small sample size and the single-centre design. Therefore, the results need to be confirmed in multicentre, randomised controlled studies with large sample sizes.

This study lacks quantitative analyses, such as the more accurate evaluation of cardiac function using single-photon emission computed tomography (SPECT) or cardiac magnetic resonance (CMR), and the evaluation of myocardial viability using SPECT or positron emission tomography (PET) imaging. There is potential for observer bias (or outcome reporting bias) in the analysis, particularly with respect to the occurrence of worsening heart failure.

This study is a comparison of nicorandil and placebo. A head-to-head comparison with other drugs is required to further demonstrate the effectiveness of nicorandil.

Hypercholesterolaemia and sulphonylureas for the treatment of diabetes mellitus may have influenced the final results.

Conclusions

In summary, the early injection of nicorandil via a suction catheter inserted distal to the lesion in the coronary artery can reduce the incidence of reperfusion injury during P-PCI in AMI patients with ST-segment elevation. Furthermore, it improved the level of myocardial perfusion and the clinical outcomes of the patients without increasing the rate of complications.

Ethics Approval and Consent to Participate

The study protocol was approved by the ethics committee of Xuzhou Central Hospital (Approval ID: XZXH1409), and written informed consent was given by each patient.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets analysed during the current study will not be publicly available to protect patient confidentiality.

Funding

This work was funded by Science and Technology Planning Project of Xuzhou (KC14SH069).

Competing Interests

The authors declare that they have no actual or potential conflicts of interest.

Acknowledgements

None.

References

[1] Kloner RA. Does reperfusion injury exist in humans. J Am Coll Cardiol 1993;21:537–45.
[2] Resnic FS, Wainstein M, Lee MK, Behrendt D, Wainstein RV, Ohno-Machado L, et al. No-reflow is an independent predictor of death and myocardial infarction after percutaneous coronary intervention. Am Heart J 2003;145:42–6.
[3] Morishima I, Sone T, Okumura K, Tsuboi H, Kondo J, Mukawa H, et al. Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with percutaneous transluminal coronary angioplasty for first acute myocardial infarction. J Am Coll Cardiol 2000;36:1202–9.
[4] Taira N. Nicorandil as a hybrid between nitrates and potassium channel activators. Am J Cardiol 1989;63:18j–24j.
[5] Ikeda N, Yasu T, Kubo N, Hashimoto S, Tsuruya Y, Fujii M, et al. Nicorandil versus isosorbide dinitrate as adjunctive treatment to direct balloon angioplasty in acute myocardial infarction. Heart 2004;90:181–5.
[6] Lim SY, Bae EH, Jeong MH, Kang DG, Lee YS, Kim KH, et al. Effect of combined intracoronary adenosine and nicorandil on no-reflow phenomenon during percutaneous coronary intervention. Circ J 2004;68:928–32.
[7] Ota S, Nishikawa H, Takeuchi M, Nakajima K, Nakamura T, Okamoto S, et al. Impact of nicorandil to prevent reperfusion injury in patients with acute myocardial infarction: Sigmart Multicenter Angioplasty Revascularization Trial (SMART). Circ J 2006;70:1099–104.
[8] Ishii H, Ichimiya S, Kanashiro M, Amano T, Imai K, Murohara T, et al. Impact of a single intravenous administration of nicorandil before reperfusion in patients with ST-segment-elevation myocardial infarction. Circulation 2005;112:1284–8.
[9] Gibson CM, Cannon CP, Piana RN, Breall JA, Sharaf B, Flatley M, et al. Angiographic predictors of reocclusion after thrombolysis: results from the Thrombolysis in Myocardial Infarction (TIMI) 4 trial. J Am Coll Cardiol 1995;25:582–9.
[10] Gibson CM, Cannon CP, Murphy SA, Ryan KA, Mesley R, Marble SJ, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. Circulation 2000;101:125–30.
[11] Tomaszuk-Kazberuk A, Korecki J, Kochman W, Dobrzycki S, Musial WJ. Rapid resolution of ST segment elevation predicts recovery of left myocardial contraction in patients with acute myocardial infarction treated with percutaneous coronary angioplasty. Przegl Lek 2002;59:638–41.
[12] The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1997;336:1621–8.
[13] Reffelmann T, Kloner RA. The "no-reflow" phenomenon: basic science and clinical correlates. Heart 2002;87:162–8.
[14] Rezkalla SH, Kloner RA. No-reflow phenomenon. Circulation 2002;105:656–62.
[15] Costantini CO, Stone GW, Mehran R, Aymong E, Grines CL, Cox DA, et al. Frequency, correlates, and clinical implications of myocardial perfusion after primary angioplasty and stenting, with and without glycoprotein IIb/IIIa inhibition, in acute myocardial infarction. J Am Coll Cardiol 2004;44:305–12.
[16] Movahed MR, Butman SM. The pathogenesis and treatment of no-reflow occurring during percutaneous coronary intervention. Cardiovasc Revasc Med 2008;9:56–61.
[17] Morishima I, Sone T, Mokuno S, Taga S, Shimauchi A, Oki Y, et al. Clinical significance of no-reflow phenomenon observed on angiography after successful treatment of acute myocardial infarction with percutaneous transluminal coronary angioplasty. Am Heart J 1995;130:239–43.
[18] de Lemos JA, Antman EM, Giugliano RP, McCabe CH, Murphy SA, Van de Werf F, et al. ST-segment resolution and infarct-related artery patency and flow after thrombolytic therapy. Thrombolysis in Myocardial Infarction (TIMI) 14 investigators. Am J Cardiol 2000;85:299–304.
[19] Tomaszuk-Kazberuk A, Musial WJ, Dobrzycki S, Korecki J. Normalisation of elevated ST segment predicts return of left ventricular systolic function and improved outcome in patients with acute myocardial infarction, treated with primary coronary angioplasty. Kardiol Pol 2004;60:541–9. discussion 50–1.
[20] Demir I, Yilmaz H, Ermis C, Sancaktar O. Treatment of no-reflow phenomenon with verapamil after primary stent deployment during myocardial infarction. Jpn Heart J 2002;43:573–80.
[21] Werner GS, Lang K, Kuehnert H, Figulla HR. Intracoronary verapamil for reversal of no-reflow during coronary angioplasty for acute myocardial infarction. Catheter Cardiovasc Interv 2002;57:444–51.
[22] Fu Q, Lu W, Huang YJ, Wu Q, Wang LG, Wang HB, et al. Verapamil reverses myocardial no-reflow after primary percutaneous coronary intervention in patients with acute myocardial infarction. Cell Biochem Biophys 2013;67:911–4.
[23] Hanna GP, Yhip P, Fujise K, Schroth GW, Rosales OR, Anderson HV, et al. Intracoronary adenosine administered during rotational atherectomy of complex lesions in native coronary arteries reduces the incidence of no-reflow phenomenon. Catheter Cardiovasc Interv 1999;48:275–8.

[24] Mahaffey KW, Puma JA, Barbagelata NA, DiCarli MF, Leesar MA, Browne KF, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial. J Am Coll Cardiol 1999;34:1711–20.
[25] Assali AR, Sdringola S, Ghani M, Denkats AE, Yepes A, Hanna GP, et al. Intracoronary adenosine administered during percutaneous intervention in acute myocardial infarction and reduction in the incidence of "no reflow" phenomenon. Catheter Cardiovasc Interv 2000;51:27–31. discussion 2.
[26] Hillegass WB, Dean NA, Liao L, Rhinehart RG, Myers PR. Treatment of no-reflow and impaired flow with the nitric oxide donor nitroprusside following percutaneous coronary interventions: initial human clinical experience. J Am Coll Cardiol 2001;37:1335–43.
[27] Wang HJ, Lo PH, Lin JJ, Lee H, Hung JS. Treatment of slow/no-reflow phenomenon with intracoronary nitroprusside injection in primary coronary intervention for acute myocardial infarction. Catheter Cardiovasc Interv 2004;63:171–6.
[28] Pasceri V, Pristipino C, Pelliccia F, Granatelli A, Speciale G, Roncella A, et al. Effects of the nitric oxide donor nitroprusside on no-reflow phenomenon during coronary interventions for acute myocardial infarction. Am J Cardiol 2005;95:1358–61.
[29] Taira N. Similarity and dissimilarity in the mode and mechanism of action between nicorandil and classical nitrates: an overview. J Cardiovasc Pharmacol 1987;10(Suppl 8):S1–9.
[30] Pieper GM, Gross GJ. Anti-free-radical and neutrophil-modulating properties of the nitrovasodilator, nicorandil. Cardiovasc Drugs Ther 1992;6:225–32.
[31] Leesar MA, Stoddard MF, Dawn B, Jasti VG, Masden R, Bolli R. Delayed preconditioning-mimetic action of nitroglycerin in patients undergoing coronary angioplasty. Circulation 2001;103:2935–41.
[32] Kostic J, Djordjevic-Dikic A, Dobric M, Milasinovic D, Nedeljkovic M, Stojkovic S, et al. The effects of nicorandil on microvascular function in patients with ST segment elevation myocardial infarction undergoing primary PCI. Cardiovasc Ultrasound 2015;13:26.
[33] Shehata M. Cardioprotective effects of oral nicorandil use in diabetic patients undergoing elective percutaneous coronary intervention. J Interv Cardiol 2014;27:472–81.
[34] Chen C, Fu X, Li W, Jia X, Bai S, Geng W, et al. Intracoronary administration of anisodamine and nicorandil in individuals undergoing primary percutaneous coronary intervention for acute inferior myocardial infarction: a randomized factorial trial. Exp Ther Med 2015;10:1059–65.
[35] Yamada K, Isobe S, Ishii H, Yokouchi K, Iwata H, Sawada K, et al. Impacts of nicorandil on infarct myocardium in comparison with nitrate: assessed by cardiac magnetic resonance imaging. Heart Vessels 2016;31:1430–7.
[36] Yang J, Zhang J, Cui W, Liu F, Xie R, Yang X, et al. Cardioprotective effects of single oral dose of nicorandil before selective percutaneous coronary intervention. Anatol J Cardiol 2015;15:125–31.
[37] Lee HC, An SG, Choi JH, Lee TK, Kim J, Kim JH, et al. Effect of intracoronary nicorandil administration prior to reperfusion in acute ST segment elevation myocardial infarction. Circ J 2008;72:1425–9.
[38] Miura T, Miki T. ATP-sensitive K+ channel openers: old drugs with new clinical benefits for the heart. Curr Vasc Pharmacol 2003;1:251–8.