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Research Article
Intracoronary Injection of Nicorandil Alleviates No-Reflow in Elderly Patients with Acute STEMI Undergoing Emergency PCI

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Abstract

Background and Objective: The incidence of slow or no reflow during emergency percutaneous coronary intervention (PCI) is as high as 10-30%. How to prevent or alleviate no-reflow and improve myocardial perfusion during PCI has become a crucial clinical issue. To evaluate the impact of intracoronary injection of nicorandil on the no-reflow phenomenon in elderly patients with acute ST-segment Elevation Myocardial Infarction (STEMI) undergoing emergency PCI. **Materials and Methods:** The clinical data of 200 elderly patients with STEMI exhibiting the no-reflow phenomenon during emergency PCI at The First Affiliated Hospital of Wenzhou Medical University from August, 2016 to December, 2018 were retrospectively analyzed. According to the different treatment methods, they were divided into control group (n = 86) for intracoronary injection of nitroglycerin and study (n = 114) group for intracoronary injection of nicorandil. The two groups were compared in terms of the following indexes: Thrombolysis in Myocardial Infarction (TIMI) flow grade, echocardiographic parameters, serum markers, hemodynamic parameters and major adverse cardiovascular events (MACE). **Results:** After injection, the study group had higher TIMI flow grade; higher left ventricular ejection fraction, antithrombin III and tissue plasminogen activator; higher E/A ratio; higher cardiac index; lower left atrium volume index, global end-diastolic index and systemic vascular resistance index; lower von Willebrand factor, creatine kinase-MB fraction, cardiac troponin I, N-terminal pro-brain natriuretic peptide, cardiac troponin T and fibrinogen and lower MACE rates than the control group ($p<0.05$). **Conclusion:** Intracoronary injection of nicorandil can effectively improve the no-reflow phenomenon and facilitate the prognosis of elderly patients with STEMI undergoing emergency PCI.

Key words: Nicorandil, intracoronary injection, no-reflow, acute ST-segment elevation myocardial infarction, percutaneous coronary intervention, prognosis

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Acute myocardial infarction (AMI) is characterized by myocardial necrosis resulting from myocardial ischemia and anoxia induced by an acute obstruction of a coronary artery. The main clinical manifestation of AMI includes acute and persistent retrosternal pain[1,2]. Due to the sudden interruption or sharp reduction of coronary blood supply, AMI can lead to acute ischemic necrosis of myocardium and even lead to death in severe case. The key to the treatment of AMI is to dredge the blocked blood vessels, promote coronary reperfusion and improve the cardiac systolic function[3,4]. Percutaneous coronary intervention (PCI) is often implemented for the treatment of such patients. The PCI can rapidly promote the reperfusion of ischemic myocardium, improve ventricular function, reduce myocardial infarction area and restore the myocardium that is on the verge of necrosis. However, some patients experience worsening of cardiac function after PCI, which may be related to ventricular remodeling, ischemic myocardial cell injury, necrosis and the no-reflow phenomenon[5].

Coronary recanalization does not guarantee myocardial reperfusion. Relevant statistics show that the incidence rate of slow/no-reflow phenomenon in patients undergoing emergency PCI is as high as 10-30%[6,7]. Therefore, preventing or improving the no-reflow phenomenon during PCI, improving myocardial perfusion, inhibiting ventricular remodeling and reducing myocardial damage remain significant concerns for physicians. Nicorandil, a novel potassium channel opener with nitrate-like effects, can dilate the epicardial coronary artery and resistance vessel, promote hyperpolarization of myocardial cellular membrane and mitochondria and regulate cardiac microcirculation, thereby protecting the myocardium[8,9]. Previous studies have revealed that perioperative intravenous injection of nicorandil can inhibit reperfusion arrhythmia and reduce the incidence rate of slow/no-reflow phenomenon. Elderly patients have more complicated diseases and poor physical fitness and are more likely to have no-reflux phenomenon. At present, whether intracoronary injection of nicorandil can improve the no-reflow phenomenon and inhibit ventricular remodeling in elderly patients with AMI undergoing PCI remain to be investigated[10,11]. Thus, this study aimed to investigate the changes in TIMI flow grade, echocardiography and myocardial damage indexes in elderly patients who received nicorandil and exhibited the no-reflow phenomenon during emergency PCI.

MATERIALS AND METHODS

Clinical data: The clinical data of 200 elderly patients with acute ST-segment Elevation Myocardial Infarction (STEMI) exhibiting the no-reflow phenomenon during emergency PCI at The First Affiliated Hospital of Wenzhou Medical University from August, 2016 to December, 2018 were retrospectively analyzed.

Among the 200 patients, 132 and 68 were male and female patients, respectively, aged 60-89 years, with an average age of 76.3±6.8 years.

Inclusion criteria were as follows: Compliance with the diagnostic criteria for AMI with elevation of the ST segment based on the "guidelines for diagnosis and treatment of acute myocardial infarction[12]" and the onset of STEMI was less than 12 hrs, patients met the indications of direct PCI, intraoperative no-reflux (TIMI $\leq$grade 2, residual stenosis $\leq$20% in target lesion after balloon dilation or stent implantation, excluding dissection or tear), grade I-IV cardiac function and voluntary signing of informed consent form. Exclusion criteria were as follows: Valvular heart disease, congenital heart disease, pericarditis and rheumatic heart disease, intraoperative no-reflow phenomenon caused by interlayer or tear, intracranial hemorrhage, hematological system diseases, cardiogenic shock and autoimmune diseases, presence of thromboembolism during PCI and unidentifiable culprit vessel, thrombosis in stent and mental disorders and cognitive dysfunction. According to the different treatment methods, the patients were divided into control group (CG, n = 86) by intracoronary injection of nitroglycerin and study group (SG, n = 114) by intracoronary injection of nicorandil. This study was approved by Xiamen Huaxia University.

Methods

Conventional basic treatment: All patients underwent emergency PCI through the green channel within 12 hrs of STEMI onset and were orally given 40 mg of atorvastatin calcium (Pfizer Pharmaceuticals Co. Ltd., USA), 300 mg of Bayer aspirin enteric-coated tablets (Bayer Healthcare Co. Ltd., Italy) and 600 mg of clopidogrel bisulfate tablets [Sanofi (Hangzhou) Pharmaceutical Co. Ltd., Hangzhou]. After a successful arterial puncture, 3000 IU of unfractionated heparin was injected through the arterial sheathing canal. Before surgery, 8000 IU of unfractionated heparin was injected, with 2500 IU being injected through the sheathing canal every hour during surgery. Transfemoral coronary angiography was

performed according to the standard Judkins technique and PCI was performed. After the occurrence of no-reflux phenomenon, the CG received an intracoronary injection of 200 μg of nitroglycerin (Specifications: 1 mL: 5 mg, Guangzhou Baiyunshan Mingxing Pharmaceutical Co. Ltd., SFDA approval number: H44020569). On the basis of the CG, the SG received an intracoronary injection of 2 mL of nicorandil (Specification: 12 mg, Beijing Sihuan Kebao Pharmaceutical Co. Ltd., SFDA approval number: H20120069) and 10 mL of normal saline. After the injection was completed within 40-60 sec, balloon dilation and stent implantation were performed in both groups. Low-molecular-weight heparin (200 IU/kg) was subcutaneously injected after surgery (Specification: 1.0 mL: 5000 AXA, Shenzhen Sciprogen Bio-pharmaceutical Co. Ltd., SFDA approval number: H20060190), once a day for 5-7 days. At the same time, aspirin enteric-coated tablets (10 mg/day) and clopidogrel bisulfate tablets [Sanofi (Hangzhou) Pharmaceutical Co. Ltd., Hangzhou] (75 mg/day) were taken orally, once a day for 12 months.

Observational indexes

TIMI flow grade: Grade 0 indicates no perfusion. Grade 1 denotes partial perfusion, where the contrast agent partially traverses the occluded site, yet fails to adequately spacify the distal coronary arteries. Grade 2 denotes partial reperfusion, where contrast agent can adequately fill the distal coronary arteries, but the rate of contrast agent entry and clearance is slower than in normal coronary arteries. Grade 3 denotes complete reperfusion with rapid filling and clearance of the contrast agent within the coronary arteries.

Echocardiography: The Left Ventricular Ejection Fraction (LVEF), Left Ventricular End-Diastolic Diameter (LVEDD), early diastolic peak flow velocity (E), late diastolic peak flow velocity (A) and Left Atrial Volume Index (LAVI) of the mitral valve orifice were measured using a GE Vingmed E9 system before and at 24 hrs after injection and the E/A value was calculated.

Serum-related indexes: Before at 24 hrs after injection, 5 mL of fasting venous blood was collected and centrifuged. The levels of Creatine Kinase isoenzymes (CK-MB), cardiac troponin Ic (cTnI), N-Terminal Pro-B-Type Natriuretic Peptide (NT-proBNP) and Cardiac Troponin T (cTnT) were measured using double-antibody sandwich enzyme-linked immunosorbent assay. Meanwhile, the levels of Antithrombin III (AT-III), Tissue Plasminogen Activator (T-PA), von Willebrand Factor (vWF) and fibrinogen (FIB) were assayed using the Beckman Coulter CL-20 automatic biochemical analyzer.

Hemodynamics: Before and at 24 hrs after injection, the systemic vascular resistance index (SVRI), cardiac index (CI) and global end-diastolic volume index (GEDI) were measured using a PICCO monitor (Pulsion Medical Systems SE, Germany).

Prognosis: At the 12 month follow-up, MACE (e.g., revascularization, recurrent angina pectoris, malignant arrhythmia and readmission owing to heart failure) were investigated.

Statistical analysis: All statistical analyses were conducted using SPSS 24.0 software. Measured data were expressed as $\bar{\chi} \pm$sec. Between-group comparisons were performed using the independent sample t-test, whereas within-group comparisons were performed using the paired sample t-test. Enumeration data were detected using χ^2 test and expressed as percentages. A p-value of <0.05 indicated statistical significance.

RESULTS

General data: No significant differences in general data were observed between the two groups ($p>0.05$) (Table 1).

TIMI flow grade: The SG had a higher TIMI flow grade than the CG after injection ($p<0.05$), indicating that intracoronary nicorandil injection was effective against the no-reflow phenomenon (Table 2).

Echocardiography: No significant differences in LVEF, LVEDD, LAVI and E/A were observed between the two groups before injection ($p>0.05$). However, in both groups, LVEF levels and E/A ratios were higher after injection than those before injection, LAVI levels were lower after injection than those before injection ($p<0.05$). Before injection, the SG had a higher LVEF level and E/A ratio and lower LAVI level than the CG, suggesting that the intracoronary injection of nicorandil improved echocardiographic parameters (Fig. 1).

Indexes of myocardial damage: No significant differences in CK-MB, cTnI, NT-proBNP and cTnT were observed between the two groups before injection ($p>0.05$). In both groups, however, the levels of CK-MB, cTnI, NT-proBNP and cTnT were lower after injection than those before injection ($p<0.05$). Moreover, the SG had lower levels of CK-MB, cTnI, NT-proBNP and cTnT than the CG ($p<0.05$), suggesting that intracoronary injection of nicorandil reduced myocardial damage (Fig. 2a-d).

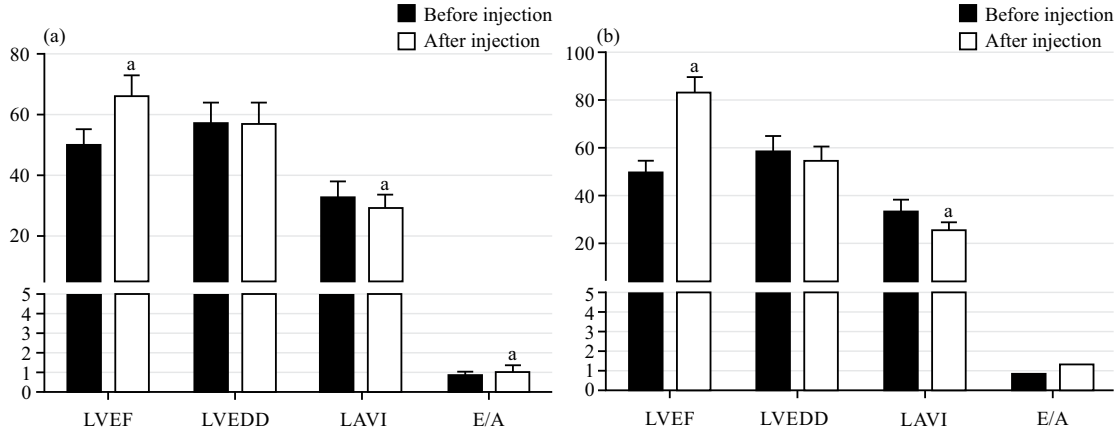

Fig. 1(a-b): Effect of intracoronary injection of nicorandil on patients' echocardiogram, (a) LVEF and E/A after injection in the control group were higher than before injection and LAVI was lower than before injection and (b) LVEF and E/A after injection in the study group were higher than before injection and LAVI was lower than before injection
Improvement of LVEF, LAVI and E/A in the study group after injection was better than that of the control group a p<0.05

Table 1: Comparison of general data between the two groups (n/$\bar{\chi}\pm$sec)

Group	M/F	Age (year)	Implantation of stents (pieces)	Smoking (case)	Door-to-balloon dilation time (min)	Complications: Diabetes/hypertension/ hyperlipemia (case)	Myocardial infarction site: Anterior wall/inferior wall/ inferior wall+posterior wall/lateral wall/lateral wall+posterior wall (case)
Control group (n = 86)	58/28	56.1±6.7	2.51±0.31	60	86.57±26.15	18/22/13	34/26/7/8/12
Study group (n = 114)	73/41	57.5±7.2	2.29±0.25	82	84.25±20.93	25/29/20	46/34/16/9/9

Table 2: Comparison of thrombolysis in myocardial infarction flow grades between the two groups [n (%)]

	Before injection				After injection			
Group	Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3
Control group (n = 86)	44 (51.16)	25 (29.07)	13 (15.12)	4 (8.14)	12 (13.95)	26 (30.23)	27 (31.40)	21 (24.42)
Study group (n = 114)	55 (48.25)	30 (26.32)	22 (19.30)	7 (6.14)	7 (6.14)	21 (18.42)	38 (33.33)	48 (42.11)[b]

Comparison with the control group after injection, [b]p<0.05

Table 3: Comparison of incidence rates of MACE between the two groups n (%)

Group	Revascularization	Recurrent angina pectoris	Malignant arrhythmia	Readmission due to heart failure	Total
Control group (n = 86)	5 (5.18)	6 (6.98)	7 (8.14)	4 (4.65)	22 (25.58)
Study group (n = 114)	4 (4.39)	6 (5.26)	2 (1.75)	3 (2.63)	16 (14.04)[b]

Compared with the control group, [b]p<0.05

Hemodynamics: No significant differences in CI, GEDI and SVRI were observed between the two groups before injection (p>0.05). However, in both groups, CI, GEDI and SVRI were higher after injection than before injection (p<0.05). Moreover, the SG had higher CI and lower GEDI and SVRI than the CG (p<0.05), indicating that intracoronary injection of nicorandil could improve patient hemodynamics (Fig. 2e-h).

Indexes of clot fibers: Both groups showed higher AT-III and T-PA levels and lower vWF and FIB levels after injection than those before injection (p<0.05). Moreover, the SG had higher AT-III and T-PA levels and lower vWF and FIB levels than the CG (p<0.05), indicating that intracoronary injection of nicorandil could regulate the clot fiber system (Fig. 3).

Prognosis: The SG had lower MACE incidence rates than the CG (14.04 vs. 25.58%) (p<0.05), demonstrating that intracoronary injection of nicorandil could reduce MACE incidence rates and improve patients' prognosis (Table 3).

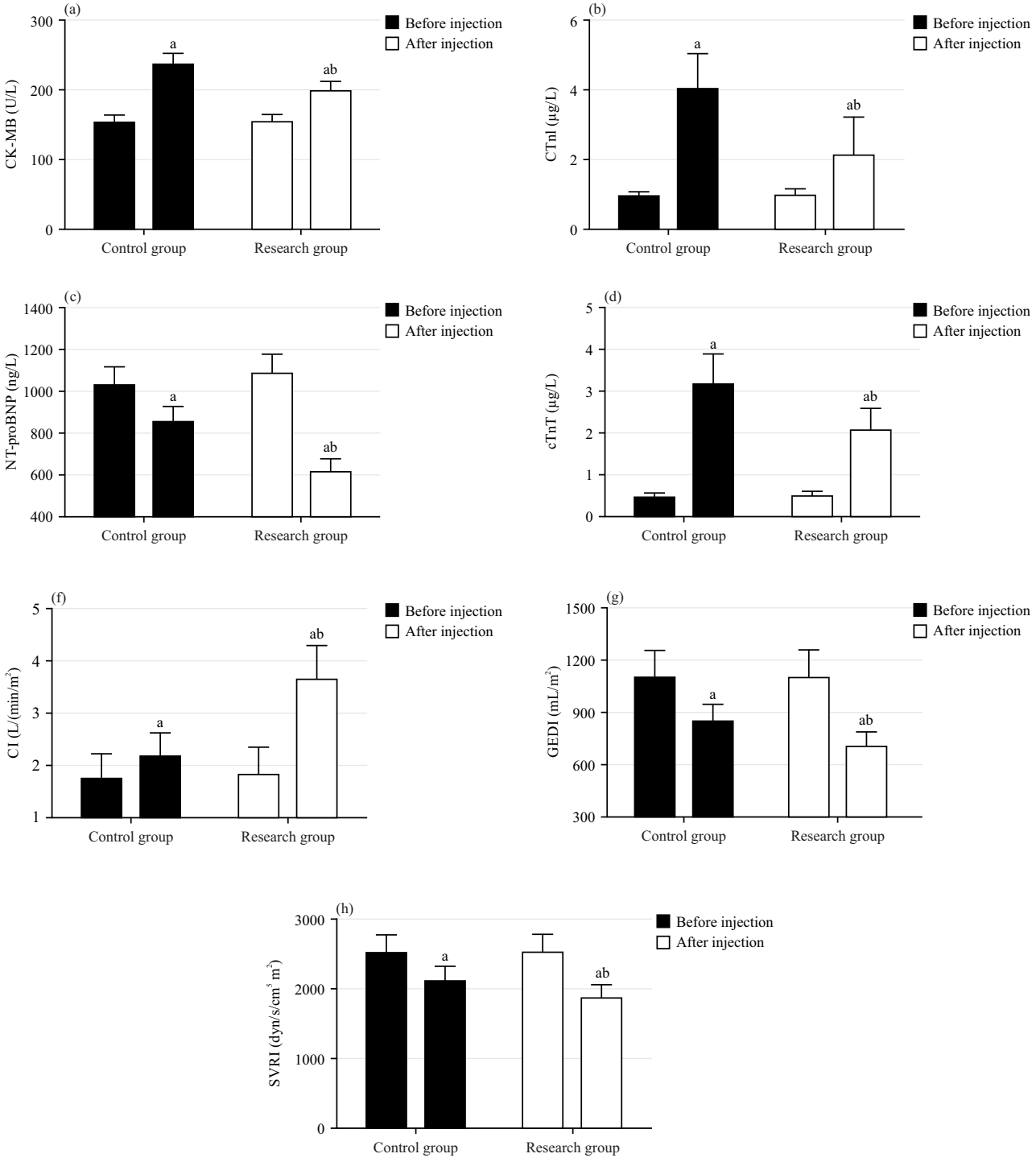

Fig. 2(a-h): Effect of intracoronary injection of nicorandil on the indexes of myocardial injury and hemodynamics, (a-d) Levels of CK-MB, cTnI, NT-proBNP and cTnT after intra-coronary injection of nicorandil in the study group was lower than that of the control group, suggesting that intra-coronary injection of nicorandil can reduce the degree of myocardial damage to patients and (e-h) CI of the study group after intra-coronary injection of nicorandil was higher than that of the control group and GEDI and SVRI were lower than those of the control group, suggesting that intra-coronary injection of nicorandil can improve the hemodynamic status of patients

Compared with the control group, $^{b}p<0.05$, compared with that before injection and $^{a}p<0.05$

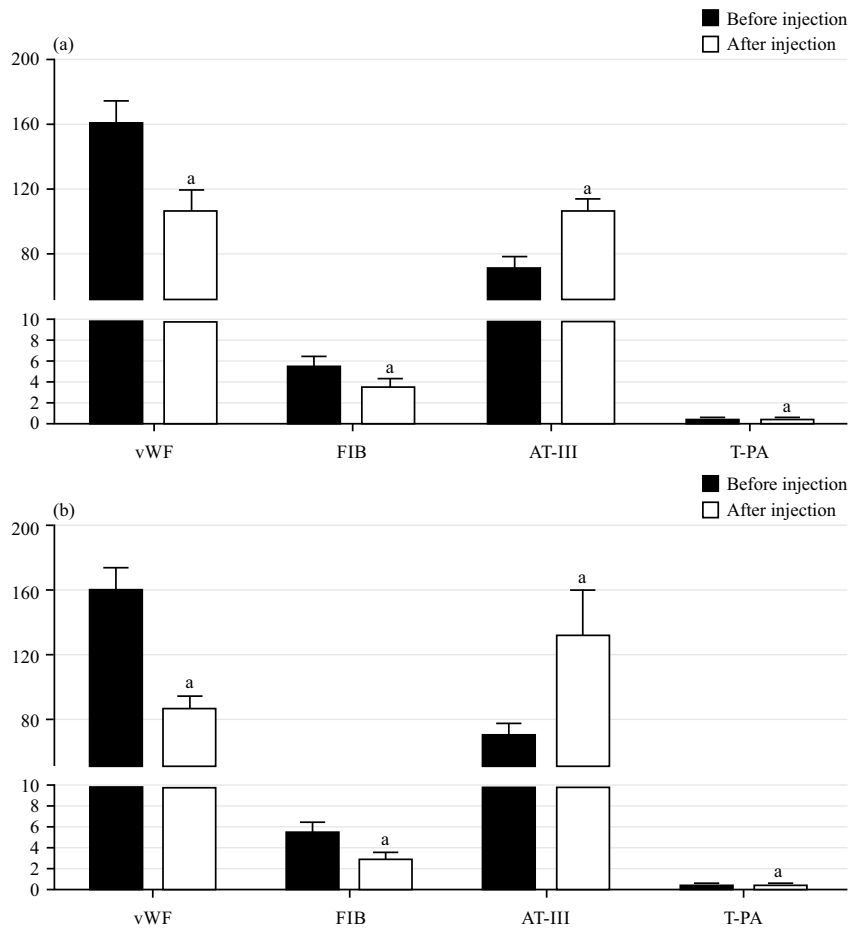

Fig. 3(a-b): Effect of intracoronary injection of nicorandil on clot fibers indexes, (a) AT-III and T-PA of control group were higher than before injection, while the vWF and FIB were lower than before injection and (b) AT-III and T-PA of study group were higher than before injection, while the vWF and FIB were lower than before injection, at the same time
Levels of vWF, FIB, AT-III and T-PA in the study group were better than those in the control group after injection and [a]p<0.05

DISCUSSION

The PCI plays an instrumental role in promoting revascularization, timely opening of blocked blood vessels and ensuring normal cardiac systolic function in patients with AMI. However, the insertion of stent or balloon easily damages the vascular endothelium, activates local platelet coagulation and inflammatory reaction, aggravates microvascular dysfunction and promotes microthrombus formation. Consequently, some patients experience complications, such as increased myocardial damage and coronary slow-flow/no-reflow phenomenon, during the perioperative period, thereby causing poor prognosis[13,14]. Therefore, drug interventions need to be implemented to facilitate the treatment of patients with AMI. Nicorandil has been shown to protect myocardium, reduce cardiac load, improve arrhythmia, relieve reperfusion injury and ensure coronary artery relaxation[15]. He *et al.*[16] found in an animal experimental study that nicorandil could stabilize the myocardial cell membrane and inhibit myocardial cell apoptosis by regulating the Nrf2/HO-1 signaling pathway. Moreover, Lee *et al.*[17] proved that nicorandil could act on the RhoA or RhoA kinase-dependent pathway, thereby delaying ventricular remodeling and myocardial fibrosis. In the current study, the SG had a higher TIMI flow grade and more remarkably improved indexes (e.g., ECG, myocardial damage and clot fiber system) than the CG after injection, suggesting that intracoronary injection of nicorandil improved the no-reflow phenomenon, cardiac function, hemodynamics, myocardial perfusion and myocardial damage and regulated clot fibers. This may be related to the following mechanisms of action of nicorandil: (1) Nicorandil increases the secretion of guanylate cyclase in smooth muscle cells and arterial blood flow, promotes NO release and stimulates coronary artery ectasia, thereby improving myocardial blood flow perfusion[18],

(2) Nicorandil opens the mitochondrial K^+- ATP channel in myocardial cells, reduces intracellular Ca^{2+} concentration and Ca^{2+} inflow, increases K^+ outflow and maintains mitochondrial function, thereby further dilating the coronary artery and restoring myocardial microcirculation. Meanwhile, it can inhibit the voltage-dependent Ca^{2+} channel in cellular membranes, reduce Ca^{2+} inflow, induce cellular membrane hyperpolarization, relax vascular smooth muscles and inhibit excitation-contraction coupling, thereby preventing coronary artery spasm, relaxing blood vessels and reducing the cardiac load[19,20], (3) Nicorandil can reverse myocardial ischemia-induced ventricular remodeling and improve cardiac function and myocardial damage by reducing sympathetic nervous excitement and simulating ischemic preconditioning process. Accordingly, Yang *et al.*[21] proved that nicorandil could reduce cTnI content and improve myocardial damage in patients with AMI undergoing elective PCI, (4) Nicorandil can prevent neutrophilic granulocyte activation, weaken microvascular resistance, reduce inflammatory reactions and prevent microvascular damage caused by neutrophilic granulocytes[22]. Moreover, Kostic *et al.*[23] found that intracoronary injection of nicorandil could improve microvascular resistance, ventricular function and coronary artery fractional flow reserve in patients with ST-elevation myocardial infarction after PCI. Additionally, our findings demonstrated that MACE incidence rates were lower in the SG than in the CG at 12 months after injection, which was consistent with the results of the study conducted by Qiang *et al.*[24]. This further indicates that intracoronary injection of nicorandil can reduce MACE incidence rates and improve patients' prognosis.

CONCLUSION

The current study showed that intracoronary injection of nicorandil can effectively improve the no-reflow phenomenon, cardiac function, hemodynamics and myocardial damage, regulate clot fibers, prevent MACE and improve the prognosis of elderly patients with STEMI undergoing emergency PCI. To date, a standardized therapeutic approach and dosage for nicorandil remain be established by medical experts, with no relevant guidelines recommending the same. Therefore, further investigations are needed to elucidate the dosage schedule and effectiveness of nicorandil.

SIGNIFICANCE STATEMENT

Despite the crucial role of percutaneous coronary intervention (PCI) in restoring coronary blood flow, complications such as no-reflow pose significant challenges. Nicorandil, with its vasodilatory and cardioprotective properties, has shown promise in mitigating such complications. This study aimed to investigate the efficacy of intracoronary nicorandil injection on no-reflow in elderly acute STEMI patients undergoing emergency PCI. The findings demonstrated that nicorandil improved myocardial perfusion, cardiac function and hemodynamics, while reducing myocardial damage and clot fiber abnormalities. Patients receiving nicorandil had lower rates of MACE at 12 month follow-up, suggesting improved prognosis. These findings underscore the potential of nicorandil as adjunctive therapy in optimizing outcomes for elderly STEMI patients undergoing PCI. Further research is warranted to establish standardized protocols for nicorandil administration.

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