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ORIGINAL RESEARCH

Effect of ticagrelor combined with nicorandil on endothelial function and coronary blood flow after PCI treatment in STEMI patients

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Abstract

This study investigated the effect of ticagrelor combined with nicorandil on endothelial function and coronary blood flow after percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI). We retrospectively analyzed 300 STEMI patients who underwent emergency PCI, 150 in the observation group and 150 in the control group. The control group was given oral ticagrelor. The observation group received oral nicorandil along with the control group. A significant improvement in peak ejection rate (PER) and left ventricular (LV) ejection fraction (EF) occurred after the operation, while LV end-diastolic volume index (LVESVI), LV end-diastolic internal diameter (LVEDD), cardiac troponin I (cTnI), and creatine kinase myoglobin (CK-MB) were significantly reduced compared to the preoperative period. Improvements in cardiac function were significantly greater in the observation group than in the control group ($p < 0.05$). After the operation, both groups' serum nitric oxide (NO) and endothelin-1 (ET-1) levels were greatly higher and lower, respectively, during the preoperative period ($p < 0.05$). The observation group's serum NO level was significantly higher than the control group's, and its ET-1 level was substantially lower than the control group's ($p < 0.05$). There was a significant increase in thrombolysis in myocardial infarction (TIMI) flow grade 3 percentage and TIMI myocardial perfusion grade (TMPG) grade 3 percentage in the observation group in the immediate postoperative period compared to the control group, despite a significantly lower corrected TIMI Frame count (CTFC) ($p < 0.05$). 1 month postoperatively, major adverse cardiovascular events (MACE) incidence was significantly lower in the observation group than in the control group ($\chi^2 = 3.914$, $p = 0.048$). The preoperative combination of ticagrelor and nicorandil in STEMI patients undergoing PCI helped attenuate vascular endothelial function impairment, improved coronary blood flow, and promoted postoperative cardiac function recovery.

Keywords

STEMI; PCI; Ticagrelor; Nicorandil

1. Introduction

Myocardial infarction (MI) is the most prevalent type of coronary heart disease and the primary cause of patient death [1, 2]. Clinically, MI is classified as ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI) based on the electrocardiograms (ECG) [3]. STEMI morbidity and mortality rates can reach 50% or higher within 1 h of disease onset [4]. Currently, percutaneous coronary intervention (PCI) is a viable method to save myocardium on the verge of necrosis and restore myocardial reperfusion in patients with STEMI. PCI rapidly unblocks occluded or stenotic lumens and restores myocardial blood supply [5]. STEMI can, however, lead to diminished vascular endothelial function, and PCI's rapid recovery of myocardial blood supply can exacerbate vascular endothelial injury [6]. Meanwhile, PCI itself can cause plaque and thrombus rupture or dislodgement, increasing the risk of in-stent thrombosis and leading to the occurrence of major adverse cardiovascular events (MACE) after the procedure [6]. Consequently, an anticoagulant or endothelial-protective drug should be chosen before PCI to reduce risks. This study aimed to examine the effect of PCI with ticagrelor and nicorandil on endothelial function and coronary blood flow in STEMI patients. As a consequence of this study, we hope to provide a reference for selecting preoperative adjuvant therapeutic agents for PCI.

2. Materials and methods

2.1 Patients

Clinical data of NSTEMI patients treated with PCI at Shanghai university of medicine & health Sciences affiliated Chongming hospital between February 2021 and February 2023 were retrospectively analyzed. Inclusion criteria: (1) Meeting the diagnostic criteria outlined in the 2021 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions coronary artery revascularization (ACC/AHA/SCAI) Guideline for Coronary Artery Revascularization [7]. (2) Admitted to the hospital within 12 hours of disease onset and received emergency PCI. (3) First-time onset of the disease. (4) Tolerating drugs. Exclusion criteria: (1) Previous PCI or bypass surgery history. (2) Combinations of severe hepatic and renal dysfunction, heart failure, or cardiovascular and cerebrovascular crises. (3) Drug allergies. (4) Administration of glycoprotein (GP) IIb/IIIa receptor antagonists or antithrombotic medications within 3 months. (5) Poor hypertension control (systolic blood pressure $\geq$160 mmHg, or diastolic blood pressure $\geq$100 mmHg). (6) Psychiatric illness or cognitive impairment history. Study approval was granted by the hospital's Ethics Committee, and all subjects gave informed consent. 300 patients were ultimately enrolled in the trial, 150 each in the control and observation groups. As part of studies involving human participants, all procedures were carried out according to the standards upheld by the Ethics Committee of Shanghai university of medicine & health sciences affiliated Chongming hospital and with those of the 1964 Helsinki Declaration and its later amendments for ethical research involving human subjects [8].

2.2 Methods

Prior to PCI, patients were routinely administered 300 mg of oral aspirin enteric-coated tablets (J20080078; Bayer S.P.A, Leverkusen, Germany). On top of this, Ticagrelor (H20120486; AstraZeneca, Wilmington, NC, USA) 90 mg was administered orally to the control group. The observation group was given nicorandil (specification 5 mg, National Drug Code HJ20160540, Nipro Pharma Corporation Kagamiishi Plant, Fukushima, Japan) 5 mg on top of the control group. PCI treatment was subsequently performed.

2.3 Observation indicators

(1) Cardiac function indexes: Left ventricular (LV) end-diastolic internal diameter (LVEDD), LV end-diastolic volume index (LVESVI), LV ejection fraction (LVEF), and peak ejection rate (PER) were detected using color ultrasound diagnostic instrument before (T0) and 24 h after (T1). We performed image analysis using Segment version 2.0 (http://segment.heiberg.se) as previously described [9–11]. (2) Cardiac enzyme indexes: Levels of cardiac troponin I (cTnI) and creatine kinase myoglobin (CK-MB) were continuously monitored by the chemiluminescence method. The peak values of each cardiac enzyme index were compared. (3) Vascular endothelial function indexes: 5 mL of elbow venous blood was collected from patients before and 24 h after surgery, respectively. The serum was separated after centrifugation at 3000 r/min for 15 min. The serum nitric oxide (NO) level was measured by the nitrate reductase method according to relevant reagent kits, purchased from Shanghai Biyuntian Biotechnology Co. (4) Coronary blood flow: The immediate postoperative coronary thrombolysis in myocardial infarction (TIMI) blood flow grade, TIMI myocardial perfusion grade (TMPG), and corrected TIMI frame count (CTFC) were recorded with a Color Doppler ultrasonic diagnostic instrument. (5) MACE occurrence: MACE within 1 month and 1 year after surgery was recorded. MACE includes death, myocardial infarction, angina pectoris, heart failure and target vessel revascularization (TVR).

2.4 Statistical analysis

Data analysis was performed with SPSS 23.0 (IBM Corp., SPSS Statistics, Armonk, NY, USA). Measurement results with normality were presented as mean $\pm$ standard deviation for comparisons between groups, Student's *t*-tests were used. Repeated-measures data were compared using repeated-measures Analysis of Variance (ANOVA). Examples of count data were presented, and a χ^2 test was conducted. $p < 0.05$ indicates statistical differences.

3. Results

3.1 Basic clinical data

Age, gender, myocardial infarction site, medical history, preoperative medication, infarcted vessel condition and stent implantation were not statistically significantly different between both groups ($p > 0.05$, Table 1).

3.2 Comparison of cardiac function indices

At T1, a significant increase in PER and LVEF was found in both groups compared with T0, while LVESVI and LVEDD significantly decreased ($p < 0.05$, Fig. 1). At T1, the observation group had significantly higher PER and LVEF and significantly lower LVESVI and LVEDD than the control group ($p < 0.05$, Fig. 1).

3.3 Comparison of myocardial injury marker levels

At T1, both groups' cTnI and CK-MB levels significantly decreased than at T0 ($p < 0.05$, Fig. 2). Comparing the observation group with the control group at T1, levels of cTnI and CK-MB were significantly lower ($p < 0.05$, Fig. 2).

3.4 Comparison of vascular endothelial function

At T1 compared with T0, serum NO levels were significantly higher and ET-1 levels were significantly lower in both groups, respectively ($p < 0.05$, Fig. 3). In the observation group, there was a significant reduction in ET-1 levels and a significant increase in serum NO than in the control group ($p < 0.05$, Fig. 3).

TABLE 1. Basic clinical data.

	Control group (n = 150)	Observation group (n = 150)	t/χ^2	p
Age (yr)	59.43 ± 8.73	58.72 ± 6.57	0.796	0.427
BMI (kg/m^2)	23.11 ± 1.44	23.08 ± 1.51	0.176	0.860
Male (n (%))	88	84	0.218	0.641
Infracted location (n (%))				
Anterior, Anteroseptal, Extensive forearm	57	51	0.521	0.470
Inferior, Posterior, Right ventricular	93	99		
Medical history (n (%))				
Hypertension	95	94	0.014	0.905
Diabetes	48	51	0.136	0.713
Hyperlipidemia	57	58	0.014	0.905
Smoking	116	121	0.502	0.478
β-blocker	108	106	0.065	0.798
ACEI	106	109	0.148	0.701
ARB	4	3	0.160	0.702
CCB	11	9	0.214	0.643
Culprit vessel				
LAD	46	47		
LCX	53	51	0.059	0.971
RCA	51	52		
Stent number				
0	0	0		
1	123	126		
2	19	17	0.214	0.899
3	8	7		
≥4	0	0		

Note: ACEI, renin angiotensin converting enzyme inhibitor; ARB, renin angiotensin receptor blocker; CCB, calcium antagonist; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; BMI, Body mass index.

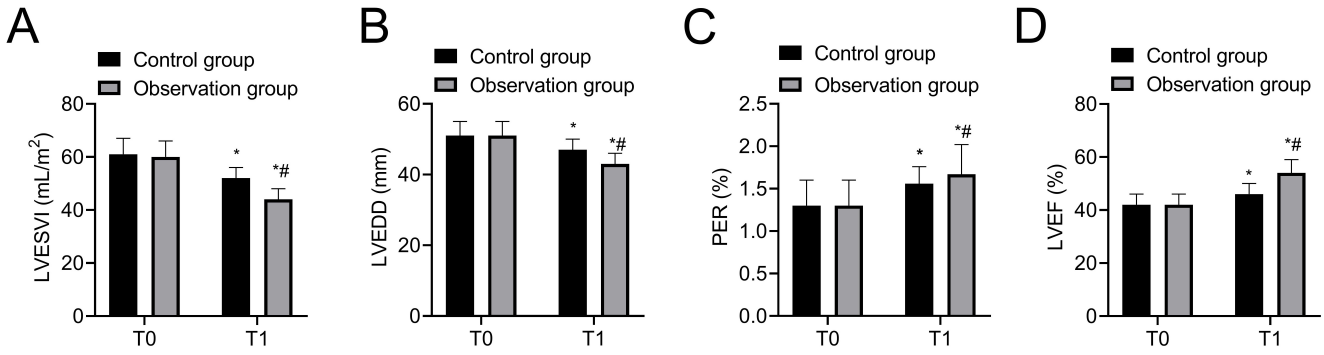

FIGURE 1. Comparison of cardiac function between the two groups. (A) LVESVI; (B) LVEDD; (C) PER; (D) LVEF. Compared with T0, *$p < 0.05$; Compared with Control group, $^{\#}p < 0.05$. LVESVI, LV end-diastolic volume index; LVEDD, LV end-diastolic internal diameter; PER, peak ejection rate; LVEF, LV ejection fraction.

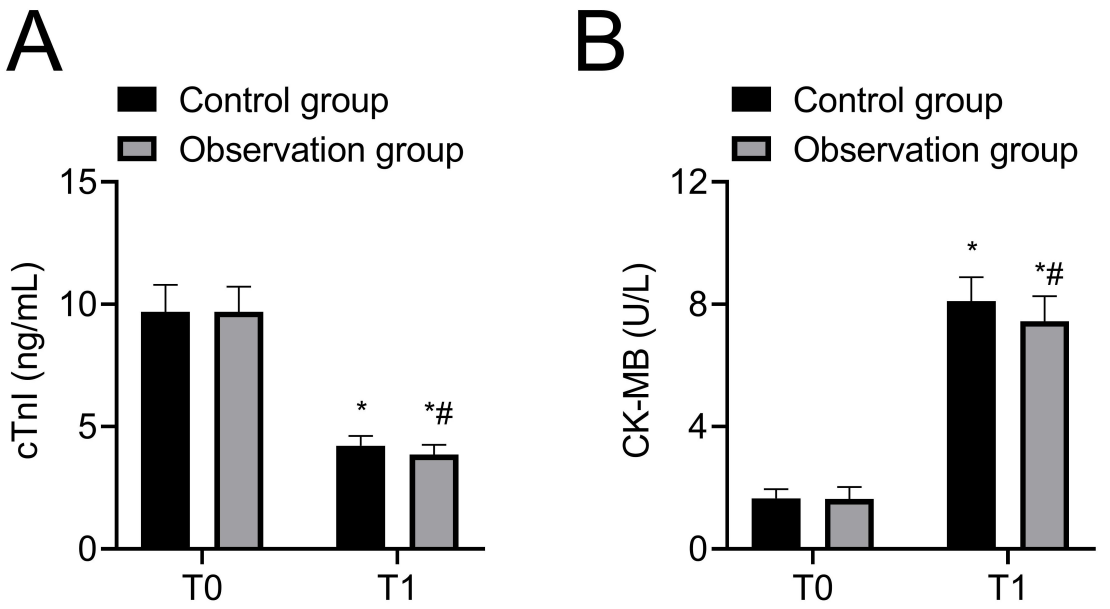

FIGURE 2. Comparison of myocardial injury marker levels between the two groups. (A) Serum cTnI levels; (B) Serum CK-MB levels. Compared with T0, *$p < 0.05$; Compared with Control group, $^{\#}p < 0.05$. cTnI, cardiac troponin I; CK-MB, creatine kinase myoglobin.

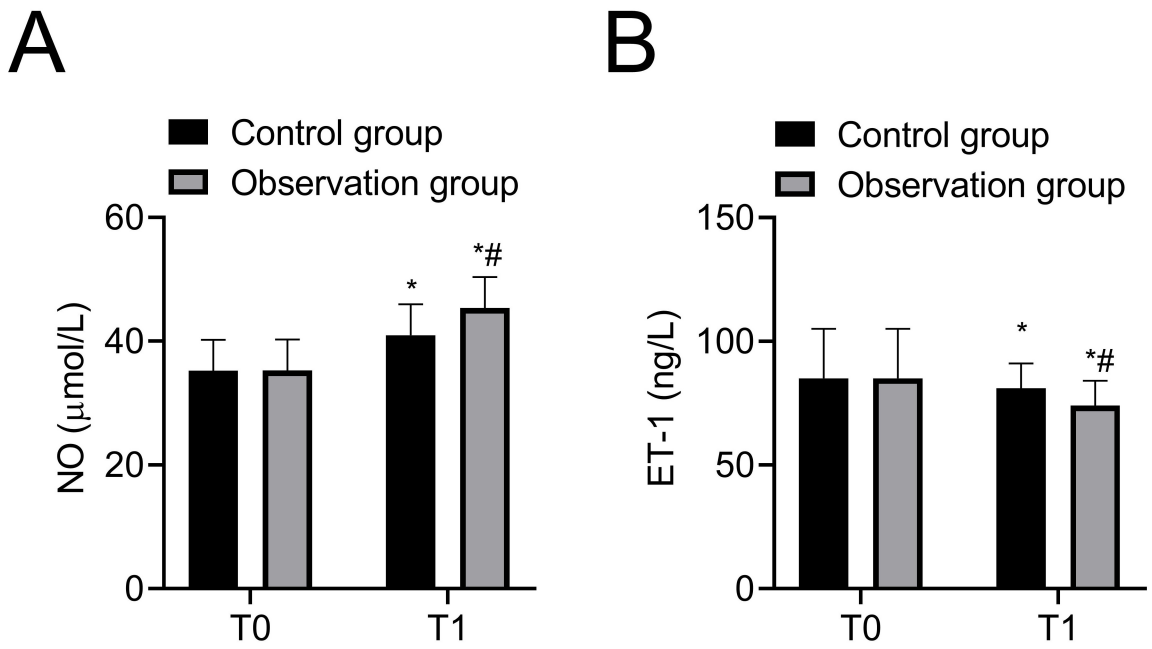

FIGURE 3. Comparison of vascular endothelial function indices between the two groups. (A) Serum NO levels; (B) Serum ET-1 levels. Compared with T0, *$p < 0.05$; Compared with Control group, $^{\#}p < 0.05$. NO, nitric oxide; ET-1, endothelin-1.

3.5 Comparison of coronary blood flow profiles

In the immediate postoperative period, the observation group had a significantly higher TIMI flow grade 3 percentage and TMPG grade 3 percentage than the control group, although the CTFC was significantly lower ($p < 0.05$, Table 2).

3.6 MACE

1-month postoperative MACE incidence was 15.33% (23/150) in the control group, 8.00% (12/150) in the observation group, and significantly lower MACE incidence in the observation group ($\chi^2 = 3.914$, $p = 0.048$) (Table 3). At 1-year postoperative follow-up, MACE incidence was 30.00% (45/150) in the control group; 22.00% (33/150) in the observation group. MACE incidence was not statistically significant between both groups ($\chi^2 = 2.495$, $p = 0.114$, Table 3).

TABLE 2. Comparison of coronary blood flow profiles.

	Control group (n = 150)	Observation group (n = 150)	χ^2/t	p
Proportion of TIMI blood flow level 3	110	132	10.345	<0.001
Proportion of TMPG3 class	101	125	10.332	0.001
CTFC (frame)	21.43 ± 4.25	15.17 ± 3.76	13.511	<0.001

TIMI, thrombolysis in myocardial infarction; TMPG3, TIMI myocardial perfusion grade 3; CTFC, corrected TIMI Frame count.

TABLE 3. Comparison of MACEs occurrence at 1-month and 1-year postoperatively.

	Control group (n = 150)	Observation group (n = 150)	χ^2	p
1-month postoperative			3.914	0.048
Death	0	0	-	-
Stable angina	13	8	1.280	0.258
MI	2	0	0.503	0.478
Cardiac failure	2	2	-	-
TVR	6	2	1.156	0.282
1-year postoperative			2.967	0.085
Death	2	1	0.337	0.562
Stable angina	18	14	0.560	0.454
MI	3	1	1.014	0.314
Cardiac failure	2	0	2.013	0.156
TVR	20	17	0.277	0.598

MI, Myocardial infarction; TVR, Target vessel revascularization.

4. Discussion

STEMI is a spontaneous infarction caused by intracoronary thrombosis due to coronary plaque rupture, fissure or entrapment. STEMI is characterized by chest pressure-like pain, which, if left untreated, can result in heart failure or shock. Myocardial perfusion can be significantly improved by PCI by opening narrowed or occluded coronary artery lumen. STEMI is primarily treated with it. Often, antiplatelet aggregation drugs are needed as adjuvant therapy before and after PCI to reduce the risk of MACE [12].

Ticagrelor is a clinically used antiplatelet agent that inhibits adenosine diphosphate (ADP)-mediated platelet activation and aggregation through its interaction with the P_2Y_{12} receptor [13]. Ticagrelor has been widely used to treat myocardial infarction, stroke and peripheral arterial disease. The combination of multiple single agents is shown to be more helpful in preserving cardiac function in STEMI patients and improving clinical outcomes [3]. Nicorandil is a nicotinamide derivative that dilates arteries and veins, reducing cardiac load by activating adenosine triphosphate-sensitive potassium channels [14]. In addition, nicorandil improves arterial blood flow, increases vascular smooth muscle relaxation, and reduces coronary artery spasms and dilatation by controlling K^+ and Ca^{2+} intra- and extracellular flow [15]. Therefore, nicorandil may reduce cardiovascular disease risk, control disease progression, and relieve pain in patients with heart failure. The use of nicorandil monotherapy on symptoms other than coronary artery disease is less effective, however. Combining this drug with other antithrombotic or antiplatelet drugs is effective compared to administering it on its own [16]. Both the observation group and control group of NSTEMI patients showed significant improvement in cardiac function and myocardial injury after surgery. Patients' cardiac function improved more in the observation group than in the control group. Therefore, the antithrombotic effect of ticagrelor combined with the vasodilator effect of nicorandil is more favorable to the recovery of cardiac function in patients after PCI.

AMI patients who suffer from vascular endothelial dysfunction are at risk of developing MACE after PCI [17]. Vascular endothelial dysfunction is an early manifestation of atherosclerosis and is considered the initiating factor for myocardial infarction pathologic changes. Moreover, PCI can also stimulate the arterial vasculature and aggravate vascular endothelial dysfunction [6]. Prognosis of emergency PCI patients can be improved by protecting vascular endothelial function. Vascular endothelial dysfunction results from an imbalance between endothelium-derived relaxing factors (*e.g.*, NO) and endothelium-derived contracting factors (*e.g.*, ET-1) [18]. NO is converted from L-arginine mainly by activation of nitric oxide synthase (NOS). Cellular function is maintained by NO, which is also important indicator of endothelial cell function. ET-1 acts as a vasoconstrictor peptide that contracts the arterial smooth muscle. Elevated levels of ET-1 correlate positively with vascular resistance and arterial pressure [19]. As a re-

sult of combining ticagrelor with nicorandil, NO production was improved and endothelial ET-1 production was inhibited, which improved vasodilatory and contractile factors imbalance, resulting in improved the vascular endothelial function after PCI in STEMI patients.

PCI is often associated with the phenomena of "no flow" and/or "slow flow", *i.e.*, restoration of epicardial coronary stenosis but loss or significant slowing of distal antegrade blood flow, failing to restore full myocyte perfusion [20]. "No reflow" and "slow flow" are associated with distal thromboembolism, ischemia-reperfusion injury, microvascular spasms, and endothelial dysfunction. Their incidence during PCI is between 5% and 50%, which significantly reduces PCI effectiveness and increases MACE and in-hospital mortality [21]. A key clinical concern is reducing the risk of "no-reflow" and "slow flow" during PCI. In this study, the observation group had a significantly higher percentage of grade 3 TIMI flow following PCI than the control group. In contrast, CTFC, which reflects microcirculatory perfusion, was significantly lower. This suggest that ticagrelor combined with nicorandil improves coronary blood flow significantly better than ticagrelor alone. The vasodilator effect of nicorandil, in addition to its antiplatelet properties, may accelerate the rapid restoration of blood flow in stenotic vessels or infarct sites. Further, observation patients had a significantly lower MACE incidence at 1 month postoperatively than control patients. Therefore, the preoperative combined application of ticagrelor combined with nicorandil before PCI can delay myocardial infarction progression in STEMI patients, reduce MACE incidence and improve the prognosis.

Many limitations remain in this study. It was a one-site study with a limited sample size. Further, the long-term effectiveness following surgery was not evaluated. This necessitates the increase of the sample size and the conduct of multicenter, extended follow-up research.

5. Conclusions

In conclusion, the preoperative combination of ticagrelor and nicorandil in STEMI patients undergoing PCI helped to attenuate vascular endothelial function impairment, improved coronary blood flow, and promoted postoperative cardiac function recovery.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

GRL—designed the study and carried them out. GRL, DMY—supervised the data collection, analyzed the data, interpreted the data; prepared the manuscript for publication and reviewed the draft of the manuscript. Both of authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Shanghai university of medicine & health Sciences affiliated Chongming hospital (Approval no. 2020065). Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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