Effect of Antiplatelet Therapy Combining Aspirin with Tirofiban After Percutaneous Coronary Intervention on the Incidence of Re-occlusion of Blood Vessels and Platelet Aggregation Rate in Patients with Acute Myocardial Infarction

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Objective. To explore the effect of antiplatelet therapy combining aspirin with tirofiban after percutaneous coronary intervention (PCI) on the incidence of re-occlusion of blood vessels and platelet aggregation rate in patients with acute myocardial infarction (AMI). Methods. A total of 104 AMI patients treated in the Department of Cardiovascular Medicine of our hospital from March 2017 to March 2018 were selected for retrospective analysis, and those who met the inclusion criteria were divided into the experimental group (n=52) and the control group (n=52) by sealed envelope randomization. After admission, all patients received the PCI, then the combined therapy of aspirin and tirofiban was given to the patients in the experimental group, and the patients in the control group orally took the clopidogrel. By detecting the values of n-terminal pro-brain natriuretic peptide (NT-proBNP) level, platelet active function indicators, etc. of patients in both groups after treatment, the treatment effect of antiplatelet in AMI patients after PCI with different drugs was analyzed. Results. After treatment, the levels of the maximum platelet aggregation rate (MPAR), CD63, CD62P, MA, NT-proBNP and left ventricular end-diastolic volume (LVEDV) were significantly lower in the experimental group than in the control group (P<0.001), and the R time, K time, CI values, left ventricular ejection fraction (LVEF), the peak velocity of early diastolic wave (peak E)/peak velocity of late diastolic wave (peak A) under mitral valve (E/A) were significantly higher in the experimental group than in the control group (P<0.001), and during follow-up, the incidence rate of re-occlusion of blood vessels was significantly lower in the experimental group than in the control group (P<0.05). Conclusion. The above results indicated that combining aspirin with tirofiban has a better effect than clopidogrel in the antiplatelet therapy for AMI patients after PCI , and therefore it is recommended.

Keywords: percutaneous coronary intervention (PCI); aspirin; tirofiban; antiplatelet treatment; acute myocardial infarction (AMI); re-occlusion of blood vessels; platelet aggregation
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A retrospective study in China[1] showed that over the past 10 years, the hospitalization rate of acute myocardial infarction (AMI) patients has increased. AMI is a cardiovascular adverse event with higher morbidity and mortality, and percutaneous coronary intervention (PCI) is a common procedure in the treatment of AMI, which can relax the patients' occluded coronary vessels and restore myocardial perfusion. However, AMI patients have a higher incidence of postoperative stricture, which may easily cause major adverse cardiovascular events (MACE) and compromise patients' life safety[2-3]. Therefore, antiplatelet drugs are required in the perioperative period for AMI patients who have undergone PCI to
improve the hypercoagulable state of blood and prevent the formation of postoperative in-stent

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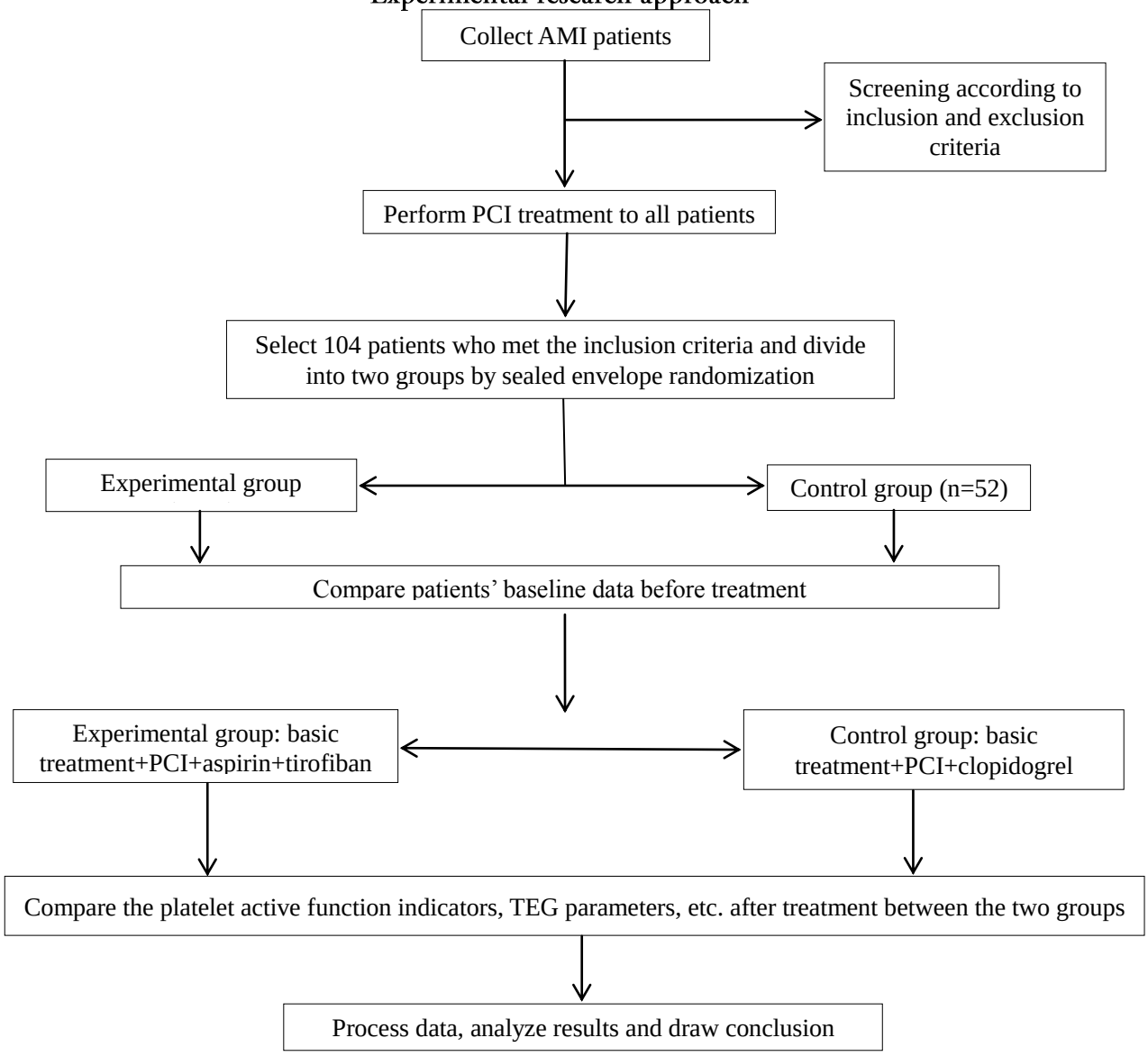
thrombosi. The standard medication recommended by medication guidelines in China is clopidogrel combined with aspirin, of which clopidogrel is a common antiplatelet therapy drug, but studies have confirmed[4] that it can exert its efficacy only after metabolized by the human liver, thus resulting in a poor effect of antiplatelet therapy. Aspirin has anti-inflammatory, fever relieving, and antirheumatic effects and can inhibit platelet aggregation, which have been demonstrated in patients with type 2 diabetes and coronary heart disease treated with antiplatelet therapy after interventional procedures[5-6]. Tirofiban, as a non-peptidic reversible antagonist of platelet glycoprotein IIb/IIIa receptor, can effectively inhibit platelet aggregation and has a rapid onset and short half-life, which has been valued for the treatment of intravascular thrombosis[7-8]. Due to the current lack of studies related to the use of aspirin plus tirofiban in the antiplatelet therapy for AMI patients after PCI, this study aimed to analyze its application effect and the influence on the incidence of re-occlusion of blood vessels and platelet aggregation rate, which was reported as follows.

PATIENT DATA AND METHODS

Patient Data

A total of 104 AMI patients treated in the Department of Cardiovascular Medicine of our hospital from March 2017 to March 2018 were selected for the retrospective study. The technology roadmap of the study was shown in Figure 1.

Figure 1
Experimental research approach



Inclusion and Exclusion Criteria

Inclusion criteria. ① The time from disease onset to visiting the hospital was less than 24 hours, and the patients met the relevant diagnosis

criteria for AMI in *Diagnosis and Treatment Technology of Coronary Heart Disease and Acute Myocardial Infarction*[9] and were diagnosed with AMI after cardiac magnetic resonance (CMR) imaging; ② the clinical patient data were complete and met the requirements for statistical analysis; ③ the indicators of PCI treatment were met; and ④ the study was reviewed and approved by the Hospital Ethics Committee, and the patients or their statutory guardians understood the study purpose and process and signed the informed consent.

Exclusion criteria for patients. ① Presence of malignant tumor and systemic immune system diseases; ② presence of dysfunction of blood coagulation or long-term usage of anticoagulants; ③ allergy to the drugs used in the study or presence of contraindications; and ④ loss to follow-up or changing the treatment regimen in the middle of the study.

Methods

After admission, patients in both groups received the basic treatment including atorvastatin calcium and isosorbide mononitrate sustained release tablets, and accepted the hypoglycemic or anti-hypertension therapy according to their condition[10-11]. PCI treatment was performed to patients in both groups by the same surgical team, and the BUMA coronary rapamycin-eluting stent system was used during PCI. After surgery, platelet treatment was performed to patients in both groups, and from day 1 after PCI, the patients in the experimental group orally took 100 mg of aspirin (manufactured: Bayer HealthCare Co., Ltd.; NMPA approval no. J20171021; specification: 0.1 g × 15 tablets × 2 packs/box) daily for continuously 1 month, and received the tirofiban (manufactured: GRANDPHARMA Co., Ltd.; NMPA approval no. H20143290; specification: 12.5 mg) treatment, i.e. dissolving 12.5 mg of tirofiban in 100 ml of normal saline, first pumping intravenously 0.4 μg/(kg·min) for 30 min, then 0.1 μg/(kg·min) for continuously 24 h.

From day 1 after PCI, the patients in the control group orally took 75 mg of clopidogrel (manufactured: Sanofi Pharmaceutical Co., Ltd.; NMPA approval no. H20056410) twice daily for continuously 1 month[12].

Evaluation Indexes

After treatment, 5 mL of fasting elbow vein blood was drawn from the patients in both groups and stored under 4°C for 45 min. The agglutinated blood was centrifuged, and the slurry in the tube was drawn to get the serum. Based on the principle of adenosine diphosphate (ADP) induced turbidimetry, 5 μmol/L of ADP was applied as the inducer, the maximum platelet aggregation rate (MPAR) induced by ADP was measured with the automatic platelet aggregation instrument (manufactured: Shanghai Hanfei Medical Equipment Co., Ltd; product model: AG800) within 24 h after blood collection; the membrane of lysosome glycoprotein (CD63) and platelet CD62P were measured by the Enzyme linked immunosorbent assay (ELISA); the levels of n-terminal pro-brain natriuretic peptide (NT-proBNP) in patients of both groups were detected by the chemiluminescence immunoassay; and relevant kits were purchased from Shanghai Jichun Industrial Co., Ltd..

With the thrombelastograph instrument (manufactured: Shanghai Jumu Medical Equipment Co., Ltd.; model: TEG-5000) and supported Kaolin accelerator agents, various parameters on the thrombelastogram (TEG) of patients in both groups were compared, including K time (time until clot reaches a fixed strength (MA was 20 mm)), R time (time of latency from the time that the blood was placed in the instrument until the initial fibrin formation), MA (the maximum strength or hardness of clot or the stability of clot formation), and CI (coagulation index, with less than -3 points indicating hypocoagulability, -3 to 3 points indicating normal, and over 3 points indicating hypercoagulability). The incidence rates of re-occlusion of blood vessels in patients of both groups after treatment were counted.

Cardiac function indicator detection. Patients in both groups accepted the echocardiography after treatment to record their left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV) and the peak velocity of early diastolic wave (peak E)/peak velocity of late diastolic wave (peak A) under mitral valve (E/A).

Statistical Methods

In this study, the data were processed by the professional statistics software SPSS23.0, the picture drawing software was GraphPad Prism 7 (GraphPad Software, San Diego, USA), the enumeration data were examined by X^2 test and expressed by [n(%)], the measurement data were examined by t-test and expressed by Mean±SD, and differences were considered statistically significant at $P<0.05$.

RESULTS

Comparison of Baseline Data between the Two Groups

No significant differences in the general data including the gender ratio, mean age, BMI, mean onset time, and heart rate of patients between the two groups were observed ($P>0.05$), see Table 1.

Table 1
Comparison of baseline data between the two groups (n=52)

Item	Experimental group	Control group	X^2/t	P
Gender			0.158	0.691
Male	29 (55.77%)	31 (59.62%)		
Female	23 (44.23%)	21 (40.38%)		
Mean age (Mean±SD, years)	58.26±4.78	58.69±4.52	0.471	0.638
BMI (Mean±SD, kg/m^2)	21.25±1.35	21.34±1.42	0.331	0.741
Mean onset time (Mean±SD, h)	8.73±1.35	8.78±1.42	0.184	0.854
Degree of vascular stenosis (Mean±SD, %)	92.36±2.37	92.41±2.41	0.107	0.915
Target lesion location				
Left anterior descending branch	34 (65.38)	36 (69.23)	0.175	0.676
Right coronary	14 (26.92)	13 (25.00)	0.050	0.823
Left circumflex branch	4 (7.69)	3 (5.77)	0.153	0.696
Diastolic blood pressure (Mean±SD, mmHg)	72.35±5.63	72.43±5.71	0.072	0.943
Systolic blood pressure (Mean±SD, mmHg)	103.26±7.68	103.31±7.46	0.034	0.973
Heart rate (Mean±SD, bpm)	75.43±5.36	75.46±5.42	0.028	0.977
Complications				
Hyperlipidemia	14 (26.92)	16 (30.77)	0.187	0.665
Diabetes	13 (25.00)	16 (30.77)	0.430	0.512
Hypertension	27 (51.92)	24 (46.15)	0.346	0.556
Place of residence [n(%)]			0.170	0.680
Urban area	17 (32.69%)	19 (36.54%)		
Rural area	35 (67.31%)	33 (63.46%)		
Educational degree [n(%)]				
Junior college and above	9 (17.31%)	6 (11.54%)	0.701	0.402
Senior high school	18 (34.62%)	19 (36.54%)	0.042	0.838
Junior high school and below	25 (48.08%)	27 (51.92%)	0.154	0.695

Comparison of Levels of Platelet Active Function Indicators in Patients after Treatment between the Two Groups

After treatment, the MPAR, CD63 and CD62P levels were significantly lower in the experimental group than in the control group (P<0.001), see Table 2.

Table 2
Comparison of levels of platelet active function indicators in patients after treatment between the two groups (Mean±SD, n=52)

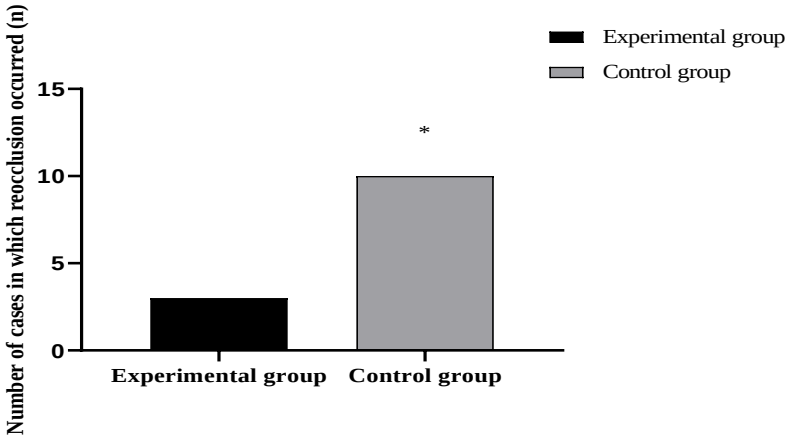
Group	MPAR (%)	CD63 (μg/L)	CD62P (μg/L)
Experimental group	60.07±3.27	15.27±2.08	18.73±1.84
Control group	63.82±3.46	26.72±2.15	23.41±1.58
t	5.680	27.601	13.915
P	<0.001	<0.001	<0.001

Comparison of incidence rates of re-occlusion of blood vessels between the two groups

During follow-up, the incidence rate of re-occlusion of blood vessels was significantly lower in the experimental group than in the control

group (P<0.05), see Figure 2.

Figure 2
Comparison of incidence rates of re-occlusion of blood vessels between the two groups [n(%)]



Note: The horizontal axis indicated the experimental group and the control group, and the vertical axis indicated the number of cases in which re-occlusion occurred (n);

There were 3 cases in the experimental group (5.77%) and 10 cases in the control group (19.23%) had re-occlusion of blood vessels; and

* indicated that the numbers of cases with re-occlusion of blood vessels were significantly different between the two groups (X^2=4.308, P=0.038).

Comparison of TEG Parameters after Treatment betweenthe Two Groups

After treatment, the R time, K time and CI values of patients in the experimental group were significantly higher than those in the control group (P<0.001), while the MA values were significantly lower in the experimental group than in the control group (P<0.001), see Table 3.

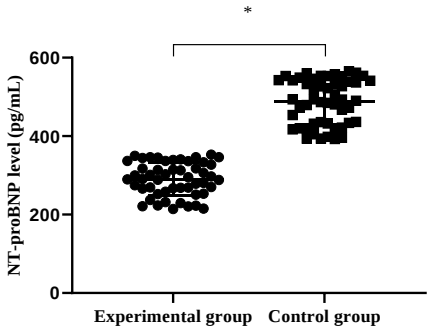
Table 3
Comparison of TEG parameters after treatment between the two groups (Mean±SD, n=52)

Group	R time (min)	K time (min)	MA value (mm)	CI value
Experimental group	7.52±0.73	3.46±0.43	44.58±6.38	-1.34±0.86
Control group	6.37±0.68	2.74±0.38	53.27±6.37	-2.21±0.69
t	8.312	9.048	6.951	5.690
P	<0.001	<0.001	<0.001	<0.001

Comparison of NT-proBNP Levels after Treatment between the Two Groups

After treatment, the NT-proBNP levels were significantly lower in the experimental group than in the control group (P<0.001), see Figure 3.

Figure 3
Comparison of NT-proBNP levels after treatment between the two groups (Mean±SD, n=52)



Note: The horizontal axis indicated the experimental group and the control group, and the vertical axis indicated the NT-proBNP levels in pg/mL;

After treatment, the mean NT-proBNP levels of the experimental group and the control group were (289.94±42.40) and (487.94±57.35), respectively; and

* indicated that the mean NT-proBNP levels were significantly different between the two groups (t=20.019, P<0.001).

Comparison of Cardiac Function Indicators in Patients after Treatment betweenthe Two Groups

After treatment, the LVEF and E/A were significantly higher in the experimental group than in the control group, while the LVEDV was significantly lower in the experimental group than in the control group (P<0.001), see Table 4.

Table 4
Comparison of cardiac function indicators in patients after treatment between the two groups (Mean±SD, n=52)

Group	LVEF/%	LVEDV/mL	E/A
Experimental group	52.15±6.72	81.24±5.38	0.81±0.11
Control group	42.34±6.36	85.23±5.24	0.64±0.08
t	7.646	3.831	9.013
P	<0.001	<0.001	<0.001

DISCUSSION

AMI is one of the common acute and severe diseases in the Department of Cardiology, with the characteristics of sudden occurrence and high mortality[13]. PCI is currently an effective treatment for AMI, which can help patients to recover myocardial blood supply quickly, achieving a recanalization rate of more than 90%[14-15]. However, stent implantation can lead to local vascular endothelial damage, postoperative platelet aggregation and activation, and then the formation of local thrombi in the microvessels of coronary arteries. Several foreign studies have confirmed[16] that the high aggregation and inflammatory reaction of platelets after PCI are important factors that result in no reflow or slow flow in the distal coronary vessels, which is an important cause of myocardial perfusion failure or poor efficacy. It has been documented[17] that the perioperative antiplatelet aggregation treatment is of great importance, because it can effectively improve slow reflow in AMI patients as well as prevent further expansion of myocardial necrosis, lower circulatory resistance, and reduce the frequency of chest pain in patients.

Clopidogrel, a commonly used oral drug to inhibit platelet aggregation, can prevent and treat heart, brain and other arterial circulation disorders caused by high platelet aggregation, but with some limitations. Oral drugs usually have the characteristics such as being diluted by body fluid, absorbed by intestinal wall and metabolism inactivation, resulting in a slow onset of action after entering the human body, and, combined with poor compliance in some patients, may not inhibit the platelet function in many ways, resulting in patients remaining at high risk of thrombosis after drug administration[18-19]. Tirofiban hydrochloride, a novel antiplatelet activating drug for intravenous injection, is a highly potent nonpeptide platelet membrane glycoprotein IIa/IIIb receptor anticoagulant with rapid onset and metabolism, which can inhibit platelets by up to 96% and effectively inhibit

platelet activation and aggregation[20]. The results of pharmacological studies showed that[21] 20-40 mg of aspirin daily for 6-12 d can inactivate 92% - 95% of cyclooxygenase and effectively inhibit thromboxane A2 formation. As platelets do not have nuclei and thus are unable to re-generate cyclooxygenase, aspirin exerts a permanent inhibitory effect on platelets[22].

A total of 104 patients who underwent PCI and took aspirin combined with tirofiban or clopidogrel for antiplatelet were included in the study for comparison. TEG parameters of coronary blood can directly reflect the extent of local platelet activation and aggregation in patients' coronary arteries and accurately assess the effect of PCI operation on the local microenvironment[23]. The results showed that the R time, K time, and CI values of the experimental group after treatment were significantly higher than those of the control group, whereas the MA values were significantly lower than those of the control group ($P<0.001$). The above parameters directly indicate platelet activation, which is closely related to thrombus formation. Therefore, the study demonstrated that the experimental group had a better inhibition of platelet activation and aggregation than the control group. It has been documented[24] that the re-occlusion of blood vessels results from a combination of thrombosis, the coagulation system, platelet activation, and the fibrinolytic system. The follow-up results of this study showed that the incidence rate of re-occlusion of blood vessels within 3 months of discharge was significantly lower in the experimental group than in the control group ($P<0.05$). A previous study[25] also had the similar conclusion, which showed that "the early combination of tirofiban after intravenous thrombolysis in minor stroke reduced the occurrence of re-occlusion of blood vessels and improved outcome without increasing the risk of symptomatic intracerebral hemorrhage".

In conclusion, for AMI patients after PCI, the combined therapy of aspirin and tirofiban has a better clinical effect than clopidogrel and can effectively reduce the incidence of re-occlusion of blood vessels and the platelet aggregation rate. However, this study did not investigate the adverse effects in patients after medication, so the combined therapy should be used flexibly according to its pharmacological effect and the actual condition of patients in future clinical practice.

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