Effect of intracoronary tirofiban on platelet alpha-granule membrane protein and myocardial perfusion level during emergency percutaneous coronary intervention

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ABSTRACT. This study aimed to investigate the effect of intracoronary application of tirofiban on platelet alpha-granule membrane protein (GMP-140) and myocardial perfusion levels during emergency percutaneous coronary intervention (PCI). A total of 70 patients who accepted emergency PCI treatment were randomly divided into tirofiban and control groups. We determined GMP-140 and troponin I (cTnI) levels before and 12 h after surgery, as well as N-terminal pro-brain natriuretic peptide levels 1 and 7 days after surgery in the two groups. The results showed that GMP-140 and cTnI levels were significantly ($P < 0.01$) lower in the tirofiban group than in the control group 12 h after operation (17.99 ± 1.01 *vs* 24.56 ± 1.96 μg/L and 50.96 ± 2.20 *vs* 58.69 ± 2.34 ng/mL, respectively). The D-value of the N-terminal pro-brain natriuretic peptide levels between 1 and 7 days after operation was significantly higher in the tirofiban group than in the control group (894.19 ± 90.91 *vs* 829.50 ± 84.18 pg/mL; $P < 0.01$). The intracoronary

application of tirofiban during emergency PCI clearly reduced the GMP-140 level, inhibited the activation function of platelets, improved myocardial perfusion, and helped recover cardiac function in patients.

Key words: Myocardial infarction; Interventional treatment; Tirofiban; Platelet alpha-granule membrane protein; Myocardial perfusion; Cardiac function

INTRODUCTION

Coronary atherosclerotic plaque instability and rupture followed by thrombosis is the main pathogenesis of acute myocardial infarction (Falk et al., 1995). Platelets play an important role in the pathogenesis of acute myocardial infarction. Tirofiban is an antagonist of platelet glycoprotein protein (GP) II b/III, a receptor that inhibits thrombosis by blocking the final pathway of platelet aggregation (EPISTENT investigators, 1998). As of this writing, emergency percutaneous coronary intervention (PCI) is the preferred method for acute cardiac infarction treatment and is the best method for achieving epicardial coronary thrombolysis in myocardial infarction (TIMI) 3 blood flow in patients with acute ST-segment elevation myocardial infarction (Ochiai et al., 1997). Emergency PCI is better than thrombolytic therapy for patient survival (Zijlstra et al., 1999; Keeley et al., 2003). However, intervention for coronary lesions with a large thrombus burden will increase the incidence of distal microcirculation embolism and no-reflow (Rezkalla and Kloner, 2002).

Previous studies have shown that platelet activation has an important role in the occurrence of no-reflow. Platelet alpha-granule membrane protein (GMP-140) is a recently discovered platelet membrane glycoprotein. GMP-140 is a protein receptor on platelet membranes that is stored in the alpha-granules of resting platelets. After the activation of platelets, GMP-140 is exposed on the cell surface by the fusion of granules and the plasma membrane. The expression of GMP-140 subsequently increases, and inflammatory response and thrombosis are activated. Platelet glycoprotein II b/III, a receptor antagonist, has a strong anti-platelet aggregation effect, reduces the incidence of distal microcirculation embolism, helps recover coronary blood flow and improves myocardial tissue perfusion level. Studies have shown that the intravenous application of tirofiban hydrochloride before and after PCI clearly improves the TIMI flow grade of the infarct-related artery after PCI and the prognosis of patients (Antoniucci et al., 2003). Information on whether or not tirofiban affects the activation of GMP-140 and subsequently reduces inflammatory response and thrombosis is lacking. The effect of tirofiban on GMP-140 level in coronary blood, myocardial tissue perfusion level and cardiac function was investigated by intracoronary bolus injection of tirofiban after balloon dilatation of culprit lesions during emergency PCI. Our findings provide information on the intracoronary application of tirofiban in emergency PCI.

MATERIAL AND METHODS

Sample collection

A total of 70 patients with acute ST-segment elevation myocardial infarction, who underwent emergency PCI in the Department of Cardiology, Affiliated Hospital of Binzhou Medical College from December 2010 to December 2011, were selected according to the diagnostic criteria for myocardial infarction of the European Society of Cardiology in 2007.

Patients were randomly divided into tirofiban and control groups. Intracoronary injection of 10 µg/kg tirofiban was performed on patients in the tirofiban group after balloon dilatation of culprit lesions and before stent implantation. Stent implantation was directly performed on patients in the control group after balloon dilatation of culprit lesions. The tirofiban group comprised 25 males and 10 females, in the age range of 53 to 75 years old (mean age, 64.28 ± 5.56 years old). The control group comprised 24 males and 11 females, in the age range of 57 to 74 years old (mean age, 64.12 ± 11.86 years old). Inclusion criteria were as follows: 1. chest-pain duration ≥30 min; 2. in electrocardiogram, two or more adjacent chest lead ST-segment elevations ≥0.3 mV or limb lead ST-segment elevations ≥0.1 mV; 3. onset of chest pain at ≤12 h; and 4. if the onset of chest pain occurred at >12 h, chest pain or continuous ST-segment elevation should still exist.

General information

The gender, age, blood lipids, blood glucose and smoking habit of patients and incidence of hypertension and infarct-related artery of patients were compared.

Primary PCI process

Bayaspirin at 300 mg was administered immediately. Clopidogrel (Plavix) at 600 mg was administered orally. After obtaining signed informed consent for emergency PCI surgery, patients were immediately sent to the catheterization room for emergency surgery. Left and right coronary angiography was used to determine the infarct-related artery lesions. Subsequently, emergency PCI was performed on the infarct-related artery. In the tirofiban group, intracoronary injection of tirofiban (Wuhan Grand Pharmaceutical Group Co., Ltd., Zhunzi, H20041165) at 10 µg/kg was performed by a guiding catheter after balloon dilatation of culprit lesions. The bolus injection of tirofiban was completed in 3 min. Patients were observed for 10 min, after which stent implantation was performed. In the control group, stent implantation was performed immediately after balloon dilatation of culprit lesions. After surgery, all patients were orally administered 100 mg bayaspirin and 75 mg clopidogrel hydrogen (Plavix) once daily. Subcutaneous injection of low molecular weight heparin was performed at 12-h intervals. Drug administration was performed for 5 days.

Determination of GMP-140 concentration

Coronary blood (5 mL) was collected after emergency PCI and placed in an EDTA-2Na anticoagulant tube. The blood was centrifuged at 3000 rpm for 10 min. The plasma was stored in a -70°C freezer until assay.

The concentration of GMP-140 (Shanghai Hufeng Biotechnology Co., Ltd.) was determined by enzyme-linked immunosorbent assay (ELISA).

Determination of related indicators of myocardial perfusion level

Blood samples (5 mL) were collected from the cubital vein before and 12 h after surgery. The samples were placed in procoagulant tubes and immediately centrifuged at 3000 rpm for 5 min to separate the serum. Troponin I (cTnI) level was determined by chemiluminescence immunoassay.

Detection of related indicators of cardiac function

Blood samples (5 mL) were collected from the cubital vein on the 1st and 7th days after surgery. The samples were placed in procoagulant tubes and immediately centrifuged twice continuously at 2500 rpm for 5 min to separate the serum. The level of N-terminal pro-brain natriuretic peptide (NT-proBNP) was determined by electrochemiluminescence immunoassay.

Statistical processing

The SPSS15.0 software package was used for statistical processing. Measurement data are reported as means ± SD and a *t*-test was used. The chi-square test or Fisher exact test was used for count data.

RESULTS

The differences in the general patient data between the two groups were not statistically significant (Table 1). The concentration of GMP-140 in the tirofiban group was significantly lower than in the control group (17.99 ± 1.01 *vs* 24.56 ± 1.96 µg/L, $P < 0.01$). The increase in troponin level 12 h after surgery in the tirofiban group was significantly lower than in the control group (50.96 ± 2.20 *vs* 58.69 ± 2.34 ng/mL; $P < 0.01$). The D-value of NT-proBNP level in serum between 1 and 7 days after surgery in the tirofiban group was significantly higher than in the control group (894.19 ± 90.91 *vs* 829.50 ± 84.18 pg/mL; $P < 0.05$) (Tables 2, 3, and 4).

Table 1. Comparisons of general clinical data.

Clinical data	Tirofiban group (N = 35)	Control group (N = 35)
Male	25	24
Age	64.28 ± 5.56	64.12 ± 11.86
Hypertension	13	11
Diabetes	3	2
Dyslipidemia	11	10
Smoking	8	10
Anterior descending artery	23	25
Circumflex artery	3	2
Right coronary artery	9	8

The differences of patient data between the two groups were not statistically significant ($P > 0.05$).

Table 2. Comparison of α-granule membrane protein (GMP140) concentration.

Groups	Cases (N)	GMP140 (µg/L)
Control group	35	24.56 ± 1.96
Tirofiban group	35	17.99 ± 1.01*

Compared with control group, *$P < 0.01$.

Table 3. Comparison of the increase of troponin I (cTnI) 12 hours after surgery.

Groups	Cases (N)	cTnI (ng/mL)
Control group	35	58.69 ± 2.34
Tirofiban group	35	50.96 ± 2.20*

Compared with control group, *$P < 0.01$.

Table 4. D-value of N-terminal pro-brain natriuretic peptide level between the 1st day and the 7th day after surgery.

Groups	Cases (N)	NT-proBNP (pg/mL)
Control group	35	829.50 ± 84.18
Tirofiban group	35	894.19 ± 90.91*

Compared with control group, *P < 0.05.

DISSCUSSION

Our research design involved intracoronary injection of tirofiban at 10 µg/kg after balloon dilatation of culprit lesions during emergency PCI. The objective of this study included two aspects. On one hand, intracoronary local medication increased drug concentration in lesions, and prevented thrombosis and microcirculation dysfunction. On the other hand, when distal coronary artery blood flow was severely damaged, drugs administered intravenously could not effectively reach blood vessels in culprit lesions; thus, drug efficacy is limited and reduced (Romagnoli et al., 2005). Previous studies showed that compared with intravenous injection of abciximab, intracoronary injection of abciximab significantly reduced the incidence of major adverse cardiac events (10.2 *vs* 20.2%, P < 0.0008) (Wöhrle et al., 2003), greatly improved myocardial survival, reduced myocardial infarct size and significantly decreased the level of cardiac enzyme peak (Bellandi et al., 2004). The potential mechanism underlying these beneficial effects may be the inhibition of platelet accumulation in the distal end of vessels by abciximab, and the thrombus formed by direct interaction of platelets and endothelial cells in reperfusion (Coller, 1999; Schwarz et al., 2002); thus, microcirculation perfusion is improved. Whether or not platelet glycoprotein IIb/IIIa receptor antagonist improves the prognosis by other means is unclear. GMP-140 is a platelet membrane glycoprotein that has an important role in the occurrence of slow blood flow and no-reflow during emergency PCI. The activation and increased expression of GMP-140 can aggravate inflammatory response and thrombosis, resulting in the aggravation of no-reflow.

Intracoronary injection of tirofiban, a platelet glycoprotein IIb/IIIa receptor antagonist, not only inhibits platelet aggregation but also reduces the activation and expression of platelet alpha-granule membrane protein. Thus, tirofiban improves the myocardial tissue perfusion level and the cardiac function of patients. Intracoronary bolus injection of tirofiban was performed after balloon dilatation of culprit lesions during emergency PCI in 70 patients who underwent emergency PCI treatment. The effect of tirofiban on the level of GMP-140 in coronary arterial blood was observed. The levels of cTnI before and 12 h after surgery, and those of NT-proBNP on the 1st and 7th days after surgery, were determined. The level of GMP-140 in coronary plasma of patients in the tirofiban group was significantly lower than in the control group (17.99 ± 1.01 *vs* 24.56 ± 1.96 µg/L, P < 0.01). Tirofiban inhibits platelet aggregation by antagonizing platelet glycoprotein IIb/IIIa receptor. Tirofiban inhibits thrombosis and improves myocardial perfusion and cardiac function after emergency PCI by inhibiting the expression of GMP-140 and inflammatory response and by reducing the activation of platelets.

Previous studies have shown that the application of platelet glycoprotein IIb/IIIa receptor antagonists before primary PCI obviously improves the prognosis of patients (Cutlip et al., 2003; Lee et al., 2003; Zeymer et al., 2005; Emre et al., 2006; Gabriel et al., 2006; Gibson et al., 2006; Rakowski et al., 2007; De Luca et al., 2008). This finding is consistent with the results of our research. We showed that the increase in cTnI 12 h after surgery in the tirofiban

group was significantly lower than in the control group (50.96 ± 2.20 *vs* 58.69 ± 2.34 ng/mL; $P < 0.01$). This finding suggests that intracoronary application of tirofiban can improve the myocardial perfusion level and reduce myocardial injury. Kurt et al. (2012) found that adjuvant tirofiban in patients treated with emergency PCI clearly improved TIMI blood flow level and reduced brain natriuretic peptide level in plasma. The D-value of NT-proBNP level between the 1st and 7th days after surgery in tirofiban group was significantly higher than in the control group. This finding suggests that intracoronary application of tirofiban can inhibit the activation of platelets, and improve myocardial perfusion and the cardiac function recovery of patients after emergency PCI.

In conclusion, intracoronary bolus injection of tirofiban after balloon dilatation of culprit lesions and before stent implantation during emergency PCI clearly reduced the activation of intracoronary GMP-140. Tirofiban inhibits platelet aggregation by antagonizing platelet glycoprotein IIb/IIIa receptor. Tirofiban inhibits thrombosis and improves myocardial perfusion and cardiac function after emergency PCI by inhibiting the expression of GMP-140 and reducing the activation of platelets.

The limitations of this research included the absence of a no-intravenous-medication group that could be used for comparison. Hence, we were unable to judge whether or not the effect of intracoronary application of tirofiban on intracoronary GMP 140 is consistent with that of intravenous application. In future studies, the sample size can be expanded to evaluate the differences between intracoronary and intravenous injections of tirofiban.

The results of this research provide clinical data for improving the clinical prognosis of patients treated with emergency PCI by upstream (i.e., before stent implantation) intracoronary application of tirofiban during emergency PCI.

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