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Safety and efficacy of intracoronary tirofiban administration in patients with serious thrombus burden and ST-elevation myocardial infarction undergoing percutaneous coronary intervention

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Abstract. – OBJECTIVE: This work aims to explore the safety and efficacy of intracoronary tirofiban administration in patients with serious thrombus burden and ST-elevation myocardial infarction (STEMI) undergoing emergency percutaneous coronary intervention (PCI).

PATIENTS AND METHODS: A total of 104 patients with serious thrombus burden and acute STEMI were randomly divided into treatment (intracoronary tirofiban administration, 56 cases) and control (48 cases) groups. Comparison of coronary blood flow, ST-segment resolution (STR), duration of hospital stay, 30-day major adverse cardiac events (MACE) and complications such as hemorrhage was conducted.

RESULTS: In treatment group, the percentage of thrombolysis in myocardial infarction-3 (TIMI-3) flow in the infarct-related artery (IRA) increased (89.3% to 85.4, $p < 0.05$), blood flow in the IRA calculated with TIMI frame count method enhanced [(1.68 ± 0.23) ml/s to (1.42 ± 0.31) ml/s, $p < 0.05$], STR on electrocardiogram (ECG) enlarged [(64.3 ± 7.84)% to (48.6 ± 6.47)%, $p < 0.05$)] and the prevalence of MACE decreased (10.7% to 18.8%, $p < 0.05$), all of which were significantly different from those of control group, but no statistical difference in complications was observed between two groups ($p > 0.05$).

CONCLUSIONS: It was simple, safe and effective to perform intracoronary tirofiban administration in patients with serious thrombus burden and STEMI when undergoing emergency PCI.

Key Words:
Acute myocardial infarction, Percutaneous coronary intervention, Tirofiban.

Introduction

The morbidity of coronary heart disease (CHD) has increased year by year in China. Emergency percutaneous coronary intervention (PCI) is one of the most effective measures to treat acute myocardial infarction (AMI) and also significantly improves the prognosis of patients with AMI[1]. Therefore, emergency PCI has been accepted in conditional hospitals as the most important treatment for revascularization in AMI patients. However, more and more researches find that, complete coronary recanalization does not mean restoration of effective myocardial reperfusion or no further expansion of myocardial infarction. In the emergency intervention, obvious thrombus burden in diseased blood vessels may result in migration and fragmentation of thrombus during balloon expansion and stent releasing, and formation of coronary microthrombus, which further causes distal vascular obstruction or spasm, slow flow and no-reflow. So the myocardial tissue can not achieve effective reperfusion, with persisting damage to coronary microcirculation. This seriously affects the prognosis of patients with AMI[2]. It is found that the prevalence of slow flow and no-reflow in patients with selective PCI is 0.6%-2%, and it is as high as 10%-30% in patients with emergency PCI[3]. Slow flow and no-reflow can cause irreparability of efficient reperfusion in myocardial tissue, and the mortality is 10 times to that in patients with normal reperfusion, seriously affecting the prognosis of AMI patients[4].

People try different ways to enhance the blood flow and improve the prognosis in patients with serious thrombus burden and STEMI, including implantation of distal protection device and thrombus suction device in coronary arteries[5]. Thrombus suction and tirofiban application in emergency PCI have been demonstrated by research to ameliorate slow flow and no-reflow in coronary arteries[6,7]. Although thrombus suction can effectively remove thrombus and elevate the blood flow in coronary arteries, the residual clot

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fragment may lead to distal vascular embolism[8]; thus, it can not be widely used due to the restrictions such as long-term clinical efficacy, medical condition and economic factors. Research[9] has discovered that tirofiban is able to inhibit the pathway of platelet aggregation, play the antiplatelet effect and reduce thrombus burden of the lesion site.

At present, many authors have discussed intravenous tirofiban application, but only few studies are exploring the efficacy of intracoronary tirofiban administration in patients with serious thrombus burden when undergoing emergency PCI. Therefore, we performed intracoronary tirofiban administration to treat acute STEMI with abundant thrombus load at emergency PCI and reported its safety and efficacy as follows.

Patients and Methods

Patients

A total of 104 STEMI patients with serious thrombus burden at emergency PCI were selected in our hospital between Apr. 2010 and Apr. 2012. Intracoronary thrombus is defined as strip, oval, or irregular filling defect in coronary arteries accompanied by contrast retention or staining. Inclusion criteria: typical ischemic chest pain lasted more than 30min, which could not be relieved by sublingual nitroglycerin; objective evidence of myocardial ischemia within 12h after onset was confirmed; ST-elevation with dynamic evolution was present in at least two adjacent leads on electrocardiogram (ECG). Exclusion criteria: patients with bleeding tendency and history of recent hemorrhage (including hemorrhagic stroke within 30 days and history of bleeding in gastrointestinal tract and urinary tract), known hepatorenal dysfunction, thrombocytopenia ($< 100 \times 10^9$/L), high blood pressure (> 180/110 mmHg, 1 mmHg = 0.133 kPa), pericarditis and aortic dissection. There were 65 males and 39 females aged from 28 to 84 years (57.4 ± 5.6 years), who were randomized into treatment (56 cases) and control (48 cases) groups. The former accepted intracoronary tirofiban administration provided by Wuhan Yuanda Pharmaceutical Group Co., Ltd., Wuhan, Hubei, China. Infarct-related arteries (IRAs) were right coronary arteries in 35 cases, anterior descending arteries in 56 cases and circumflex arteries in 13 cases. There were three cases of left main coronary artery disease, 29 cases of triple-vessel disease, 50 cases of double-vessel disease and 22 cases of single-vessel disease. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Henan Science and Technology University. Written informed consent was obtained from all participants.

Methods

All the patients after admission orally took 300 mg of Aspirin and 300 mg of clopidogrel (Sanofi-Aventis Company, Hangzhou, China), were subcutaneously injected with 100 IU/kg low molecular weight heparin (LMWH), and pumped intravenously and continuously with tirofiban (Grand Pharmaceutical (China) Co., Ltd., Wuhan, China), the antagonist of platelet membrane glycoprotein IIb/IIa receptor, with a speed of 0.1 g/(kg•min). Then, emergency coronary angiography and PCI were performed 90 min after admission. When large amount of thrombi or slow flow and no-reflow were observed, the patients in the treatment group were injected with 10 g/kg tirofiban into coronary artery through catheter within five minutes, and the intravenous pumping was continued for 48h with a speed of 0.1 g/(kg•min). The dosage of normal heparin (Jilin Sino-Kang Pharmaceutical Co., Ltd., Dunhua, China) during surgery was 50 IU/kg. PCI was performed only on IRAs in patients with lesions in multiple vessels. Every 12 hours, 100 IU/kg LMWH was injected subcutaneously after surgery for consecutive five to seven days. Patients orally took 100 mg of aspirin and 75 mg of clopidogrel once per day.

Observation Indicators

Blood stream in coronary artery before and after treatment[10-11], including TIMI (Thrombolysis In Myocardial Infarction) flow grade in IRAs, coronary blood flow calculated with TIMI frame count method: coronary blood flow (ml/s) = 21÷ (the TIMI frame number observed)×1.7. (2) The ST-segment resolution (STR) rate in ECG 90 min after surgery[12]: The amplitude of ST-segment elevation was measured from 0.04s after J point and the PR segment was considered as the control baseline from the superior border of the baseline to the superior border of ST segment. The ST-segment elevation summation of I, aVL and V1-V6 leads for the patients with acute anterior myocardial infarction (AAMI), and II, III, aVF and V5-V6 leads for the patients with acute non-anterior myocardial infarction were measured, re-

spectively. Then the STR summation was calculated: ∑STR = [∑ST (before surgery)-∑ST (after surgery)]/∑ST (before surgery). (3) Hemorrhagic complications according to the TIMI bleeding grade criteria: massive bleeding included intracranial hemorrhage and the hemoglobin level reduction that was larger than 50 g/L; minimal bleeding included Spontaneous hematuresis, haematemesis and observable bleeding that the reduction of hemoglobin was more than 30 g/L; thrombocytopenia was defined as the concentration of platelet was less than 60×10^9/L. (4) Major adverse cardiac events (MACE) in hospital and within 30 days, including: cardiac death for any reason, recent myocardial infarction, post-infarction angina pectoris and revascularization.

Statistical Analysis

Statistical software SPSS 11.5 was applied to analyze all data. The measurement data was presented as . The comparison between groups was performed using *t*-test. Enumeration data was analyzed with x^2 test. $p < 0.05$ was considered as statistically significant.

Results

General Clinical Data

There were no statistical differences in age, gender, risk factors, time from onset to intervention, IRAs and blood flow grade in IRAs of patients between two groups ($p > 0.05$, Table I).

TIMI flow Grade, Blood Flow, STR on ECG and Thrombocytopenia

In treatment group, the percentage of TIMI-3 flow and blood flow in the IRAs increased and STR on ECG enlarged, which were distinctly different from those of control group ($p < 0.05$). No distinct difference in the appearance of hemorrhage and thrombocytopenia was observed between two groups ($p > 0.05$, Table II).

Follow-up

MACE in hospital and within 30 days were shown by follow-up that the incidences of cardiac death, recent myocardial infarction, post-infarction angina pectoris and revascularization were lower compared with those of control group (10.7% to18.8%, $p < 0.05$, Table III).

Discussion

STEMI mainly results from platelet activation and aggregation induced by the rupture of vulnerable plaque in coronary artery, which causes thrombosis, acute occlusion of blood vessels and interruption of blood flow. Guideline has identified emergency PCI as preferred therapy of myocardial reperfusion for patients with STEMI[13]. Some research[14] has discovered that blood flow of myocardial tissue do not recover in over 25% of patients with TIMI-3 flow in IRAs indicated by coronary arteriography, i.e. coronary artery recanalization does not mean the reperfusion of

Table I. Comparison of general data of patients between two groups.

General data	Treatment group (n=56)	Control group (n=48)
Age (years)	59.3 ± 4.8$^\Delta$	58.9 ± 6.2
Male/Female	29/27 $^\Delta$	30/18
Smoking	23 (41.1%)$^\Delta$	17 (35.4%)
Hypertension	35 (62.5%)$^\Delta$	33 (68.0%)
Diabetes mellitus	24 (42.9%)$^\Delta$	19 (39.6%)
Low density lipoprotein (mmol/L)	3.71 ± 1.32$^\Delta$	3.68 ± 1.24
Body mass index (kg/m^2)	26.4 ± 3.25$^\Delta$	26.8 ± 4.12
Time from onset to intervention (h)	6.5 ± 3.41$^\Delta$	6.4 ± 2.98
IRAs		
LAD/RCA/LCX31/18/7$^\Delta$	23/18/7	
Preoperative IRAs		
TIMI grade		
Grade 0	45(80.4%)$^\Delta$	38 (79.2%)
Grade 1~2	11(19.6%)$^\Delta$	10 (20.8%)
IRAs calculated with	TIMI frame count method	
Blood flow (ml/s)	0.54 ± 0.13$^\Delta$	0.52 ± 0.17

Note: LAD, left anterior descending arteries; RCA, right coronary arteries; LCX, left circumflex artery; Compared with control group, $^\Delta p > 0.05$.

Table II. Comparison of coronary blood flow, STR, hemorrhage and thrombocytopenia in patients between two groups after treatment.

Items	Treatment group (n = 56)	Control group (n = 48)
Blood flow grade in coronary arteries (Cases)		
Grade 1~2	6 (10.7%)$^{\Delta}$	7 (14.6%)
Grade 3	50 (89.3%)$^{\Delta}$	41 (85.4%)
Coronary blood flow (ml/s)	1.68 ± 0.23$^{\Delta}$	1.42 ± 0.31
90 min STR (%)	64.3 ± 7.84$^{\Delta}$	48.6 ± 6.47
Hemorrhage (Cases)		
Massive hemorrhage (Cases)	2 (3.6%)$^{\Delta}$	1 (2.2%)
Minimal hemorrhage (Cases)	8 (14.3%)$^{\Delta}$	7 (14.6%)
Thrombocytopenia (Cases)	1$^{\Delta}$	0

Note: Compared with control group, $^{\Delta}p < 0.05$; $^{\Delta\Delta}p > 0.05$.

myocardial tissue. As for the CHD patients with heavy thrombus load, only percutaneous transluminal coronary angioplasty (PTCA) and/or stent placement are unable to effectively remove thrombus; coronary intervention will inevitably increase the possibility of thrombus detachment and distal microcirculatory embolism, which lead to coronary blood flow or perfusion on tissue level beyond recovery and finally cause no-reflow or slow flow. Guideline[13] has not recommended the application of distal protection devices in coronary artery of STEMI patients undergoing emergency PCI. In addition, strengthened anticoagulation and antiplatelet therapy may be helpful in reducing the occurrence of thromboembolism, no-reflow and slow reflow[15].

Glycoprotein (GP) IIb/IIIa receptor on the surface of platelet plays a decisive role in platelet adhesion and aggregation. The ultimate pathway of platelet aggregation is that fibrinogen simultaneously binds to two activated GP IIb/IIIa receptors on the surface of platelet membrane, which forms cross-bridge between adjacent platelets, induces platelet cross-linking and further results in platelet aggregation. Tirofiban hydrochloride is a non-peptide, short-acting and high selective platelet GP IIb/IIIa receptor antagonist, which antagonizes fibrinogen or vascular pseudohemophilia-related factors mediated platelet aggregation through binding to GP IIb/IIIa receptor on the surface of platelet, inhibits the final pathway of platelet aggregation, plays the antiplatelet effect and reduces thrombus burden of the lesion site[16]. Inhibition of platelet can reach 93%-96% 5 min after intravenous administration of tirofiban with a half life of 2h; plasma concentration is at a stable state 1h after continuous intravenous drip infusion; 50% of platelet function can recover in 1.5-4h after drug withdrawal[17]. In addition, tirofiban also improves vascular endothelial function[18]. Foreign research has confirmed that early application of platelet GP IIb/IIIa receptor antagonist ameliorates the efficacy of PCI in patients with acute coronary syndrome and the prognosis of reperfusion therapy[19,20]. Van't Hof et al[21] have revealed that after reperfusion recovers in myocardium, myocardial ischemia and cell membrane permeability improve, increased extracellular K^+ induced by ischemia is terminated and ST-segment elevation shows rapid resolution. Moreover, relief degree of myocardial ischemic injury positively correlates with degree of STR.

Table III. MACE of patients in two groups.

Group	Posttreatment MACE (Cases)				
	Cardiac death	Recent AMI	Post-infarction angina pectoris	Revascularizatio	Sum (%)
Treatment group (n = 56)	3	2	1	0	10.7$^{\Delta}$
Control group (n = 48)	2	3	3	1	18.8

Note: AMI, acute myocardial infarction; Compared with control group, $^{\Delta}p < 0.05$.

The therapeutic effect of intravenous administration of tirofiban on slow flow or no-reflow after emergency PCI has not been reported, but it is found that, intravenous bolus injection of tirofiban can increase the possibility of bleeding. Therefore, seeking a kind of safe method significantly increasing drug concentration in blood has become the focus of our research. Intravenous administration of tirofiban can only reach plasma concentration peak after 10-30 min, with delayed time of taking effect. At the same time, due to liver metabolism, the intravenous administration reduces the drug concentration at coronary artery lesions, leading to reduced anti-platelet aggregation effect[22]. Compared with intravenous administration, the direct drug injection via coronary artery can quickly achieve effective drug concentration for treatment. The drug concentrations in epicardial coronary artery and microcirculation are improved by several hundred times. So, almost all platelet membrane glycoprotein IIb/IIIa receptors in microcirculation combine with drug, but not the fibrin. Finally, the formation of white thrombus in coronary microcirculation is reduced. The higher the blocking degree of platelet membrane glycoprotein IIb/IIIa receptor is, the smaller the possibility of thrombosis in coronary microcirculation is. This is more conducive to improvement of myocardial perfusion and clinical endpoints.

PCI can cause vascular endothelial damage, expose subendothelial collagen and further promote platelet adhesion and aggregation. Although intervention therapy opens epicardial coronary arteries, fragments of atheromatous plaques, necrotic lipid and inflammatory substances produced in the process of treatment flow to distal end, which activates platelet again and induces new thrombosis, including platelet thrombus and fibrin thrombus. Tirofiban has an antagonistic effect on both red and white thrombi.

In our research the percentage of TIMI-3 flow in the IRAs increased (89.3% to 85.4, $p < 0.05$) in treatment group; blood flow in the IRA calculated with TIMI frame count method in treatment group was superior to that of control group [(1.68 ± 0.23) ml/s to (1.42 ± 0.31) ml/s, $p < 0.05$]; STR on ECG enlarged in treatment group compared with that of control group [(64.3 ± 7.84)% to (48.6 ± 6.47)%, $p < 0.05$)]; the incidence of 30-day MACE (cardiac death, recent myocardial infarction, post-infarction angina pectoris and revascularization) was lower than that of control group (10.7% to 18.8%, $p < 0.05$). These findings were associated with that tirofiban could thoroughly inhibit platelet aggregation, prevent platelet thrombus formation, improve coronary microcirculation, antagonize red and white thrombi and ameliorate vascular endothelial function. Tirofiban has a short half life; platelet function can rapidly recover after drug withdrawal; the incidence of hemorrhage is low and the safety is high. Our study also showed that no statistical difference in the occurrence of hemorrhage and thrombocytopenia was observed between treatment and control groups ($p > 0.05$).

Conclusions

Our research results preliminarily displayed that as for acute STEMI patients with heavy thrombus burden, intracoronary administration of tirofiban could markedly improve coronary blood flow and myocardial perfusion, as well as reduce the prevalence of 30-day MACE. In addition, the appearence of hemorrhagic complications was as low as it was in control group ($p > 0.05$), which was consistent with the results of related research[23,24]. Therefore, it was simple, safe and effective to perform intracoronary tirofiban administration in STEMI patients with serious thrombus burden when undergoing emergency PCI. At present, only few clinical studies are exploring the efficacy of intracoronary tirofiban administration; thus, there is no experience can be used as reference, and the sample size is small in our study, which requires large clinical trials for further confirmation.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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