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Comparison of antithrombotic effect between tirofiban and urokinase in emergency percutaneous coronary intervention.

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Abstract

This study aims to compare and evaluate safety and antithrombotic effect of tirofiban and urokinase in emergency percutaneous coronary intervention (PCI). Twenty patients with relatively large thrombus burden in emergency PCI were selected; 12 patients received tirofiban and others received urokinase during operation. Operation success rate, thrombus score and incidence of hemorrhagic complications and major adverse cardiac events [MACEs, including death, acute myocardial infarction (AMI) and emergency revascularization] during perioperation and three months after discharge were recorded. Coronary thrombi in tirofiban group disappeared earlier than that of urokinase group; the incidence of bleeding was comparable between two groups; no MACEs were observed at hospital and during three-month follow-up. In tirofiban group, thrombus score significantly decreased and operation success rate was 100%, without death, recurrent MI and target vessel revascularization. Tirofiban is safe and effective in emergency PCI, which shows antithrombotic effect and significantly decreases thrombus score.

Keywords: Tirofiban, Urokinase, Percutaneous coronary intervention, Thrombus score, Effective

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Introduction

Direct percutanous coronary intervention (PCI) was an effective way of emergency reperfusion for patients with ST-elevation myocardial infarction (STEMI) [1]. In the very early days, however, persons realized that reinfarction, or reocclusion, occurs in 10-20% of patients in whom reperfusion was initially successful [2]. In 1999, Oshima et al. demonstrated that in patients with acute myocardial infarction, PCI combined with pre-treatment of a low dose of urokinase was much more effective than PCI alone, especially for those patients who have a large coronary thrombus [3]. On the one hand, Patients with complicated PCI operations need sufficient anticoagulation. Acute or subacute thrombosis resulted from not sufficient anticoagulation would induce acute myocardial infarction, even sudden death [4]; On the other hand, the application of intensive anticoagulation may induce hemorrhage, even more serious outcome [5].

Tirofiban is a newly synthesized nonpeptidesmall-molecule platelet glycoprotein (GP) IIb/IIIa receptor antagonist, characterized by high selectivity and short-term effect. Many clinical studies [6-9] have confirmed that tirofiban inhibits *in vitro* platelet aggregation induced by various agonists, including adenosine diphosphate (ADP), collagen, epinephrine and thrombin, thus to exert an antithrombotic effect. Recently, the use of tirofiban in patients with acute myocardial infarction was paid more attention. Jia et al. reported that to the Chinese patients with acute myocardial infarction undergoing primary PCI, upstream administration of tirofiban was slightly superior to deferred injection for short-term clinical outcomes [10]. Li et al. reported that the combination therapy of fondaparinux and tirofiban is of good safety and efficacy in high risk UA patients undergoing complex PCI [11]. As far as we know, there was no research about Comparison of antithrombotic effect between tirofiban and urokinase in emergency PCI. So our research aimed to observe effect of tirofiban on coronary thrombosis in percutaneous coronary intervention.

Materials and Methods

Subjects

Twenty patients with coronary thrombus undergoing emergency PCI between May 2004 and August 2008 were selected; including 13 males and 7 females aged 44~77 years with mean age of (57.4 ± 6.4) years. Patients had onset of more than 4 h and ST-elevation myocardial infarction (STEMI) within 12 h, consistent with World Health Organization (WHO) diagnostic criteria for acute myocardial infarction (AMI). All the subjects were observed with large thrombus burden, 18 of whom underwent primary PCI and two underwent rescue PCI after failed thrombolysis. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee

of Capital Medical University. Written informed consent was obtained from all participants.

Evaluation of coronary blood flow

Thrombolysis in myocardial infarction (TIMI) flow grade was employed as criteria to evaluate coronary blood flow in coronary angiography (CAG) [12] as follows: TIMI 0 flow refers to the absence of any antegrade flow beyond a coronary occlusion; TIMI 1 flow is faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed; TIMI 2 flow is delayed antegrade flow (>three cardiac cycles) with complete filling of the distal territory; TIMI 3 is normal flow which completely fills the distal coronary bed and its clearance is in three cardiac cycles.

Routine preoperative and intraoperative treatment

Twenty patients who were diagnosed with AMI within 12h after onset orally took 300 mg of aspirin (100 mg, Bayer HealthCare Manufacturing S.r.l, Via Delle Groane, 126, 20024 Garbagnate Milannese MI, Italy, batch number: H20130192) and 300 mg of plavix (75 mg, Sanofi Pharma Bristol-Myers Squibb SNC, 1rue de La Vierge, Ambares & Lagrave F-33565 Carbon Blanc Cedex, France, batch number: H20130296) immediately, followed by CAG to identify infarct-related artery (IRA). All the subjects with thrombus score ≥ 2 (Thrombus score: 0=no thrombus, 1=possible thrombus, 2=definite thrombus <1/2 of vessel diameter, 3=definite thrombus with 1/2~2 times of vessel diameter, 4=definite thrombus>twice vessel diameter) [13,14] were randomized into two groups. Twelve patients received tirofiban (5 mg/100 ml, Yuanda Pharmaceutical Group Co., Ltd., Wuhan, China, batch number: H20041165) with intravenously loading dose of 20 μg/kg over 2 min, followed by continuous intravenous pumping of 0.15 μg/(kg.min) for 24 h, which was reduced to half dose if subcutaneous bleeding or bleeding tendency was observed.

Eight patients received 250000 IU urokinase (Luoxin, 250000 IU/vial, Tianpu Biochemical Pharmaceutical Co, Ltd. Guangdong, China, batch number: 07060101) in 30 min. CAG was performed 60 min after tirofiban or urokinase injection to observe whether thrombus was dissolved and thrombus score was reevaluated. Another dose of 250000 IU urokinase was injected in 30 min if CAG showed unsatisfying result. PCI was performed via radial artery to recanalize IRA. Stent (2.25 mm-4.0 mm/12 mm-30 mm, Medtronic SNC, Parkmore Business Park West, Galway, Ireland, batch number: 0006669515) implant following predilation was conducted in all patients. The pressure for balloon pre-dilation and stent implantation was 8~12 atm and 12~18 atm, respectively. Stent totally covered lesions and stent-to-vessel-diameter ratio was 1:1~1.1. Operation success rate, thrombus score, resolution of intracoronary thrombus and incidence of hemorrhagic complications and major adverse cardiac events (MACEs, including death, AMI and emergency revascularization) during perioperation and three months after discharge were recorded. Patients received 100 U/kg heparin (12500 IU/2 ml, Qianhong Biochemical Pharmaceutical Co., Ltd., Changzhou, China, batch number: H20041165) intraoperatively.

Postoperative treatment

Tirofiban group postoperatively received continuous intravenous pumping of 0.15 μg/(kg.min) tirofiban for 24 h, which was reduced to half dose if subcutaneous bleeding or bleeding tendency was observed. Other treatment was the same in two groups. Patients postoperatively received oral anti-platelet drugs and pumping of 500~1000 U/h heparin for 24 h. Activated partial thromboplastin time (APTT) was controlled 1.5~2.5 times higher than that before treatment, followed by subcutaneous injection of 1 mg/kg low-molecular-weight heparin clexane (60 mg/0.6 ml, Sanofi-aventis, 1-13, boulevard Romain Rolland 75014 Paris, France, batch number: H20090095) every 12 h for 5~7days.

Postoperative observation

Symptoms, bleeding, change in electrocardiogram, myocardial markers and MACEs, (death, AMI and emergency revascularization) were observed and followed up for three months.

Statistical analysis

Measurement data was presented as means ± SE (x ± s). Comparison of data before and after operation utilized t-test. $P<0.05$ was considered statistically significant.

Success criteria for operation

Success operation was defined as TIMI 3 flow and residual stenosis <10% shown by CAG 60 min after operation.

Results

CAG and PCI results

Among 20 patients undergoing PCI, there were 12, 6 and 2 cases of single, double and triple-vessel disease, respectively; 28 vascular lesions in 13 left anterior descending (LAD) arteries, six left circumflex (LCX) arteries and nine right coronary arteries (RCA) were treated with percutaneous transluminal coronary angioplasty (PTCA) and stent implantation without postoperative residual stenosis.

Comparison of intracoronary thrombus score

CAG showed relatively large intracoronary thrombus burden; patients with large thrombus burden after routine PTCA or stent implantation and undissolved thrombus in 5 min after removal of main coronary artery stenosis were recruited in our research. All the subjects had thrombus score ≥ 2 (Thrombus score: 0=no thrombus, 1=possible thrombus, 2=definite thrombus <1/2 of vessel diameter, 3=definite thrombus with 1/2 ~2 times of vessel diameter, 4=definite thrombus>twice vessel diameter). CAG displayed TIMI 3 flow in thrombus-related coronary arteries and thrombus score <1 60 min after

tirofiban application. Change in thrombus score was shown in Table 1.

Table 1. Comparison of intracoronary thrombus score before and 60 min after tirofiban application

Patients undergoing PCI in tirofiban group (n=12)	before tirofiban	60min after tirofiban
Thrombus Score	2.8 ± 0.8	0.5 ± 0.5
Note: P<0.01		

Resolution of intracoronary thrombus

TIMI 3 flow in coronary arteries with thrombus was observed 60 min after application of tirofiban or urokinase in two groups. The parameters for thrombus resolution were shown in Table 2 that coronary blood flow improved in both groups but coronary thrombus resolution and TIMI 3 flow were observed earlier in tirofiban group than that of urokinase group.

Table 2. Resolution of intracoronary thrombus in two groups.

	Tirofiban group	Urokinase group
Previous coronary blood flow (TIMI grade)	1.6 ± 1.0	1.4 ± 1.1
Time to recover TIMI 3 flow (min)*	12.3 ± 7.5	28.6 ± 13.3
Number of patients with thrombus burden 60 min later*	0	4
Note: *P<0.01		

Complications during perioperation and one to three-month follow-up

Patients in two groups were observed without MACEs, (AMI, reperfusion, and death) in hospital and during three-month follow-up. In tirofiban group, there were three cases of bleeding from venipuncture site 24 h after operation and one case of gum bleeding, while there were one case of minimal bleeding from radial artery puncture site, one case of gum bleeding and one case of hematuresis 24~48 h after operation in urokinase group. The incidence of mild bleeding was not significantly different between two groups and no complications of severe internal bleeding, such as cerebral hemorrhage and massive gastrointestinal hemorrhage were observed in hospital. There were no acute or subacute thrombotic events and bleeding during three-month follow-up.

Discussions

The present study was to verify effectiveness efficacy, tolerability and safety of tirofiban for patients with emergency PCI to prevent reinfarction, or reocclusion, occurs of thrombosis. The results demonstrated lower intracoronary thrombus score of tirofiban group than urokinase group, and fast-acting tirofiban reduces the incidence of bleeding and complications and is suitable for rapid adjustment as platelet activity recovers quickly after drug withdrawal. Although intensive therapy with plavix plus aspirin and low-molecular-weight heparin have been extensively applied [15-20], intracoronary thrombosis in emergency PCI is still common in AMI patients. Therefore, treatment for intracoronary thrombosis in emergency PCI directly affects operation success rate and prognosis [21]. Currently, balloon-dilation and stent implantation can eliminate vascular luminal stenosis and restore blood flow in PCI, thus facilitate thrombus removal. However, thrombus is still observed or even larger in some patients after blood flow restoration.

Tirofiban is a fast-acting and highly selective platelet aggregation inhibitor, as well as a newly synthesized nonpeptide small-molecule platelet GP IIb/IIIa receptor antagonist with short-term effect, which functions in the final common pathway of platelet aggregation: it occupies the cross-linking site of platelet GP IIb/IIIa via RGD (Arg-Gly-Asp) sequence and competitively inhibits fibrinogen [or von willebrand factor (VWF)]-mediated platelet aggregation. Fast-acting tirofiban is highly specific to platelet GP IIb/IIIa receptor and suitable for repeated administration as platelet activity recovers 4~10 h after drug withdrawal [22]. Tirofiban shows a good effect on acute coronary syndrome (ACS) [23,24], thrombosis after PCI [25] and no-flow. A randomized, double-blind, placebo-controlled clinical trial [26] has demonstrated that tirofiban application based on the standard therapy for ACS (aspirin and heparin) can more thoroughly inhibit platelet aggregation and thrombosis, thus effectively reduce thrombosis in patients during PCI.

In our research, significant coronary thrombus regression was observed 60 min after drug application. Although tirofiban is platelet aggregation inhibitor, coronary thrombi are mainly new and in a dynamic change between thrombus formation and regression in PCI. Previously, intravascular thrombolysis and distal protection device were employed to remove thrombi, but the efficacy was bad because urokinase promoted thrombosis and neutralized thrombolysis. Tirofiban showed superior efficacy to urokinase in our study. Tirofiban exerts an antiplatelet aggregation effect and prevent thrombosis in the last step [22]. Therefore, intracoronary and intravenous injection of tirofiban should be firstly considered to treat intracoronary thrombus in emergency PCI in addition to restoring coronary blood flow by surgery, because oral antiplatelet drugs cannot act immediately, thus antithrombosis can only depend on heparin and intravenous or intracoronary injection of tirofiban. There was no significant discomfort or adverse reaction in our patients. Most patients continued to receive tirofiban 24 h after operation with minimal bleeding, which indicated that intravenous or intracoronary injection of tirofiban is safe. Nowadays, drug-coated stent has been widely used, but high incidence of acute and subacute stent thrombosis concerns many people, thus tirofiban application during perioperation may be safer based on conventional anticoagulant and antithrombotic treatment.

In our study, patients were admitted in hospital late with onset more than 4 h, which might result in high thrombus score, while patients had more thrombi due to activation of

coagulation system after failed thrombolysis: thrombus score more than 4 was observed in two patients with failed thrombolysis. Tirofiban can effectively dissolve thrombus, suggesting that tirofiban should be prepared before rescue PCI. Previous experiments [27] displayed that early intervention therapy was harmful to patients with non ST-elevation ACS, but these patients did not undergo antiplatelet therapy with tirofiban. We speculate that application of tirofiban in these patients during perioperation may improve prognosis and reduce mortality, which requires more clinical trials, longer follow-up and further investigation.

In the study, we compared the two groups (tirofiban and urokinase) in the parameters for thrombus resolution, complications during perioperation and three-month follow-up. The most important result shows that coronary thrombus resolution and TIMI 3 flow were observed earlier in tirofiban group than that of urokinase group. Patients in both tirofiban and urokonase groups were observed without MACEs, (AMI, reperfusion, and death) in hospital and during three-month follow-up. There was no significant difference in patients with complications. In conclusion, tirofiban is safe and effective with good acceptability and tolerance for patients with emergency PCI to prevent reinfarction, or reocclusion, occurs of thrombosis.

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