Acute Coronary Syndrome

Effects of Coronary Arterial Injection of Tirofiban on Diabetes Mellitus Complicated with Acute Myocardial Infarction in the Elderly

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Objective: This work aims to explore the short-term efficacy and safety of coronary arterial injection of tirofiban in elderly diabetic patients complicated with acute myocardial infarction (AMI) who underwent emergency percutaneous coronary intervention (PCI).

Methods: Ninety-seven elderly diabetic patients complicated with ST-elevation myocardial infarction (STEMI) who underwent emergency PCI were selected and randomized into control (group A, 49 cases) and tirofiban (group B, 48 cases) groups. Another 129 nonelderly diabetic patients (group C) complicated with STEMI who underwent emergency PCI and tirofiban treatment in the corresponding period were also involved for comparison.

Results: Thrombolysis in myocardial infarction 3 (TIMI3) flow was significantly higher in groups B and C than in group A after PCI ($p < 0.01$). TIMI myocardial perfusion grades (TMPG) 0 to 1 and 2 were distinctly lower ($p < 0.01$, $p < 0.05$) and TMPG3 was obviously higher ($p < 0.01$) in groups B and C than in group A. The average length of hospital stay, post-infarction angina pectoris, severe arrhythmia, and cardiac function Killip III to IV were markedly lower in groups B and C than in group A ($p < 0.01$, $p < 0.05$). Meanwhile, mucocutaneous hemorrhage was significantly higher in groups B and C than in group A ($p < 0.01$).

Conclusions: Tirofiban effectively improved TIMI flow and TMPG perfusion in elderly diabetic patients complicated with AMI and reduced the incidence of serious complications without increasing the occurrence of severe hemorrhage.

Key Words: Acute myocardial infarction • Diabetes mellitus • Emergency percutaneous coronary intervention • Tirofiban

INTRODUCTION

Early, continuous, and full dredging of infarct-related artery is the most important principle in treating acute myocardial infarction (AMI). Platelet membrane glycoprotein (GP) IIb/IIIa receptor antagonist can block the combination of fibrinogen receptor with the GP IIb/IIIa complex and inhibit the final pathway of platelet aggregation, thereby exhibiting a powerful antiplatelet effect. In clinical practice, Gp IIb/IIIa receptor antagonist is often selectively used in patients with the following manifestations: thrombus imaging visible to naked eye in radiography, slow blood flow in radiography, and diabetes mellitus (DM) complicated with ST-elevation myocardial infarction (STEMI). Abnormal glucose metabolism is one of the major risk factors of arteriosclerosis.[1] DM is considered as a coronary heart disease (CHD) risk equivalent. The incidence of no-reflow and slow flow after percutaneous coronary intervention (PCI) is significantly higher in diabetic patients complicated with

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AMI than in non-diabetic patients,[2,3] especially in elderly diabetic patients with AMI, which is one of the main reasons for increased cardiovascular events after PCI.[4] Sufficient evidence-based medical data show that GP IIb/IIIa receptor antagonist helps restore the coronary artery blood flow and myocardial tissue reperfusion in AMI patients after emergency PCI.[5,6] However, the efficacy and safety of the GP IIb/IIIa receptor antagonist tirofiban hydrochloride for elderly diabetic patients with AMI who underwent emergency PCI have yet to be verified. In this study, the efficacy and safety of coronary arterial injection of tirofiban on elderly diabetic patients with AMI who underwent emergency PCI were investigated.

MATERIALS AND METHODS

Subjects

Ninety-seven elderly (over 60 years old) diabetic patients complicated with STEMI who underwent emergency PCI in the coronary care unit (CCU) between Jan 2010 and Jan. 2013 were selected and randomized into control (group A, 49 cases) and tirofiban (group B, 48 cases) groups. Group A comprised of 24 males and 25 females with an average age of (68.6 $\pm$ 5.9) years old; group B comprised of 25 males and 23 females with an average age of (69.5 $\pm$ 6.8) years old. Another 129 nonelderly diabetic patients (group C) complicated with STEMI who underwent emergency PCI and tirofiban treatment in the corresponding period were also involved for comparative analysis with groups A and B. Group C comprised of 67 males and 62 females with an average age of (51.7 $\pm$ 6.8) years old. The diagnostic criterion of AMI was according to the ACC/AHA 2007 guidelines for the management of patients with ST-elevation myocardial infarction.[7] The diagnostic criteria for DM were based on the American Diabetes Association diabetes diagnostic criteria.[8] The inclusion criteria were as follows: (1) onset of STEMI was within 12 h, (2) patients were diagnosed with DM, (3) patients agreed with emergency PCI. The exclusion criteria were as follows: (1) onset of STEMI was more than 12 h, (2) patients were suspected with aortic dissection, (3) uncontrolled hypertension $\geq$ 180/110 mmHg, (4) second PCI after thrombolysis treatment, (5) history of cerebral hemorrhage and history of ischemic stroke within a year, (6) severe hepatic or renal dysfunction, (7) history of coagulopathy, and (8) AMI complicated with cardiogenic shock and severe left heart failure. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the People's Hospital of Zhengzhou. Written informed consent was obtained from all participants.

Emergency PCI

After being admitted to the hospital, 18-lead electrocardiogram (ECG) was applied to the patients, who also underwent electrocardiograph monitoring, oxygen inhalation, blood glucose, blood lipid, myocardial enzyme and troponin tests, and other related biochemical and routine tests. At the same time, the patients took 300 mg of aspirin and 600 mg of clopidogrel by chewing. The Judkins Technique of coronary angiography was employed, in which the catheter was guided through the blood vessel to the opening of the coronary arteries. The patients received 3000 and 7000 U heparin through sheathing canal before and after angiography. A thrombus suction catheter was utilized to remove the thrombus if its shadow was visible after angiography. The guidewire was passed through the culprit lesion, followed by balloon dilatation. In groups B and C, tirofiban was injected into the coronary arteries after the guidewire passed through the lesion at 10 μg/kg within 3 min, followed by continuous intravenous (IV) administration at 0.15 μg/(kg·min) by pumping for 24 h. Tirofiban was not applied in the control group. Coronary angiography was repeated to check coronary blood flow. Percutaneous transluminal coronary angioplasty with stent implantation or primary stenting was performed according to the disease condition. All selected patients were treated with rapamycin eluting stent [Cepu (Beijing) Medical Equipment Co., Ltd., Beijing, China]. The level of myocardial enzymes and troponin, ECG, ultrasonic cardiogram, and hepatic or renal function were reviewed after surgery. The patients continued to receive 100 mg/d aspirin, 75 mg/d clopidogrel, statins, β-receptor blocker, and hypoglycemic agent. Only criminal vessels were treated in emergency PCI. The rest were processed in second surgery after 7 d to 14 d.

Observation indexes

The characteristics of lesions in the three groups were analyzed according to the results of coronary arteriography. These characteristics include length of hospital stay, average times from admission to balloon dilatation, number of patients who were implanted with more than two stents during PCI emergency, second PCI during hospitalization, angina after infarction, reinfarction, acute and subacute thrombosis stent, severe arrhythmia (ventricular tachycardia, ventricular fibrillation, type II second-degree atrioventricular block, or third-degree atrioventricular block), cardiac function Killip class III/IV and cardiogenic shock, 30-day mortality rate, cerebral, gastrointestinal, and mucocutaneous hemorrhage, bleeding or hematoma at puncture site, and so on. Thrombolysis in myocardial infarction trial (TIMI) and TIMI myocardial perfusion grade (TMPG) of infarction-related blood vessels after PCI were recorded.[10,11] The following are the criteria for TIMI blood stream: grade 0, vessel was occluded with no distal forward blood stream; grade 1, the contrast agent can partially pass the occlusion part but cannot fill the vessel; grade 2, the contrast agent can fill the vessel completely, and the speeds of filling and clearance of the agent are slower than that of a normal coronary artery; grade 3, the contrast agent can fill the vessel completely, and the speeds of filling and clearance of the agent are the same as that of a normal coronary artery. Therefore, TIMI 0 and TIMI 1 indicated that the coronary artery was unsuccessfully clear again, whereas TIMI 2 and TIMI 3 indicated the opposite. The following are the criteria for TMPG: grade 0, myocardium was not or barely stained during the injection and clearance of the contrast agent; grade 1, myocardium was slowly and only partially stained, exhibiting diffuse punctate staining during the next injection; grade 2, myocardium can be stained, but staining and fading were so slow that staining could last until the end of the clearance phase; grade 3, blood stream was normal, and myocardium was generally stained, which could barely last until the end of the clearance phase or not at all.

Statistical analysis

The statistical software SPSS16.0 was applied to analyze the data, which were presented as mean ± standard deviation. Enumeration and measurement data were analyzed with χ^2 and t tests, respectively. Significant difference was considered at $p < 0.05$.

RESULTS

General information

As shown in Table 1, no significant differences in gender, hypertension, smoking history, hyperlipemia, renal function, PCI history, preinfarction angina, and family history of CHD were observed among the patients in the three groups ($p > 0.05$). The age of nonelderly group was significantly lower than that of elderly group ($p < 0.01$), with no significant difference between the control and nonelderly groups ($p > 0.05$).

Coronary artery lesions

No distinct differences in single-vessel, 2-vessel, or 3-vessel lesions, left main lesions, and target vessels treated in emergency PCI were found among the

Table 1. Comparison of general data among patients in three groups

Item	Control group (49 cases, group A)	Elderly tirofiban group (48 cases, group B)	Nonelderly tirofiban group (129 cases, group C)
Male, cases (%)	26 (53.1)	25 (52.1)	65 (50.4)
Age, years old	68.6 ± 5.9*	69.5 ± 6.8*	51.7 ± 6.8
Hypertension, cases (%)	35 (71.4)	37 (77.1)	97 (75.2)
Smoking history, cases (%)	31 (63.3)	32 (66.7)	84 (65.1)
Hyperlipemia, cases (%)	25 (51.0)	26 (54.2)	67 (51.9)
Serum creatinine (mmol/L)	90.2 ± 11.21	89.6 ± 12.5	88.98 ± 16.3
PCI history, cases (%)	10 (20.4)	10 (20.8)	23 (17.8)
Preinfarction angina, cases (%)	21 (42.9)	19 (39.6)	52 (40.3)
History of CHD, cases (%)	6 (12.2)	5 (10.4)	16 (12.4)

* $p < 0.01$ compared with group C.

patients in the three groups ($p > 0.05$). TIMI3 flow was significantly higher in the elderly and nonelderly tirofiban groups (groups B and C) than in the control group (group A) after PCI ($p < 0.01$). TMPG0 and TMPG1 were distinctly lower ($p < 0.01$, $p < 0.05$) and TMPG3 was obviously higher ($p < 0.01$) in groups B and C than in the control group. No statistical difference was observed between groups B and C ($p > 0.05$, Table 2).

Balloon dilatation

No statistical differences in average time from admission to hospital to balloon dilatation, the number of patients with two stents, the incidence of second PCI, reinfarction, acute and subacute stent thrombosis and cardiogenic shock, as well as 30-day mortality rate were found ($p > 0.05$). The average length of hospital stay, post-infarction angina pectoris, severe arrhythmia, and cardiac function Killip III to IV were markedly lower in groups B and C than in group A ($p < 0.01$, $p < 0.05$). No statistical difference was observed between groups B and C ($p > 0.05$). No significant differences in thrombocytopenia (< $100*10^9$/L), severe intracranial and gastrointestinal hemorrhage, and the number of patient required blood transfusion were observed. The incidence of mucocutaneous hemorrhage was much higher in groups B and C than in group A ($p < 0.01$, Table 3).

DISCUSSIONS

The most important therapeutic principle of AMI is the continuous and complete opening of infarction-related blood vessels as soon as possible to save dying myocardium, prevent further infarction, narrow the range of myocardial ischemia, and protect and maintain cardiac function to the maximum extent.[12,13]

The disturbance of carbohydrate metabolism is one of the most important risk factors of arteriosclerosis.[14]

Table 2. Comparison of characteristics of coronary artery lesions among patients in three groups [cases (%)]

Characteristics of lesions	Control group (49 cases, group A)	Elderly tirofiban group (48 cases, group B)	Nonelderly tirofiban group (129 cases, group C)
Single branch lesions	5 (10.2)	4 (8.3)	12 (9.3)
Doublebranch lesions	21 (42.9)	22 (45.8)	56 (43.4)
Triple branch lesions	23 (46.9)	22 (45.8)	61 (47.3)
Left main lesions	11 (22.5)	9 (18.8)	25 (19.4)
Incidence of thrombosuction	5 (10.2)	4 (8.3)	9 (7.0)
Target vessels in emergency PCI			
LAD	23 (46.9)	25 (52.1)	63 (48.8)
LCX	12 (24.5)	8 (16.7)	26 (20.2)
RCA	14 (28.6)	15 (31.3)	40 (31.0)
TIMI grade			
Preoperative TIMI 0~1	43 (87.8)	45 (93.8)	122 (94.6)
Preoperative TIMI 2	6 (12.2)	3 (6.3)	7 (5.4)
Preoperative TIMI 3	0	0	0
Postoperative TIMI 0~1	3 (6.1)‡	0‡	2 (1.6)‡
Postoperative TIMI 2	11 (22.5)	2 (4.2)	2 (1.6)
Postoperative TIMI 3	35 (71.4)‡	46 (95.8)*‡	125 (96.9)*‡
Preoperative TMPG grade			
Grade 0~1	47 (95.9)	47 (97.9)	125 (96.9)
Grade 2	2 (4.1)	1 (2.1)	4 (3.1)
Grade 3	0	0	0
Postoperative TMPG grade			
Grade 0~1	9 (18.4)§	1 (2.1)†§	4 (3.1)*§
Grade 2	9 (18.4)	2 (4.2)*	6 (4.7)*
Grade 3	31 (63.3)§	45 (93.8)*§	119 (92.3)*§

* $p < 0.01$; † $p < 0.05$ compared with control group; ‡ $p < 0.01$ compared with preoperative TIMI; § $p < 0.01$ compared with preoperative TMPG.

Table 3. Comparison of the length of hospital stay, PCI characteristics and incidence of complications among patients in three groups

Item	Control group (49 cases, group A)	Elderly tirofiban group (48 cases, group B)	Nonelderly tirofiban group (129 cases, group C)
Average length of hospital stay (d)	13.2 ± 3.3	10.2 ± 2.7†	10.7 ± 3.1†
Average time from admission to hospital to balloon dilatation (min)	87.7 ± 28.2	82.9 ± 39.8	89.76 ± 41.6
Number of patients with two stents [cases (%)]	10 (20.4)	11 (22.9)	33 (25.6)
Second PCI [cases (%)]	25 (51.0)	26 (54.2)	62 (48.1)
Post-infarction angina [cases (%)]	16 (32.7)	8 (16.7)†	22 (17.1)†
Re-infarction [cases (%)]	4 (8.2)	4 (8.3)	10 (7.8)
Stent thrombosis [cases (%)]	1 (2.0)	0 (0)	2 (1.6)
Severe arrhythmia [cases (%)]	16 (32.7)	4 (8.3)*	9 (7.0)*
Cardiac function Killip III~IV [cases (%)]	7 (14.3)	2 (4.2)†	5 (3.9)*
Cardiogenic shock after PCI [cases (%)]	2 (4.1)	1 (2.1)	3 (2.3)
30-day mortality rate [cases (%)]	1 (2.0)	0 (0)	1 (0.8)
Hemorrhage [cases (%)]			
Thrombocytopenia (< $100*10^9$/L)	0 (0)	1 (2.1)	2 (1.6)
Intracranial hemorrhage	0 (0)	0 (0)	1 (0.8)
Gastrointestinal hemorrhage	1 (2.0)	1 (2.1)	2 (1.6)
Blood transfusion	1 (2.0)	1 (2.1)	1 (0.8)
Mucocutaneous hemorrhage	3 (6.1)	16 (33.3)*	45 (34.9)*
Bleeding or hematoma at puncture site	4 (8.2)	5 (10.4)	13 (10.1)

* $p < 0.01$; † $p < 0.05$ compared with control group.

DM is considered as a CHD risk equivalent; the risk factors of arteriosclerosis in diabetic patients is two to four times that in non-diabetic patients,[14] and the efficacy of antiplatelet therapy in diabetic patients is worse than that in non-diabetic patients.[15] CHD always involves multiple blood vessels with diffuse lesions and usually complicates with microangiopathy and diabetic cardiomyopathy.[16] Thrombus suction can remove visible thrombus with coronary angiography, but only 39% of the thrombus was visible in AMI. For the invisible thrombus, emergency PCI increases the possibility of thrombosis and distal embolization in microcirculation, which is the main cause of no-reflow and slow flow after PCI[17,18] and is also one of the reasons for increased incidence of complications, such as heart failure, arrhythmia, and cardiogenic shock in diabetic patients with AMI.[17-19] Compared with non-diabetic patients, diabetic patients have a higher incidence of re-infarction, heart failure, stroke, and death regardless of the acute or chronic phase.[19]

The incidence of no-reflow and slow flow after PCI is significantly higher in diabetic patients complicated with AMI than in non-diabetic patients,[2,3] especially in elderly diabetic patients with AMI.[4,15,17,20] Tirofiban hydrochloride is a potent non-peptide platelet membrane glycoprotein IIb/IIIa receptor antagonist that effectively reduces the incidence of no-reflow and slow flow after PCI.[21] Restored forward flow of infarction-related arteries to TIMI3 has been considered as the gold standard for successful reperfusion treatment.[9] However, a significant difference in perfusion level exists between peripheral coronary arteries; even the blood flow of epicardial coronary artery achieves TIMI3. Research has demonstrated that myocardial tissues in 25% to 30% of patients still have insufficient reperfusion (i.e., no-reflow and slow flow) when PCI restores epicardial blood flow to normal level.[10,11] In fact, successful reperfusion on myocardial tissue level is the final standard. TMPG, as a standard for perfusion on myocardial level, includes the filling and emptying of the contrast medium in myocardium and can evaluate the perfusion on myocardial level more accurately.[11] Microangiopathy and microvascular dysfunction always complicate diffuse lesions of epicardial coronary arteries in diabetic patients. In addition, hyperglycemia enhances inflammatory reaction and platelet-dependent microthrombosis, as well as weakens endothelium-dependent vasodilation, thereby aggravating the perfusion distur-

bance of coronary microcirculation.[9,10,15] Many studies have shown that the mortality of patients with TMPG0 to TMPG1 is much higher than that of patients with TMPG2 to TMPG3 as well as patients with normal TIMI3 flow in epicardial coronary vessels.[3-5,19] Our research revealed that coronary arterial injection of tirofiban effectively reduced the occurrence of no-reflow and slow flow, improved TIMI flow and TMPG perfusion, and decreased the incidence of AMI complication.

Stent thrombosis is one of the severe complications after PCI, which can be effectively prevented by sufficient antiplatelet and anticoagulant.[5,6,14,18,21] Dual-antiplatelet therapy is an important preventive measure against thromboembolic events after PCI, and the resistance to aspirin and clopidogrel is one of the important causes of thrombotic events. Early detection of patients with aspirin and clopidogrel resistance and application of other antiplatelet drugs are important preventive measures against thrombotic events. For example, the use of tirofiban can effectively reduce the formation of acute and subacute thrombosis after PCI. One case of acute stent thrombosis and one case of subacute stent thrombosis were found 6 h after surgery and 4 d after PCI in our control group, respectively. No thrombotic event was observed in the tirofiban group, but no statistical difference was observed between the two groups. Theoretically, tirofiban is a reversible platelet membrane glycoprotein IIb/IIIa receptor antagonist that discontinues the production of antiplatelet effect after drug withdrawal. However, if it can delay antithrombotic effect requires further investigation.

Arrhythmia, especially malignant arrhythmia, is one of the common complications of AMI. In our study, the incidence of malignant arrhythmia in the control group was up to 32%. This result can be ascribed to elevated blood sugar that aggravated endothelial dysfunction, increased inflammatory reaction, exacerbated reperfusion injury induced by free radicals, and boosted the excitability of β-receptors, thereby causing damaged myocardial cell membrane, unbalanced calcium inside and outside the membrane, and arrhythmia.[3,4,18,20] Diabetic patients with AMI have relative or absolute lack of insulin and elevated concentration of plasma free fatty acid, which increases oxygen consumption by damaged myocardium, expands the infarction area, aggravates ventricular remodeling, decreases cardiac function, induces heart failure and cardiogenic shock, and increases mortality.[14,15,19,20] Arrhythmia was significantly reduced after tirofiban treatment. This finding may be correlated with improved microvascular perfusion.

In our research, the patients with cardiac function Killip III to IV accounted for 15% in the control group, indicating that diabetic patients had reduced cardiac function after AMI and that elderly patients with AMI were more vulnerable to heart failure. The incidence of heart failure dramatically decreased after tirofiban treatment, which might be correlated with improved microvascular perfusion, enhanced myocardial reperfusion, increased energy supply of myocardial cells, and reduced myocardial cell death.[5,21,22]

Tirofiban has a strong antiplatelet effect and can be used in dual antiplatelet therapy with aspirin and clopidogrel, which are commonly used for AMI. Thrombocytopenia and hemorrhage complication have attracted signficant attention from cardiovascular doctors,[23] especially in elderly diabetic patients with AMI. One case of thrombocytopenia ($10*10^9$/L) was found 12 h after PCI in the tirofiban group. The patient recovered 5 d after the adrenocortical hormone therapy with discontinuation of aspirin, heparin, and tirofiban and application of clopidogrel. No severe hemorrhage was observed except for subcutaneous congestion. Intracranial hemorrhage occurred in one patient whose blood pressure was more than 170/110 mmHg for a long time. Two cases of gastrointestinal hemorrhage with ulcer history were found in both control and tirofiban groups. However, no statistical difference in the incidence of hemorrhage was observed between the groups, indicating that tirofiban was safe for elderly diabetic patients with AMI. Hyporrhea, including mucocutaneous hemorrhage, occurred more often in the tirofiban group than in the control group without adverse consequences. Hemorrhoea can be avoided with the application of tirofiban as long as we thoroughly inquired the medical history of the patient, controlled strict indications, and reviewed the platelet of patients in a timely manner.

CONCLUSIONS

In conclusion, the coronary arterial injection of tirofiban can effectively improve TIMI flow and TMPG

perfusion in elderly diabetic patients complicated with AMI and reduce the incidence of severe arrhythmia and heart failure without increasing bleeding complication.

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