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Therapy with ticagrelor for ST-elevated acute coronary syndrome accompanied by diabetes mellitus

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Abstract. – OBJECTIVE: To investigate the protective effect of ticagrelor on the myocardium of patients with ST-elevated acute coronary syndrome accompanied by diabetes mellitus.

PATIENTS AND METHODS: 210 patients with diabetes mellitus receiving emergency percutaneous coronary intervention (PCI) due to ST-elevated acute coronary syndrome from December 2014 to June 2018 in the Hospital were selected and randomly divided into ticagrelor group and clopidogrel group. The myocardial microcirculation perfusion was evaluated via ST-segment elevation resolution (STR) in electrocardiogram (ECG) and myocardial blush grade (MBG). Myocardial necrosis markers, including creatine kinase (CK), CK-MB, and cardiac troponin I (cTnI), were evaluated. Moreover, the cardiac function was assessed using brain natriuretic peptide (BNP) level and left ventricular ejection fraction (LVEF). Finally, patients were followed up for one month on average, and the adverse cardiovascular and bleeding events were recorded.

RESULTS: The results showed that CK, CK-MB, cTnI, and BNP levels in ticagrelor group were lower than those in clopidogrel group, and the differences were statistically significant ($p<0.05$). Thrombolysis in myocardial infarction (TIMI) flow grading after the operation had no statistically significant difference between the two groups, and the usage rate of tirofiban in ticagrelor group was lower than that in clopidogrel group ($p<0.05$). Besides, the myocardial microcirculation perfusion level after the operation in ticagrelor group was significantly higher than that in clopidogrel group. The proportions of STR ≥50% in ECG and MBG2 in ticagrelor group were significantly higher than those in clopidogrel group ($p<0.01$). The incidence rate of mild bleeding in ticagrelor group was higher than that in clopidogrel group ($p<0.05$).

CONCLUSION: The application of ticagrelor in the treatment of ST-elevated acute coronary syndrome accompanied by diabetes mellitus can increase the level of myocardial microcirculation perfusion and improve the left heart function.

Key Words:
Acute coronary syndrome, Diabetes mellitus, Ticagrelor, Percutaneous coronary intervention.

Introduction

Reperfusion therapy has become a standard treatment method for ST-elevated acute coronary syndrome, namely the ST-elevated myocardial infarction (STEMI). The distal coronary microthrombus, no-reflow during the operation, and stent thrombosis after the operation occur more easily in patients with ST-elevated acute coronary syndrome accompanied by diabetes mellitus in emergency percutaneous coronary intervention (PCI). This, further damages the myocardium and leads to cardiac insufficiency[1]. Previous studies have demonstrated that ticagrelor is effective and reliable in clinical application, and at the same time, it can improve the adenosine concentration in plasma and increase the adenosine-mediated biological effects by inhibiting the adenosine transporter, equilibrative nucleoside transporter 1 (ENT1), especially those in ischemia and tissue damage sites. Besides, adenosine can dilate the coronary arteries, increase the coronary blood flow, weaken the excitatory effect of catecholamines on the heart, and reduce the release of norepinephrine, exerting a protective effect on heart[2-4]. However, there are few reports on whether ticagrelor has a protective effect on the myocardium of patients with ST-elevated acute coronary syndrome accompanied by diabetes mellitus. This work aims to evaluate the protective effect

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of ticagrelor on the myocardium of patients with ST-elevated acute coronary syndrome accompanied by diabetes mellitus.

Patients and Methods

Patients

A total of 210 patients with diabetes mellitus receiving emergency PCI due to ST-elevated acute coronary syndrome from December 2014 to June 2018 in the Hospital were selected as objects of the study. Inclusion criteria: 1) patients whose onset time of ST-elevated acute coronary syndrome was within 6 h; and 2) patients who agreed to receive emergency PCI. The diagnostic criteria for ST-elevated acute coronary syndrome were based on the Guidelines for the Diagnosis and Treatment of STEMI in China in 2015. Exclusion criteria: 1) patients with non-ST-elevated acute coronary syndrome; 2) patients with serious heart failure on admission or who could not lie on the back; 3) patients with a history of hemorrhagic diseases; 4) patients with intracranial tumors, arterial malformations or aneurysms; 5) patients with severe liver or kidney dysfunction; 6) patients with a history of serious lung diseases, such as asthma or pulmonary fibrosis; or 7) patients who changed the anti-platelet treatment program due to the wishes of patients or their families. Patients were randomly divided into two groups: ticagrelor group and clopidogrel group. Only the infarct-related coronary arteries were treated in all patients *via* radial artery or brachial artery approach with intraoperative heparin anticoagulation (100μ/kg). All patients chewed 300 mg aspirin enteric-coated tablets (Bayer), 180 mg ticagrelor or 600 mg clopidogrel on admission, and continued to take 100 mg aspirin enteric-coated tablets qd, 90 mg ticagrelor bid or 75 mg clopidogrel qd after the operation; 20 mg atorvastatin calcium was routinely given qn, and angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), and β-blockers were given when there were no contraindications. After the operation, the low molecular heparin was routinely injected subcutaneously for anticoagulant therapy. Informed consent was obtained from patients about the above therapies. The research was approved by the Ethics Committee of Binzhou City Center Hospital.

Myocardial Microcirculation Perfusion Evaluation

1) ST-segment elevation resolution (STR) in electrocardiogram (ECG): the 18-lead ECGs before PCI and at 2 h after PCI were recorded, respectively. The ST-segment complete resolution was compared (complete resolution: the ST-segment elevation after PCI is reduced by more than 50% compared with that before PCI) to obtain the noninvasive indexes for complete reperfusion[5]; 2) Assessment of myocardial blush grade (MBG), MBG 0: no myocardial development or contrast agent density; MBG 1: a little myocardial development or contrast agent density; MBG 2: moderate myocardial development or contrast agent density, but less than the myocardial development or contrast agent density in ipsilateral or contralateral non-infarct-related arteriography, and partial myocardial perfusion; MBG 3: normal myocardial development or contrast agent density. MBG 0-1 indicates no myocardial reperfusion, while MBG 2-3 indicates myocardial reperfusion[6].

Comparisons of Myocardial Necrosis Markers and Cardiac Function Indexes After Operation Between Two Groups

Venous blood was drawn immediately on admission and at 12 h after the onset of the disease. The creatine kinase (CK), CK-MB, and cardiac troponin I (cTnI) were detected, respectively. The cardiac function indexes included brain natriuretic peptide (BNP) and left ventricular ejection fraction (LVEF). The BNP level was detected using the Triage MeterPro analyzer at 48 h after onset of disease; LVEF was detected by the method of dual-pane Simpson *via* transthoracic echocardiography under routine position.

Follow-up of Adverse Cardiac Events and Bleeding Events

Patients were followed up for one month on average for clinical and bleeding events. Clinical events included the adverse events during follow-up, such as death, re-infarction, target vessel revascularization, and stroke. While, bleeding events were assessed according to GUSTO bleeding grading[7]: 1) serious or life-threatening bleeding: intracranial hemorrhage or hemodynamic damage requiring intervention; 2) moderate bleeding: hemorrhage requiring blood transfusion but not resulting in hemodynamic damage; 3) mild bleeding: hemorrhage not meeting the requirements of severe and moderate bleeding. Dyspepsia symptoms included the upper abdominal pain and discomfort, burning sensation, acid reflux, belching or nausea and vomiting, while digestive tract hemorrhage was manifested as hematemesis, hemafecia or positive in fecal occult blood testing (excluding hemorrhoids-caused results).

Table I. Comparisons of baseline data between two groups.

	Ticagrelor group (n=108)	Clopidogrel group (n=100)	p
Age (years old)	68.27±4.65	69.13±5.13	>0.05
Female [n (%)]	50 (46.30)	42 (42.00)	>0.05
Visit time (h)	4.1±2.4	4.3±3.5	>0.05
History of myocardial infarction [n (%)]	12 (11.11)	8 (8.00)	>0.05
History of PCI [n (%)]	10 (9.26)	11 (11.00)	>0.05
History of hypertension [n (%)]	56 (51.85)	48 (48.00)	>0.05
History of hyperlipidemia [n (%)]	34 (31.48)	36 (36.00)	>0.05
History of cerebrovascular diseases [n (%)]	10 (9.26)	6 (6.00)	>0.05
Smoking [n (%)]	52 (48.15)	46 (46.00)	>0.05
Family history [n (%)]	38 (35.2)	34 (34.00)	>0.05
Basal heart rate	73.9±22.5	74.4±24.2	>0.05
Systolic pressure (mmHg)	145.6±22.5	147.2±19.7	>0.05
Diastolic pressure (mmHg)	81.4±12.5	79.9±13.9	>0.05
Average hospitalization period (d)	6.5±2.5	6.3±2.7	>0.05

Statistical Analysis

Measurement data were presented as mean ± standard deviation; the *t*-test was used for the intergroup comparison. Enumeration data were presented as a percentage. Chi-square test was used for the comparison of rate. Statistical Product and Service Solutions (SPSS) 19.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. $p<0.05$ suggested that the difference was statistically significant.

Results

Comparisons of Baseline Data Between Two Groups

210 patients were enrolled in this study, among which 2 cases were lost to follow-up. Finally, there were 108 cases in ticagrelor group and 100 cases in clopidogrel group. There were no significant differences in age, gender, visit time, history of myocardial infarction, history of PCI, history of hypertension, history of hyperlipidemia, history of cerebrovascular diseases, smoking, family history, basal heart rate, blood pressure, and average hospitalization period between the two groups ($p>0.05$) (Table I).

Comparisons of Serological Indexes Before Operation Between Two Groups

Serological indexes, including total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride (TG), fasting blood glucose (FBG), serum creatinine (Scr), homocysteine (HCY), and high-sensitivity C-reactive protein (hs-CRP), had no statistically significant differences before the operation between the two groups ($p>0.05$) (Table II).

Table II. Comparisons of serological indexes before operation between two groups.

	Ticagrelor group (n=108)	Clopidogrel group (n=100)	p
TC (mmol/L)	5.41±0.93	5.34±1.04	>0.05
LDL-C (mmol/L)	2.98±0.53	2.93±0.60	>0.05
HDL-C (mmol/L)	0.91±0.33	0.89±0.31	>0.05
TG (mmol/L)	1.08±0.53	1.21±0.62	>0.05
FBG (mmol/L)	4.92±0.93	5.13±1.00	>0.05
Scr (μmol/L)	89.8±35.6	92.3±31.9	>0.05
HCY (μmol/L)	13.8±1.73	14.9±1.65	>0.05
Hs-CRP (mg/L)	0.98±0.53	1.03±0.71	>0.05

Table III. Comparisons of myocardial necrosis markers and cardiac function indexes after operation between two groups.

	Ticagrelor group (n=108)	Clopidogrel group (n=100)	p
CK (U/L)	1235.41±122.05	1449.34±123.56	<0.05
CK-MB (U/L)	232.98±53.32	293.05.±45.62	<0.05
cTnI (ng/mL)	15.9±4.33	18.9±5.31	<0.05
BNP (pg/mL)	208.5±15.3	336.3±20.6	<0.05
LVEF (%)	52.2±2.93	51.3±2.43	>0.05

Table IV. Comparisons of coronary angiography and myocardial perfusion between two groups.

	Ticagrelor group (n=108)	Clopidogrel group (n=100)	p
Double/triple-vessel diseases [n (%)]	64 (59.3)	67 (67)	>0.05
Lesion involving the left main coronary artery [n (%)]	11 (10.2)	13 (13)	>0.05
Anterior descending branch as infracted vessel [n (%)]	38 (35.2)	34 (34)	>0.05
D2B time (min)	87.4±32.0	85.3±27.5	>0.05
Thrombus aspiration [n (%)]	12 (11.1)	14 (14)	>0.05
Radial artery pathway [n (%)]	104 (96.3)	99 (99)	>0.05
Tirofiban [n (%)]	17 (15.7)	19 (19)	<0.05
Grade-3 TIMI flow after operation [n (%)]	101 (93.5)	91 (91)	>0.05
STR ≥ 50% [n (%)]	92 (85.2)	71 (71)	<0.01
MBG ≥ grade 2 [n (%)]	96 (88.9)	78 (78)	<0.01

Comparisons of Myocardial Necrosis Markers and Cardiac Function Indexes After Operation Between Two Groups

CK, CK-MB, cTnI, and BNP levels in ticagrelor group were lower than those in clopidogrel group, and the differences were statistically significant (p<0.05). The differences of LVEF between the two groups were not statistically significant (p>0.05) (Table III).

Comparisons of Coronary Angiography and Myocardial Perfusion Between Two Groups

The radial artery pathway, the incidence rate of double/triple-vessel diseases, rate of a lesion involving the left main coronary artery, anterior descending branch as the infracted vessel, the usage rate of thrombus aspiration and door-to-balloon (D2B) time had no statistically significant differences between the two groups (p>0.05). TIMI flow grading after the operation had no statistically significant difference between the two groups, while the usage rate of tirofiban in ticagrelor group was lower than that in clopidogrel group. Also, the difference was statistically significant between the two groups (p<0.05). Besides, the proportions of STR ≥50% in ECG and MBG2 in ticagrelor group were markedly higher than those in clopidogrel group (p<0.01) (Table IV).

Comparisons of Cardiovascular Events and Bleeding Events Between Two Groups

The incidence rates of death, re-infarction, target vessel revascularization, stroke, and massive bleeding during follow-up had no statistically significant differences between the two groups (p>0.05). The incidence rate of mild and moderate bleeding in ticagrelor group was higher than that in clopidogrel group (Table V).

Discussion

Previous reports have shown that diabetes mellitus is an independent risk factor for atherosclerotic cardiovascular disease and an influencing factor of coronary heart disease. Patients with diabetes mellitus often have a variety of risk factors, including the small and dense LDL, hyperglycemia and various metabolic products (advanced glycation end products, reactive oxidative species, increased free fatty acids, and changes in endothelial cells, smooth muscle cells, and mac-

Table V. Comparisons of cardiovascular events and bleeding events between two groups.

	Ticagrelor group (n=108)	Clopidogrel group (n=100)	p
Death [n (%)]	2 (1.9)	2 (2)	>0.05
Re-infarction [n (%)]	1 (0.9)	1 (1)	>0.05
Target vessel revascularization [n (%)]	0 (0)	0 (0)	>0.05
Stroke [n (%)]	0 (0)	1 (1)	>0.05
Bleeding event [n (%)]	8 (7.4)	5 (5)	>0.05
Massive bleeding [n (%)]	1 (0.9)	1 (1)	>0.05
Mild and moderate bleeding [n (%)]	7 (6.5)	4 (4)	<0.05

rophages), promoting the inflammatory response. Therefore, atherosclerotic lesions develop rapidly and more seriously in patients with diabetes mellitus[8-10]. At the same time, platelets in patients with diabetes mellitus are highly reactive. Platelet-activation, adhesion, and aggregation occur more easily and their mechanisms include the hyperglycemia-induced P-selectin expression, activation of protein kinase C, glycosylation of platelet surface proteins, and increased platelet adhesion and aggregation. Insulin resistance impairs the reactivity of prostacyclin, thereby increasing the intracellular calcium concentration and enhancing the platelet degranulation *via* insulin receptor substrate[11-13]. Compared with that in non-diabetic patients, the atherosclerotic disease is more severe, and the proportion of the multi-vessel disease is also higher in STEMI patients complicated by diabetes mellitus. In this research, there were 131 cases of multi-vessel disease in both groups, accounting for 63% in the total. Acute coronary syndrome is a kind of cardiovascular disease with high incidence, high disability, and high mortality rates, seriously endangering human health. The key factors in the occurrence of the acute coronary syndrome are plaque rupture and activation of platelets. Therefore, antiplatelet therapy is crucial for acute coronary syndrome patients accompanied by diabetes mellitus[14]. The dual anti-platelet therapy of aspirin and clopidogrel can significantly reduce the risk of cardiovascular events (including stent thrombosis) in patients with acute coronary syndromes, including those after PCI. However, individual differences in the treatment effect of clopidogrel are relatively large due to the influence of metabolic pathways; in other words, some patients have clopidogrel resistance, significantly increasing the risk of recurrent cardiac events[15-17]. Ticagrelor is a new type of antiplatelet drug, which is not affected by genes and metabolic pathways *in vivo*, and can inhibit the platelets more quickly in a more constant manner. On the one hand, it exerts an antiplatelet effect *via* inhibiting platelet P2Y12 receptors; on the other, it can also increase the effect of local adenosine by inhibiting the re-uptake of red blood cells to adenosine, which further inhibits the platelet aggregation and activation with vasodilation and myocardial protection effects[18]. Pollack et al[19] studied and suggested that compared with clopidogrel, ticagrelor can reduce the incidence rate of cardiovascular events in patients with the acute coronary syndrome. CK, CK-MB, cTnI, and BNP levels in ticagrelor group were lower than those in clopidogrel group, while the proportions of STR ≥50% in ECG and MBG2 in ticagrelor group were markedly higher than those in clopidogrel group. This indicated that ticagrelor can further alleviate the myocardial damage, better improve the micro-perfusion of myocardial cells, and protect cardiac function of patients compared with clopidogrel. The results of this study showed that there were no significant differences in adverse cardiovascular events between the two groups after treatment. Foreign studies[20] have found that ticagrelor can have a higher platelet inhibition rate in patients with no or low response to clopidogrel; after administration of ticagrelor for 6 months, the overall incidence rate of adverse cardiovascular events in STEMI patients complicated by diabetes mellitus was significantly lower than that in clopidogrel group, suggesting that the curative effect of ticagrelor is significantly superior to that of clopidogrel[21]. No decrease in cardiovascular events was found in our study, which was associated with the small sample size and short follow-up time. Also, the risks of thrombosis and bleeding should be weighed in anti-platelet therapy[22]. Moreover, it was found that the incidence rate of moderate and mild bleeding in ticagrelor group was higher than that in clopidogrel group; however, there was no statistically significant dif-

ference in the fatal bleeding event between two groups. Besides, the usage of tirofiban was reduced by ticagrelor.

Conclusions

We found that ticagrelor has a stronger anti-platelet effect in the treatment of patients with ST-elevated acute coronary syndrome accompanied by diabetes mellitus, compared with clopidogrel, which improves the myocardial perfusion and cardiac function of patients to a certain degree.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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