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Original Article

Effects of oral ticagrelor or clopidogrel before emergent PCI on the inflammatory mediators and endotheliocyte functions in STEMI patients

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Abstract: Objective: To investigate the effects of oral ticagrelor or clopidogrel before emergent percutaneous coronary intervention (PCI) on the inflammatory mediators and endotheliocyte functions in patients with ST elevation myocardial infarction (STEMI). Methods: Totally 349 STEMI patients from February 2013 to February 2016 were enrolled. All the patients were treated with aspirin. In addition to the treatment with aspirin, 155 patients were given ticagrelor (test group) and the other 194 patients given clopidogrel (control group). The changes in inflammatory mediators (tumor necrosis factor-related activator protein (CD40L), P selectin, and C reactive protein (CRP)) and endotheliocyte function indexes (nitric oxide (NO), von Willebrand disease factor (vWF), and plasma soluble intercellular adhesion molecule (sICAM-1)) were observed and compared before PCI, during PCI, and 4 weeks after PCI between the two groups. Results: Both ticagrelor and clopidogrel could effectively decrease the intra-operative levels of CD40L and P selectin (compared with those before PCI, $P<0.05$) and maintain the CRP levels stable during and after PCI (compared with that before PCI, $P>0.05$); 4 weeks after PCI, CD40L and P selectin were increased compared with those during PCI ($P<0.05$), but the CD40L level was still decreased compared with that before PCI ($P<0.05$), and P selectin was recovered to a level similar to that before PCI ($P<0.05$). Four weeks after PCI, both groups had significantly improved NO but decreased vWF, and sICAM-1 compared with those before and during PCI (all $P<0.05$). Four weeks after PCI, the test group had a significantly higher NO level but significantly lower vWF and sICAM-1 levels than the control group (all $P<0.05$), and the differences in the other indexes at the other time points between the two groups were statistically insignificant. The two groups had insignificantly different incidences of adverse events ($P>0.05$). Conclusion: Both ticagrelor and clopidogrel can effectively improve the inflammatory mediators and endotheliocyte functions in STEMI patients; the two groups have similar effects on inflammatory mediators, but the ticagrelor group has significantly better improving effects on endothelium-dependent diastolic function than the clopidogrel group.

Keywords: Ticagrelor, clopidogrel, ST elevation myocardial infarction, inflammatory mediator, endotheliocyte function

Introduction

ST elevation myocardial infarction (STEMI) is myocardial necrosis caused by persistent myocardial ischemia secondary to sharp decrease or even disappearance of the blood supply ability of the coronary artery secondary to coronary artery diseases; meanwhile, the rupture of coronary atherosclerotic plaque activates the blood coagulation system and results in coronary artery embolization, which is the main reason for death in patients with coronary atherosclerotic heart disease [1-3]. Reperfusion treatment is a predominant method to decrease the myocardial infarction area, recover the blood supply ability of the coronary artery, protect heart function, and decrease the death rate in STEMI patients. Among them, percutaneous coronary intervention (PCI) is fully affirmed in the field because of its early, sufficient, and constant abilities to unblock the embolized arteries and recover blood supply [4, 5]. Whereas, it is another research objective of clinicians to further decrease the incidence of adverse events of PCI. Inflammatory reaction and oxidative stress are two inevitable events

Table 1. Comparison of general data between the two groups

	Test group (n=155)	Control group (n=194)	Statistical magnitude	P
Age (years old)	57.93±12.50	59.55±11.30	1.2312	0.2191
Sex			1.2233	0.2687
Male	117 (75.5%)	156 (80.4%)		
Female	38 (24.5%)	38 (19.6%)		
Body weight (kg)	71.77±14.42	72.27±13.72	0.2621	0.7935
History of smoking			0.8344	0.3610
No	81 (52.3%)	92 (47.4%)		
Yes	74 (47.7%)	102 (52.6%)		
Application of insulin treatment			1.4995	0.2208
No	144 (92.9%)	186 (95.9%)		
Yes	11 (7.1%)	8 (4.1%)		
Killip granding			1.1314	0.3069
I	134 (86.5%)	180 (92.8%)		
II	14 (9.0%)	9 (4.6%)		
III	7 (4.5%)	5 (2.6%)		
The site of myocardial infarction				
Front wall	77 (49.7%)	87 (44.8%)	0.7561	0.3846
Back wall	11 (7.1%)	18 (9.3%)	0.5931	0.4412
Inferior wall	80 (51.6%)	111 (57.2%)	0.9334	0.3340
Right ventricle	5 (3.2%)	14 (7.2%)	2.0685	0.1504
Side wall	3 (1.9%)	5 (2.6%)	Fisher	1.0000
Other	1 (0.6%)	1 (0.5%)	Fisher	1.0000

of interventional treatment, greatly and adversely affect vascular endotheliocyte functions, and further activate the blood coagulation system. In severe cases, it may cause no reflow phenomenon of the coronary artery and constant myocardial injury, and hinder the reperfusion of the microcirculation of myocardial tissues [6, 7]. Ticagrelor and clopidogrel have good effects in antiplatelet treatment, and can alleviate the inflammatory reaction and improve vascular endothelium functions in cardiovascular diseases [8-10]. This study observed the efficacy of ticagrelor and clopidogrel used before PCI in 349 STEMI patients and compared the effects of the two drugs in improving inflammatory mediators and vascular endothelium functions in STEMI patients to decrease the incidence of adverse events and elevate the efficacy of PCI.

Materials and methods

Case selection

This study was approved by Medical Ethics Committee of the Ji'nan Central Hospital, and the patients or the family had signed informed consent. The subjects included 349 STEMI patients treated with PCI in our hospital from February 2013 to September 2017. All the patients were treated with aspirin (loading dose: 300 mg each person-time PO; then 100 mg qd; Bayer Health Care Manufacturing S. R. L., Germany). According to random number table, the patients were divided into two groups; in addition to the treatment with aspirin, 155 patients were given ticagrelor (test group), and the other 194 patients given clopidogrel (control group). The patients were enrolled referring to the diagnostic criteria for STEMI of World Health Organization, and all of them had signed the informed consent. The following patients were excluded: patients with intermittent myocardial infarction; those allergic to clopidogrel, ticagrelor, or aspirin; those with histories of coronary heart disease or had in terventional procedures including PCI; those with cerebrovascular disease or infectious disease; those with severe cardiac dysfunction; those with tumors, hypertension, or liver or kidney failure; and those with mental disorders or learning dysfunction [11].

Grouping and treatments

PCI: Both groups underwent PCI successfully using drug-eluting stents.

The 155 patients of the test group were given ticagrelor (loading dose: 180 mg; then 90 mg bid; AstraZeneca, AB, Sweden) in addition to the treatment with aspirin before PCI.

And the 194 patients of the control group were given clopidogrel (loading dose: 600 mg PO;

Table 2. Statistical analysis results of CD40L level in the peripheral venous blood of the subjects (ng/mL)

	Test group (n=155)	Control group (n=194)	P
Before PCI	8,801.0±9,194.8	8,346.3±8,021.9	0.6682
During PCI	2,564.0±4,592.3[a]	2,856.9±4,841.6[a]	0.6455
4 weeks after PCI	6,987.5±7,447.6[b]	7,740.0±7,362.4[b]	0.4893

Note: Both groups had significantly lower CD40L levels during PCI than those before PCI and at 4 weeks after PCI, [a]P<0.05; and both groups had significantly lower CD40L levels at 4 weeks after PCI than before PCI, [b]P<0.05; CD40L, tumor necrosis factor-related activator protein.

Table 3. Statistical analysis results of P selectin level in the peripheral venous blood of the subjects (pg/mL)

	Test group (n=155)	Control group (n=194)	P
Before PCI	146.38±179.88	147.49±152.60	0.4446
During PCI	98.20±149.86[a]	93.32±103.31[a]	0.7900
4 weeks after PCI	131.84±134.59[b]	136.66±138.09[b]	0.6338

Note: Both groups had significantly lower P selectin levels during PCI than those before PCI and at 4 weeks after PCI, [a]P<0.05; and both groups had significantly lower P selectin levels at 4 weeks after PCI than before PCI, [b]P<0.05.

then 75 mg qd; Sanofi Winthrop Industrie, France) in addition to the treatment with aspirin before PCI.

Observation indexes

Totally 4 mL of peripheral venous blood was sampled by a nurse before PCI (before medication), during PCI, or 4 weeks after PCI, and was tested in the Department of Clinical Laboratory of Jinan Central Hospital. The changes in inflammatory mediators (tumor necrosis factor-related activator protein (CD40L), P-selectin, and C reactive protein (CRP)) and endotheliocyte function indexes (nitric oxide (NO), von Willebrand disease factor (vWF), and plasma soluble intercellular adhesion molecule (sICAM-1)) were observed and compared before PCI, during PCI, and at 4 weeks after PCI between the two groups. NO was tested on a portable nitric oxide detector (Guangdong Skesen Gas Detection Equipment Co., Ltd), and the other factors were tested by immunoturbidimetry.

Statistical analysis

The data were treated with SPSS 19.0 (Asia Analytics Formerly SPSS China). The comparison of rate was tested by X^2 test. Measurement data were expressed by mean ± standard deviation ($\bar{x}$ ± sd), and inter-group comparison was analyzed by one-factor analysis of variance (when homoscedasticity) or tested by non-parameter K-S test (when heterogeneity of variance). Intra-group comparisons of data of different time points were treated with analysis of variance after repeated measurement. When P<0.05, the difference was statistically significant.

Results

General data

Of the 349 STEMI patients, 155 STEMI patients were of the test group, including 117 males and 38 females, and aged (57.93± 12.50) years; and the other 194 STEMI patients were of the control group, including 156 males and 38 females, and aged (59.55±11.30) years. The two groups had insignificantly different basic data, such as sex, age, history of smoking, and body weight (P>0.05, **Table 1**).

Statistical analysis results of CD40L level in the peripheral venous blood of the subjects

The two groups had insignificantly different CD40L levels at each time point (P>0.05); both groups had significantly lower CD40L levels during PCI and 4 weeks after PCI than before PCI (P<0.05), and both groups had significantly lower CD40L levels during PCI than those at 4 weeks after PCI (P<0.05, **Table 2**).

Statistical analysis results of P selectin level in the peripheral venous blood of the subjects

The two groups had insignificantly different P selectin levels at each time point (P>0.05); both groups had significantly lower P selectin levels during PCI and at 4 weeks after PCI than before PCI (P<0.05), and both groups had significantly lower P selectin levels during PCI than those at 4 weeks after PCI (P<0.05, **Table 3**).

Statistical analysis results of CRP level in the peripheral venous blood of the subjects

The two groups had insignificantly different CRP levels at each time points (P>0.05); both groups had insignificantly different CRP levels

Table 4. Statistical analysis results of CRP level in the peripheral venous blood of the subjects (mg/L)

	Test group (n=155)	Control group (n=194)	P
Before PCI	540.10±379.57	545.77±373.49	0.9050
During PCI	548.19±417.84	506.99±349.79	0.4332
4 weeks after PCI	510.67±339.99	495.09±346.12	0.7729

Note: CRP, C reactive protein.

Table 5. Statistical analysis results of NO level in the peripheral venous blood of the subjects (μmol/L)

	Test group (n=155)	Control group (n=194)	P
Before PCI	51.31±10.57	52.11±13.48	0.5456
During PCI	54.97±7.15	54.64±7.33	0.7462
4 weeks after PCI	57.59±6.84[a]	55.67±7.12[a]	0.0074

Note: Both groups had significantly higher NO levels at 4 weeks after PCI than those before and during PCI, [a]P<0.05; NO, nitric oxide.

Table 6. Statistical analysis results of vWF level in the peripheral venous blood of the subjects (mg/L)

	Test group (n=155)	Control group (n=194)	P
Before PCI	118.77±25.31	120.14±27.85	0.3402
During PCI	119.94±24.77	121.28±26.62	0.2902
4 weeks after PCI	104.29±25.17[a]	107.44±26.38[a]	0.0217

Note: Both groups had significantly lower vWF levels at 4 weeks after PCI than those before and during PCI [a]P<0.05; vWF, von Willebrand disease factor.

Table 7. Statistical analysis results of sICAM-1 level in the peripheral venous blood of the subjects (ng/mL)

	Test group (n=155)	Control group (n=194)	P
Before PCI	157.32±58.27	154.77±49.69	0.8481
During PCI	159.73±54.34	157.28±56.17	0.3846
4 weeks after PCI	140.29±50.11[a]	143.74±49.39[a]	0.0314

Note: Both groups had significantly lower sICAM-1 levels at 4 weeks after PCI than those before and during PCI ([a]P<0.05); sICAM-1, plasma soluble intercellular adhesion molecule.

in the same group among different time points (P>0.05, **Table 4**).

Statistical analysis results of NO level in the peripheral venous blood of the subjects

Both groups had significantly increased NO levels at 4 weeks after PCI compared with those before and during PCI (P<0.05); the test group had a significantly higher NO level than the control group at 4 weeks after PCI (P<0.05); the two groups had insignificantly different NO levels before and during PCI (P>0.05, **Table 5**).

Statistical analysis results of vWF level in the peripheral venous blood of the subjects

Both groups had significantly decreased vWF levels at 4 weeks after PCI compared with those before and during PCI (P< 0.05); the test group had a significantly lower vWF level than the control group at 4 weeks after PCI (P<0.05); the two groups had insignificantly different vWF levels before and during PCI (both P>0.05, **Table 6**).

Statistical analysis results of sICAM-1 level in the peripheral venous blood of the subjects

Both groups had significantly decreased sICAM-1 levels at 4 weeks after PCI compared with those before and during PCI (P<0.05); the test group had a significantly lower sICAM-1 level than the control group 4 weeks after PCI (P<0.05); the two groups had insignificantly different sICAM-1 levels before and during PCI (both P>0.05, **Table 7**).

Summary of adverse events

Totally 2 patients of the test group and 2 patients of the control group experienced adverse events: of the test group, one patient experienced dyspnea complicated by gingival bleeding and the other experienced simple gingival bleeding; of the control group, one patient experienced respiratory and circulatory failure and the other experienced acute cerebral infarction. The two groups had insignificantly different incidences of adverse events (P>0.05, **Table 8**).

Discussion

Inflammatory reaction greatly affects the efficacy of PCI. Celik et al. reported in their study that CRP could activate neutrophilic granulocyte and complement, cause capillary vessel injury, and then trigger no reflow phenomenon

Table 8. Summary of adverse events

	Test group (n=155)	Control group (n=194)	Statistical magnitude	P
Total cases of adverse events	3	2	Fisher	1.0000
Dyspnea	1	0		
Respiratory and circulatory failure	0	1		
Acute cerebral infarction	0	1		
Gingival bleeding	2	0		
Total case number of adverse events			Fisher	1.0000
Yes	2 (1.3%)	2 (1.0%)		
No	153 (98.7%)	192 (99.0%)		

Note: The total case number of adverse events indicates the case number of subjects experiencing adverse events; and when a subject experienced at least an adverse event, it was considered as "yes".

after PCI, or even causing spontaneous [12]. Many studies discover post-PCI endothelium dysfunction is closely related with inflammatory reaction. Blum et al. reported in their study that abnormal endothelium-dependent vasodilatation was related with inflammatory reaction [13]. They discovered that the CRP level in patients with blood-flow-mediated endothelium-dependent vasodilatation was higher than those with non-endothelium-dependent vasodilatation. Therefore, how to effectively down-regulate the inflammatory factor levels and improve endotheliocyte functions before and after PCI is a key to elevating the efficacy of PCI.

This study analyzed the medical data on 349 STEMI patients treated with ticagrelor or clopidogrel and analyzed the improving effects of the two drugs on inflammatory mediators and endotheliocyte functions.

The results of this study did not discover the difference in the expression levels of inflammatory mediators at the same time points (before PCI, during PCI, and 4 weeks after PCI) between the two groups, meaning this study did not discover the difference in effects of improving inflammatory factor levels between ticagrelor and clopidogrel. Intra-group comparison analysis results discovered that both ticagrelor and clopidogrel could effectively decrease intra-operative levels of CD40L and P selectin and maintain the CRP levels stable during and after PCI; at 4 weeks after PCI, CD40L and P selectin were increased compared with those during PCI, but the CD40L and P selectin levels were still decreased compared with that before PCIPCI. CD40L is a ligand of CD40, can adjust the inflammatory reaction of vascular endothelial cells [14]. Di Stefano et al. reported in their study that CD40L was an important marker suggestive of STEMI in patients with coronary syndrome [15]. Li et al. reported in their study that CD40L might promote the expression of pregnancy-related plasma protein A to result in the rupture of plaque and re-stenosis of coronary artery after PCI [16]. P selectin is a glucoprotein expressed on vascular endothelial cells, and has convergence effects during WBC penetrating into the injured sites [17]. Stellos et al. reported that increased expression of P selectin might promote the occlusive thrombosis in STEMI patients [18]. Tardif et al. reported in their study that pre-PCI use of P selectin antagonist could decrease myocardial damage [19]. Thus, ticagrelor and clopidogrel have good effects of down-regulating CD40L levels before and after PCI and maintain the P selectin and CRP levels stable, which has positive significance of improving the efficacy of PCI.

We also analyzed the endotheliocyte functions; NO, vWF, and sICAM-1 are all effective markers to evaluate endotheliocyte functions [20, 21]. As revealed by this study, both groups had significantly increased NO but decreased vWF, and sICAM-1 at 4 weeks after PCI compared with those before and during PCI, suggesting ticagrelor and clopidogrel had good effects of improving endotheliocyte functions after PCI; comparison at the same time points discovered that the test group had better effects of improving endotheliocyte functions than the control group; at 4 weeks after PCI, the test group had higher NO level and lower vWF and sICAM-1 levels than the control group; the differences in the three indexes during PCI between the two groups were statistically insignificant, and the differences before PCI were also statistically insignificant, suggesting both ticagrelor and clopidogrel can maintain the endotheliocyte

functions stable during PCI, but ticagrelor had better effects of recovering endotheliocyte functions than clopidogrel. Barbato et al. reported in their study that NO could effectively improve the endotheliocyte dysfunctions after PCI in STEMI patients [20]. Bundhoo et al. reported in their study that clopidogrel could effectively improve the metabolism of NO after PCI in the patients [21]. Siller-Matula et al. reported in their study that vWF might be related with the postoperative prognosis death in patients undergoing PCI [22].

Patti et al. reported in their study that decreasing sICAM-1 level could improve the myocardial damage after PCI in the patients [23]. Hence, ticagrelor and clopidogrel can maintain the endothelium functions stable during PCI and improve the recovery of endothelium functions after PCI in STEMI patients.

Seen from the statistical result of incidence of adverse events in all the patients in this study, both ticagrelor and clopidogrel have good safety profiles. Totally 2 patients of the test group and 2 patients of the control group experienced adverse events: of the test group, one patient experienced dyspnea complicated by gingival bleeding and the other experienced simple gingival bleeding; this may be dose-dependent, and the dosages of aspirin and ticagrelor will be adjusted in studies in the future; of the control group, one patient experienced respiratory and circulatory failure and the other experienced acute cerebral infarction; the reasons were still unknown, and might be related with the postoperative rupture of coronary atherosclerotic plaque activating blood coagulation system. Seen from the results of complications of the two groups, the test group had a significantly lower severity degree than the control group, but it is unable to statistically analyze the data because of too small sample size, and larger sample size is required to investigate it. Although ticagrelor and clopidogrel didn't increase or aggravate CRP, no effects of them in decreasing CRP were observed, which might be associated with the dose we used, and we will study it further.

To sum up, ticagrelor and clopidogrel can effectively decrease the inflammatory factor levels during PCI, stabilize intra-operative endotheliocyte functions, and down-regulate postoperative inflammatory reactions in STEMI patients, and ticagrelor has better effects of recovering the endotheliocyte functions after PCI than clopidogrel.

Disclosure of conflict of interest

None.

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