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Pre-PCI medication using clopidogrel and ticagrelor in the treatment of patients with acute myocardial infarction

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Abstract. – OBJECTIVE: This study aimed to compare preoperative treatment using clopidogrel and ticagrelor for patients with acute myocardial infarction (AMI) undergoing emergent percutaneous coronary intervention (PCI), and to investigate the efficacy and safety of these medications in the management of AMI.

PATIENTS AND METHODS: Between February 2013 and December 2014, 74 patients with AMI admitted for emergent PCI therapy were included in the study and randomly divided into two groups: study group and control group. Patients in the study group received different pre-PCI treatment with a loading dose of 180 mg ticagrelor, and those in the control group received treatments with a loading dose of 600 mg clopidogrel. After PCI procedure, all patients were orally administered 75 mg clopidogrel once a day for maintenance therapy, and patients were monitored for one week at the hospital and further followed up for one month Platelet aggregation rates (PAR) of each patient was measured before medication, at 30 min, 2h, 24h and one week after medication, respectively. PAR, thrombolysis in myocardial infarction (TIMI) flow, clinical outcomes and adverse reactions were compared between groups.

RESULTS: No significant differences were observed in PAR before treatment between groups ($p>0.05$), whereas PARs were significantly different after treatment between groups ($p<0.05$), with the efficacy of medications peaking at 2h after the treatment. In addition, PARs were significantly different between different time points after treatment ($p<0.05$). Evaluation of TIMI flow grade showed that in study group, 6 patients (16.22%) were grade 2 and 31 (83.78%) were grade 3 for the study group; for the control group, 11 patients (27.73%) were grade 2 and 26 (72.27%) were grade 3. No significant differences were observed in TIMI flow grades between different groups ($p>0.05$). No recurrence of the disease was observed, but one case (2.70%) of mucosal bleeding in the nasal cavity and four cases (10.81%) of vomiting were found in the study group. However, in the control group, four patients (10.81%) presented with recurrent disease, six patients (16.22%) experienced mucosal bleeding in the nasal cavity and 11 patients (29.73%) vomited. Significant differences were observed in the incidence of adverse events between different groups ($p<0.05$).

CONCLUSIONS: Compared with 600 mg clopidogrel, a loading dose of 180 mg ticagrelor could effectively inhibit platelet reactivity at the early stage of AMI, resulting in more favorable clinical outcomes and lower occurrence of adverse events and, thereby, can be used in clinical practice.

Key Words:
Ticagrelor, Clopidogrel, Acute myocardial infarction, Percutaneous coronary intervention.

Introduction

Acute myocardial infarction (AMI) is featured by insidious onset and high mortality. Currently, percutaneous coronary intervention (PCI) remains the mainstay of AMI treatment[1]. However, the main disadvantage of PCI procedure is the possibility of aggravating endothelial damage, which will further stimulate relevant intracellular components, exacerbating hypercoagulable state in patients and resulting in thrombosis. To this end, oral administration of clopidogrel and aspirin are required before receiving emergent PCI for patients with AMI to achieve antiplatelet effect. However, this combined medication could cause a series of unfavorable outcomes, including slow onset of drug effect, inability to rapid recovery of platelet function within a short peri-

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od of time after termination of drug intake and variability in the efficacy among different patients[2]. Ticagrelor is an active agent and a direct P2Y12 receptor inhibitor, which can directly interact with P2Y12 receptor without hepatic transformation[3]. Besides, both ticagrelor and its active metabolite are P2Y12 antagonists. Ticagrelor potently inhibits platelet activation and aggregation, and its action is not affected by CYP2C19 gene polymorphism. Therefore, ticagrelor is a prospective agent with extensive application in the treatment of patients of AMI[4]. It has only been employed in China for a short period of time. Therefore, 74 patients with AMI undergoing acute PCI treatment between February 2013 and December 2014 were included in the present study. Patients were provided with certain dose of ticagrelor or clopidogrel before PCI followed by clopidogrel treatment. The study is presented as follows.

Patients and Methods

Patients

Between February 2013 and December 2014, 74 patients with AMI hospitalized for PCI therapy were enrolled in the present study. Patients were randomly divided into two groups: study group and control group, with 37 in each group. Patients in the study group were treated with ticagrelor and those in the control group were treated with clopidogrel. A loading dose of 180 mg ticagrelor or 600 mg clopidogrel was administered in two groups of patients, respectively 1h before PCI. There were 21 male and 16 female patients with an age ranging from 52 to 66 years and a mean age of 59.5±4.63 years in the study group. There were 20 males and 17 females with an age ranging from 53 to 70 years and mean age of 60.2±4.23 years in the control group. All patients were confirmed with AMI by featured clinical manifestation and imaging findings. Inclusion criteria were as follows: (1) The presence of persistent chest pain lasting over 30 min; (2) electrocardiography alterations including presence of ST segment depression or elevation, T-wave inversion, or Q wave formation in at least two contiguous leads; (3) A positive troponin [5]. Patients with the following conditions were excluded from the study: (1) presence of coagulation disorders, liver and kidney dysfunction or requiring hemodialysis; (2) a major bleeding occurring within one month or having received a puncture leading to major bleeding; (3) Having received studied medications within one week prior to the present study or being allergic to these medications. No significant differences were observed between the two groups in terms of gender and age (p>0.05).

Methods

Both groups of patients were admitted for PCI treatment but received different pre-PCI medications, with ticagrelor for the study group and clopidogrel for the control group. In study group, patients were orally administered a loading dose of 180 mg ticagrelor combined with 300 mg aspirin. While clinical conditions of patients were monitored, based on which, an intravenous heparin of 2000-10000 IU and tirofiban (10 μg/kg) were given. Coronary angiography was performed in two three dimensional views to assess the details of infarction. PCI was initiated by insertion of a guiding catheter through a 6F radial artery sheath followed by advancing a percutaneous transluminal coronary angioplasty (PTCA) wire via the guiding catheter to reach coronary lesions. In case that thrombus aspiration was required, an aspiration catheter was inserted via the guide wire to the location of occlusion and negative pressure aspiration was performed, with an 10ml aspiration each time for 5-6 times until the shadow of thrombus disappeared on gauze. Finally, stent placement with or without balloon dilation was performed based on the conditions of occlusions.

Patients of the control group received pre-PCI oral treatment of 600 mg clopidogrel plus 300 mg chewable aspirin. The remaining perioperative treatment was the same as that for the study group.

At the completion of the procedure, all patients were orally administered with 75 mg clopidogrel, once a day, monitored for one week at the hospital and followed up for one month.

Determination of Platelet Aggregation Rate

Platelet aggregation rates (PAR) of each patient was measured using TEG5000 Thrombelastograph hemostatis analyzer system (Haemonetics Corporation, Braintree, MA, USA). Venous blood samples of patients were collected prior to the treatment, and at 30 min, 2h, 24h and 7d after taking medications. Blood samples were treated with 2.7 ml sodium citrate (3.18%) and centrifuged at 1000 r/min for 10 min at 28°C. A supernatant containing 0.3 ml plasma was collected

Table I. Comparison of PARs between groups (%, $\bar{x}$, ± SD).

Groups	Pre-medication	Post-medication			
		30 min	2h	1d	7d
Study group	87.1±3.61	80.4±6.34	63.2±4.32	58.7±4.38	62.5±8.75
Control group	86.9±4.21	65.3±5.43	42.1±3.65	46.2±5.22	51.2±8.63
t	0.219	11.003	22.694	11.158	5.593
p	0.827	0.000	0.000	0.000	0.000

for determination of adenosine diphosphate (ADP)-induced PAR using nephelometric method.

Outcome Measures

(1) PARs before and at different time points after treatment. (2) Thrombolysis in Myocardial Infarction (TIMI) blood flow according to the following grading scale: Grade 0 (no perfusion) referred to the absence of any antegrade flow beyond a coronary occlusion. Grade 1 (penetration without perfusion) referred to the faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed. Grade 2 (partial reperfusion) referred to delayed or sluggish antegrade flow with complete filling of the distal territory. Grade 3 (complete perfusion) referred to normal flow with complete filling of the distal coronary bed. (3) Adverse reactions at one month post-PCI, mainly including bleeding, gastrointestinal reactions and breathing difficulties.

Statistical Analysis

Statistical analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as mean ± standard deviation (± SD). Data between groups were analyzed using *t*-test. Qualitative data were expressed as number of cases (%) and difference between groups was analyzed using χ^2 test. $p<0.05$ was considered statistical significant.

Results

Comparison of PAR Between Groups

No significant differences were observed in PAR before treatment between groups ($p>0.05$), but significant differences in PAR were found after treatment between groups ($p<0.05$), with the greatest efficacy of the medications at 2h after treatment. In addition, PARs were significantly different between different time points after treatment ($p<0.05$) (Table I).

Comparison of Restoration of TIMI Flow Grade Between Groups

TIMI flow grade were evaluated during post-PCI follow-up. In the study group, 6 patients (16.22%) were grade 2 and 31 (83.78%) were grade 3. In the control group, 11 patients (27.73%) were grade 2 and 26 (72.27%) were grade 3. No significant differences were observed in TIMI flow grades between groups ($p>0.05$) (Table II).

Comparison of Prevalence of Adverse Reactions Between Groups

Prevalence of adverse events during the one-month follow-up was compared between groups. In the study group, no recurrence of AMI was observed, but there were one case (2.70%) of mucosal bleeding in the nasal cavity and four cases (10.81%) of vomiting. In the control group,

Table II. Comparison of TIMI flow restoration between groups (n, %).

Groups	Number of cases	TIMI flow restoration		
		2		3
Study group	37	6 (16.22)		31 (83.78)
Control group	37	11 (27.73)		26 (72.27)
χ^2			1.909	
p			0.167	

recurrence of the disease was observed in 4 patients (10.81%). Six patients (16.22%) experienced mucosal bleeding in the nasal cavity and 11 patients (29.73%) vomited. Significant differences were observed in the occurence of adverse events between groups ($p<0.05$) (Table III).

Discussion

Currently, emergent PCI therapy is the treatment of choice for the management of AMI[6-8]. Antiplatelet therapy is required before PCI procedure. Administration of clopidogrel combined with aspirin serves as a conventional antiplatelet therapy[9], as platelet aggregation (PR) is effectively inhibited 2h after treatment and the inhibition reaches up to 90% 6h after the treatment. However, emergent PCI operation should be performed within 2h of the onset of the disease[10-12]. In addition, 5%-40% patients were shown to have a partial response or no response to clopidogrel, which was defined as "clopidogrel resistance"[13]. Meanwhile, high occurence of gastrointestinal reactions can lower the efficacy of drug absorption and may lead to increased possibility of adverse reactions.

Ticagrelor, a cyclopentyl triazolopyrimidine, is an adenosine ADP receptor antagonist that selectively binds to P2Y12ADP receptor[14-16]. While it has a similar mechanism of action as clopidogrel, ticagrelor demonstrates significant advantages by reversibly binding to P2Y12 ADP receptor. As a result, platelet reactivity can be restored once drug action is terminated, platelet function is not affected, and thereby long-term medication will not cause increased risk of thrombosis. Furthermore, due to the fact that ticagrelor exerts direct effect without hepatic metabolism, it has a faster onset of action than clopidogrel. Therefore, a number of studies suggested that ticagrelor could be widely used in clinical management of cardiovascular diseases[17-19].

In the present study, PAR was measured before ticagrelor treatment, and at 30 min, 2h, 24h and 7d after the treatment. The results showed that PAR at 30 min and 2h after the treatment were significantly lower than that before treatment ($p<0.05$), whereas PAR at 1d and 7d after the treatment did not show significant differences. These results indicated that both clopidogrel and ticagrelor exerted platelet inhibition at the early stage of drug action and platelet inhibition effect of both drugs peaked at 2h after medication. At 24h after medication, ticagrelor was shown to be more effective than clopidogrel in terms of PA inhibition. Patients of the study group were switched to clopidogrel treatment as a maintenance therapy. No significant differences were observed in post-PCI TIMI flow between groups ($p>0.05$). Comparison of adverse events between groups demonstrated that no recurrence was observed, but one case (2.70%) of mucosal bleeding in the nasal cavity and four cases (10.81%) of vomiting in patients were found in the study group. In the control group, four patients (10.81%) presented with recurrent disease, six patients (16.22%) experienced mucosal bleeding in the nasal cavity and 11 patients (29.73%) vomited. Significant differences were observed in the prevalence of adverse events between groups ($p<0.05$). The underlying mechanism was probely due to the fact that clopidogrel could lead to higher incidence of vomiting and poor drug absorption, thereby resulting in longer wait time for surgery and increased surgical risk[20].

Conclusions

The pre-PCI administration of ticagrelor in patients of study group effectively inhibited PA at the early stage of medication, posed less risk of bleeding and resulted in fewer gastrointestinal reactions. This treatment could reduce surgical risk and complications, thereby improving the efficacy of treatment. The limitations of the present study include small sample size, non-unified measurement of PAR in China and relatively short follow-up time. To this end, further studies

Table III. Comparison of incidence of adverse reactions between groups (n, %).

Groups	Number of cases	Recurrence	Bleeding	Vomiting
Study group	37	0 (0.00)	1 (2.70)	4 (10.81)
Control group	37	4 (10.81)	6 (16.22)	11 (29.73)
χ^2		4.229	3.945	3.874
p		0.040	0.047	0.049

with a larger sample size or a longer period of time are required.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Saberi F, Adib-Hajbaghery M, Zohrehea J. Predictors of prehospital delay in patients with acute myocardial infarction in kashan city. Nurs Midwifery Stud 2014; 3: e24238.
2) Zeymer U, Mochmann HC, Mark B, Arntz HR, Thiele H, Diller F, Montalescot G, Zahn R. Double-blind, randomized, prospective comparison of loading doses of 600 mg clopidogrel versus 60 mg prasugrel in patients with acute ST-segment elevation myocardial infarction scheduled for primary percutaneous intervention: the ETAMI Trial (early Thienopyridine treatment to improve primary PCI in patients with Acute Myocardial Infarction). JACC Cardiovasc Interv 2015; 8: 147-154.
3) Lhermusier T, Lipinski MJ, Tantry US, Escarcega RO, Baker N, Bliden KP, Magalhaes MA, Ota H, Tian WJ, Pendyala L, Minha S, Chen F, Torguson R, Gurbel PA, Waksman R. Meta-analysis of direct and indirect comparison of ticagrelor and prasugrel effects on platelet reactivity. Am J Cardiol 2015; 115: 716-723.
4) Winter JL, Lindefjeld DS, Veas N, Veas N, Guarda E, Valdebenito M, Méndez M, Pérez O, Zuanic K, Mestas M, Martínez A. Angiographic and electrocardiographic parameters of myocardial reperfusion in angioplasty of patients with ST elevation acute myocardial infarction loaded with ticagrelor or clopidogrel (MICAMI-TICLO trial). Cardiovasc Revasc Med 2014; 15: 284-288.
5) Xu X, Bao H, Strait K, Spertus JA, Lichtman JH, D'Onofrio G, Spatz E, Bucholz EM, Geda M, Lorenze NP, Bueno H, Beltrame JF, Krumholz HM. Sex differences in perceived stress and early recovery in young and middle-aged patients with acute myocardial infarction. Circulation 2015; 131: 614-623.
6) Shemirani H, Tafti FD, Amirpour A. Comparison of no-reflow phenomenon after percutaneous coronary intervention for acute myocardial infarction between smokers and nonsmokers. J Res Med Sci 2014; 19: 1068-1073.
7) Njerve IU, Solheim S, Lunde K, Hoffmann P, Arnesen H, Seljeflot I. Fractalkine levels are elevated early after PCI-treated ST-elevation myocardial infarction; no influence of autologous bone marrow derived stem cell injection. Cytokine 2014; 69: 131-135.
8) Limalanathan S, Andersen GØ, Kløw NE, Abdelnoor M, Hoffmann P, Eritsland J. Effect of ischemic postconditioning on infarct size in patients with ST-elevation myocardial infarction treated by primary PCI results of the POSTEMI (POstconditioning in ST-Elevation Myocardial Infarction) randomized trial. J Am Heart Assoc 2014; 3: e000679.
9) Simsek C, Magro M, Patterson MS, Onuma Y, Ciampichetti I, van Weenen S, van Domburg RT, Serruys PW, Boersma E, van Geuns RJ. Magnetic navigation System assisted stenting of coronary bifurcation lesions. Euro Intervention 2011; 6: 970-976.
10) Peng Y, Fu X, Li W, Geng W, Xing K, Ru L, Sun J, Zhao Y. Effect of intracoronary anisodamine and diltiazem administration during primary percutaneous coronary intervention in acute myocardial infarction. Coron Artery Dis 2014; 25: 645-652.
11) Keeley EC, Mehran R, Brener SJ, Witzenbichler B, Guagliumi G, Dudek D, Kornowski R, Dressler O, Fahy M, Xu K, Grines CL, Stone GW. Impact of multiple complex plaques on short- and long-term clinical outcomes in patients presenting with ST-segment elevation myocardial infarction (from the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI] Trial). Am J Cardiol 2014; 113: 1621-1627.
12) Zhang D, Wang L, Du J, Wang H, Xu L, Li W, Ni Z, Xia K, Liu Y, Yang X. Effect of intracoronary tirofiban combined with nitroprusside injection through thrombus aspiration catheter during primary percutaneous coronary intervention on acute anterior myocardial infarction patients with heavy thrombosis burden. Zhonghua Xin Xue Guan Bing Za Zhi 2014; 42: 25-30.
13) Cresci S, Depta JP, Lenzini PA, Li AY, Lanfear DE, Province MA, Spertus JA, Bach RG.. Cytochrome p450 gene variants, race, and mortality among clopidogrel-treated patients after acute myocardial infarction. Circ Cardiovasc Genet 2014; 7: 277-286.
14) Mahaffey KW, Held C, Wojdyla DM, James SK, Katus HA, Husted S, Steg PG, Cannon CP, Becker RC, Storey RF, Khurmi NS, Nicolau JC, Yu CM, Ardissino D, Budaj A, Morais J, Montgomery D, Himmelmann A, Harrington RA, Wallentin L; PLATO Investigators. Ticagrelor effects on myocardial infarction and the impact of event adjudication in the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol 2014; 63:1493-1499.
15) Perl L, Zemer-Wassercug N, Rechavia E, Vaduganathan M, Orvin K, Weissler-Snir A, Lerman-Shivek H, Kornowski R, Lev EI. Comparison of platelet inhibition by prasugrel versus ticagrelor over time in patients with acute myocardial infarction. J Thromb Thrombolysis 2015; 39: 1-7.
16) Bonaca MP, Bhatt DL, Braunwald E, Cohen M, Steg PG, Storey RF, Held P, Jensen EC, Sabatine MS. Design and rationale for the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial. Am Heart J 2014; 167: 437-444.

18) Wallentin L, Becker RC, Cannon CP, Held C, Himmelmann A, Husted S, James SK, Katus HS, Mahaffey KW, Pieper KS, Storey RF, Steg PG, Harrington RA. Review of the accumulated PLATO documentation supports reliable and consistent superiority of ticagrelor over clopidogrel in patients with acute coronary syndrome: Commentary on: DiNicolantonio JJ, Tomek A. Inactivations, deletions, non-adjudications, and downgrades of clinical endpoints on ticagrelor: serious concerns over the reliability of the PLATO trial. Int J Cardiol 2014; 170: e59-62.

19) Montalescot G, Lassen JF, Hamm CW, Lapostolle F, Silvain J, ten Berg JM, Cantor WJ, Goodman SG, Licour M, Tsatsaris A, van't Hof AW. Ambulance or in-catheterization laboratory administration of ticagrelor for primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: rationale and design of the randomized, double-blind Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery (ATLANTIC) study. Am Heart J 2013; 165: 515-522.

20) Depta JP, Lenzini PA, Lanfear DE, Wang TY, Spertus JA, Bach RG, Cresci S. Clinical outcomes associated with proton pump inhibitor use among clopidogrel-treated patients within CYP2C19 genotype groups following acute myocardial infarction. Pharmacogenomics J 2015; 15: 20-25.