

Research Article

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Analysis of ticagrelor's cardio-protective effects on patients with ST-segment elevation acute coronary syndrome accompanied with diabetes

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Abstract: Background. To analyze the cardio-protective effects of ticagrelor in patients with acute coronary syndrome with S-T segment elevation.

Methods. The sample was 200 patients who had been diagnosed with acute coronary syndrome accompanied by diabetes Mellitus type II. Only patients having ST segment elevation before the treatment were included. Then, the subjects were further randomly divided into an observation group and a control group. The control group of 100 patients received clopidogrel; the observation group of 100 patients of ticagrelor. The serum creatine kinase CK-MB, functional cardiac indexes of left ventricular end diastolic diameter (LVDD), cardiac troponin I, ventricular ejection fraction, and relevant major adverse cardiovascular events (MACE) were compared between the two groups.

Results. One month after a percutaneous coronary intervention (PCI) the observation group showed better results against angina, stent thrombosis, and all-cause mortality compared with those of the control subjects. Six months after treatment, both groups suffered adverse reactions. The number of patients who suffered adverse reactions in respiratory tract in the observation group was higher than in the control group. The inhibition of platelet aggregation IPA of ticagrelor was found to be significantly higher than clopidogrel, having a significant p value.

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Conclusion. Ticagrelor can effectively protect myocardial function for patients with ST-segment elevation acute coronary syndrome accompanied by diabetes and can reduce the incidence of adverse reactions..

Keywords: clopidogrel, ticagrelor, acute coronary syndrome, adenosine-mediated anti-platelet activity

1 Introduction

Among all types of acute coronary syndromes (ACS), STEMI is considered to be the most common. Relevant review of literature reveals that diabetes mellitus (DM) can accelerate the development of ACS [1-2]. Statins and platelet antagonists have become the first-line medication guiding clinical treatment because of their distinct curative effect in treating ACS. Ticagrelor can act on P2Y₁₂ receptor selectively and exert an inhibitory effect. Moreover, it can inhibit the formation of blood clots and has a positive effect on reducing thrombus [2-5]. However, the research on the clinical effect of ticagrelor on ACS accompanied with DM remains insufficient. Therefore, we have conducted research to analyze ticagrelor's cardioprotective effects on patients with ST-segment elevation ACS accompanied by DM.

Most studies have concluded that ticagrelor inhibits adenosine uptake by equilibrative nucleoside transporter-1 (ENT-1) pathways, leading to a strong effect on the aggregation of platelets when compared with the clopidogrel. Adenosine has been considered a very important mediator of platelet inhibition. Some authors also suggested that the ticagrelor stimulated the cAMP, which further inhibits platelet aggregation; therefore, ticagrelor could a dual effect on inhibition of platelet aggregation as compared to clopidogrel.

Clopidogrel has been medication most frequently prescribed for myocardial revascularization for ACS patients,

but it does not have an inhibitory effect on adenosine cellular uptake. Most of the literature regarding the effect of ticagrelor on adenosine metabolism has been produced from the various in vitro studies which are conducted on animal model and taken the sample from the healthy subjects. Not a single study has been conducted in this regard in the ACS subjects that showed the effect of ticagrelor in comparison with clopidogrel on the cAMP pathways.

2 Aim and objectives

Comparative evaluation of cardio protective drugs clopidogrel versus ticagrelor in management of patients with ACS having S-T segment elevation.

3 Materials and methods

Ethical clearance was obtained from the institutional ethics board before starting the study. Written informed consent of the patients will be obtained. The total sample size included in the study was 200 patients who had been diagnosed with STEMI accompanied with DM. The patients were treated at the Department of Cardiology in our hospital from January 2011 to January 2015. Inclusion Criteria: The diagnosis and classification of STEMI are in accordance with the 2007 European Guidelines for the Management of ACS [5]. Those who met the following conditions and who have received PC treatment were included in the study group. First, the onset time of ischemic chest pain lasts for more than half an hour and the symptom is not relieved by taking nitroglycerin orally. Second, there were two or more adjacent limb lead or chest lead ST-segment elevations; the level of CK-MB and cTnI tend to rise and fluctuate and no coronary stent implantation has been conducted in the recent treatment period. DM diagnostic criteria conform to the DM related evaluation indexes by 2010 American Diabetes Association (ADA) [6].

Exclusion criteria were: patients having contraindication for anticoagulant drugs, patients of poor compliance, patients on ticagrelor drug therapy, having a history of cardiac and peripheral vascular disease, patients who had recently undergone coronary bypass surgery. ACS induced by treatment with percutaneous coronary intervention (PCI), patients having dysfunctional coagulation of the liver and kidney; patients suffering from acute inflammation, respiratory diseases, cancer, immune deficiency disease or digestive ulcer. The patients were randomly divided into the two groups, an observation group and a

control group. Percutaneous coronary intervention was conducted in each and every patient and convention medicine was given to the patients. Percutaneous coronary intervention (PCI), also known as coronary angioplasty, is a nonsurgical technique for treating obstructive coronary artery disease, including unstable angina, acute myocardial infarction (MI), and multivessel coronary artery disease (CAD) Patients in the control group received clopidogrel orally 300 mg per day; the dose was adjusted to 1/4 of the original after percutaneous coronary intervention. Patients in the observation group received ticagrelor orally 180 mg per day; the dose was adjusted to 1/2 of the original after percutaneous coronary intervention (PCI). The course of treatment was 6 months or longer for both two groups.

Observation Indexes: Serous CK-MB and cTnI of two groups was assessed before treatment, after 24 hours, and after 72 hours post-operatively. The above operations were handled by a single operator. Specific procedures were in accordance with the instruction, and internal quality was effectively controlled. Follow-up observation was conducted for six months to observe and evaluate the occurrence of major adverse cardiovascular events (MACE), including recurrent myocardial infarction, recurrent angina, and heart failure. Adverse reactions caused by medication, such as hemorrhage, contusion, rash, and gastrointestinal and respiratory adverse reactions, were also observed and evaluated.

3.1 Statistical methods

The statistical analysis was conducted using SPSS software version 19.0. Measurement data comparison among groups was checked by independent sample paired *t*, and enumeration data comparison among groups was checked by χ^2 . P value of less than 0.05 considered to be the significant values. P value of more than 0.05 considered to be the non significant value.

4 Results

4.1 Basic clinical data of patients in both the groups is listed in the Table 1

The composition of age and gender between two groups was of not statistically different ($P>0.05$) (Table 1).

Table 1: Basic clinical data of patients in both the groups

Items	the control group (n=100)	the observation group (100)	χ^2/t	P
Gender (male/female)	61/39	55/45	0.169	0.681
Age (year)	79.1±9.4	70.8±8.9	1.031	0.219
Hypertension [case]	26	29(38.8)	0.400	0.527
Hyperlipidemia[case]	29(38.8)	27(34.7)	0.176	0.675
Smoking history [case]	38(57.1)	36(53.1)	0.087	0.768
Fasting blood glucose (mmol/L)	8.3±0.4	8.4±0.6	0.984	0.365
Random blood glucose(mmol/L)	12.6±0.8	12.7±0.9	0.838	0.421
Duration of DM (year)	7.9±3.3	8.4±3.6	1.259	0.106

4.2 Comparison of CK-MB and cTnI between the groups

CK-MB and cTnI of observational and control group were compared before treatment; there were no statistical significance differences ($P>0.05$). After 24 hours of PCI, the serous CK-MB of patients in the observation group had improved statistically significant P value. ($t=2.08$, $P<0.05$). After 72 hours of PCI, the serous CK-MB and cTnI of the two groups tended to be normal and showed substantial improvement, and a non-statistically significant difference was found ($t=18.01$, $t=8.60$, $P>0.05$). The improvement in the observation group was more pronounced; the difference was statistically significant, with a P value less than 0.05 (Table 2).

One week after the PCI, the comparison of adenosine diphosphate (ADP), and cardiac function indexes of left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVDD) revealed that in both groups the clinical improvement of the patients can be observed at a statistically significant p value of <0.05 . 6 months after the PCI, indexes of ADP, LVEF, and LVDD of patients in both groups had improved, more significantly in the observation group compared with the control group; the differences were statistically significant ($P<0.05$) (Table 3).

4.3 Comparison of MACE Incidence after PCI between the groups

One month after the PCI, the observation group's results were better than those of the control group, with only rele-

vant major adverse cardiovascular events with no obvious difference in other aspects ($P>0.05$). See Table 4.

4.4 Comparison of Adverse Reactions Incidence between Groups after PCI

One month after PCI, patients in both groups showed improvement in hemorrhage, contusion, rash, and gastrointestinal adverse reactions. 6 months after treatment, patients of both groups still were suffering from adverse reactions. Meanwhile, the number of patients who suffered adverse reactions in the respiratory tract in the observation group was increased. Only one patient showed the same symptoms in the control group with a statistically significant p value. (Table 5).

4.5 Mortality rate after Kaplan-Meier analysis

After the Kaplan Meier analysis, this has become statistically very clear that the unadjusted 1 year rate of survival was much higher in observational group when comparison was done with the control group with 99 % vs 90 % with non significant p value (Table 6).

5 Discussion

Relevant data have indicated that the prevalence of diabetes mellitus (DM) keeps increasing in recent years and more than half of ACS patients suffer DM at the same time

Table 2: Comparison of CK-MB and cTnI between both the groups

Group	CK-MB(U/L)			cTnI(ng/ml)		
	Before treatment	24 h after PCI	72 h after PCI	Before treatment	24 h after PCI	72 h after PCI
control group	34.8±9.6	31.8±6.0	10.0±3.7 ^Δ	2.1±0.9	1.9±1.1	0.7±0.3 ^Δ
observation group	35.3±9.7	32.0±5.4 ^Δ	8.3±4.0 ^{ΔΔ}	1.9±1.1	1.7±1.1	0.5±0.3 ^{ΔΔ}
t	0.256	0.17	2.19	0.99	0.90	3.30
P	>0.05	>0.05	<0.05	>0.05	>0.05	<0.05

Note: Compared with levels before treatment, ^ΔP<0.05, ^{ΔΔ}P<0.01.

Table 3: Cardiac function indexes LVEF and LVDD comparison between both groups

Group	LVEF(%)			LVDD(mm)		
	Before treatment	One week after PCI	Six month after PCI	Before treatment	One week after PCI	Six month after PCI
control group	41.5±7.9	51.0±7.4 [#]	58.7±8.2 [#]	62.8±10.7	54.5±10.1 [#]	50.6±7.6 [#]
observation group	43.9±12.3	53.9±7.6 [#]	62.0±6.9 ^{*#}	64.0±11.1	57.7±8.9 [#]	46.8±7.1 ^{**}

* Compared with the control group P<0.05; [#]Compared with levels before treatment P<0.01

Table 4: Comparison of MACE Incidence after PCI between two groups [case%]

Group	Myocardial infarction		Angina		Heart failure		Stent thrombosis		All-cause mortality	
	One month	Six months	One month	Six months	One month	Six months	One month	Six months	One month	Six months
the control group	3(6.1)	6(12.2)	2(4.1)	6(12.2)	1(2.0)	2(4.1)	1(2.0)	4(8.2)	1(2.0)	5(10.2)
the observation group	2(4.1)	4(8.2)	1(2.0)	2(4.1)	1(2.0)	1(2.0)	1(2.0)	1(2.0)	1(2.0)	1(2.0)
χ ²	0.37	0.45	0.10	4.00	0.07	0.10	0.00	2.83	0.07	3.67
P	>0.05	>0.05	>0.05	<0.05	>0.05	>0.05	>0.05	<0.05	>0.05	<0.05

Table 5: Comparison of Adverse Reaction Incidence between two groups after PCI

Group	Hemorrhage		Contusion		Gastrointestinal symptoms		Dyspnea		Rash	
	One month	Six months	One month	Six months	One month	Six months	One month	Six months	One month	Six months
control group	2(4.1)	4(8.2)	1(2.0)	3(6.1)	1(2.0)	3(6.1)	0(0.0)	1(2.0)	0(0.0)	1(2.0)
observation group	2(4.1)	3(6.1)	1(2.0)	4(8.2)	1(2.0)	3(6.1)	2(4.1)	4(8.2)	0(0.0)	2(4.1)
χ ²	0.26	0.12	0.07	0.12	0.07	0.18	1.37	2.35	0.07	0.29
P	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	<0.05	<0.05	>0.05	>0.05

Table 6: Kaplan-Meier survival analysis for ticagrelor (*red*) vs clopidogrel (*black*) for 1 year of follow-up

Events at risk	1 week	1 month	6 months	12 months
the Control Group	0	1	5	10
the Observation Group	0	1	1	1

[7]. The exceeded blood glucose could be harmful to the relevant function of vascular endothelial cells to some extent which further causing the formation of atherosclerosis and unstable plaque, thus increasing the risk of death [8]. Therefore, timely early diagnosis and proposal of scientific and effective therapy are of great significance for patients with ACS and DM in clinical practice which can improve prognosis and exert a positive effect on improving the quality of life of the patients [8-9]. Compared with other P2Y₁₂ receptor antagonists, the antiplatelet activity of Ticagrelor does not need metabolic activation pathway. Instead, it can inhibit platelet aggregation by the induction of non-competitive antagonist ADP. In this study in patients of ACS and DM, authors have found that the incidence of thrombus formation, all causes of mortality and the stent, the result of these indexes of the patients who took Ticagrelor were much better than those who took Clopidogrel ($P < 0.05$).

In this research, the author compared the improvement of myocardial function, clinical outcome and induction of adverse reactions during the mediation process between the observational and control group in patients with STEMI and DM. The results showed that both drugs had a significant effect on inhibition of platelet aggregation and showed improved patient therapeutic outcome to some extent [10-12]. Antiplatelet drugs can effectively inhibit the platelet aggregation, reduce damages caused by thrombus of vascular endothelial cells & myocardial cells. Therefore, these drugs have clinical values in protecting blood vessels and myocardial. The focus of this research lies in the comparison of the ADP of patients who have received PCI. The result showed that ADP of both groups was improved in different extent post-operatively. However, the observational group was improved significantly more than the control group. The result of this study verified that Ticagrelor had advantages over Clopidogrel in inhibiting platelet aggregation and thrombus formation. The coronary blood supply and myocardial blood demand of ACS patients could not keep balanced for a long period, therefore, the contractility, systolic velocity, ejection velocity, the systolic and diastolic function of left ventricular, all suffered from different degrees of damage. In this study, two cardiac function indexes, LEVF and LVDD, were compared one week and 24 weeks after PCI respectively. The results showed that the LVEF of patients in both the groups increased, while LVDD reduced, suggesting that the left ventricular systolic and diastolic functions have been improved. The data analysis showed that the patients in the observational group improved significantly when comparison was done with the control group.. So, this study stressed that the Ticagrelor was

better in improving patients cardiac function than Clopidogrel. Researchers have shown that, CK-MB and cTnI had high sensitivity to the damage of myocardium [12].

In this study, all patients showed different degrees of improvement in above two indexes before treatment and after 24 hours of PCI. The two indexes of both groups still stayed high. 72 hours after PCI, all levels of related indexes returned to normal range and the indexes of the observation group were more reduced than that of the control group with significant p value. This result verified that Ticagrelor could effectively inhibit platelet aggregation, as well as reduces the incidence of thrombus, and it could protect the patients cardiovascular dysfunction [10]. In this research, in order to conduct further research on the midterm effect of Ticagrelor on patients with STEMI and DM, researchers conducted a 6-month tracing observation. The result showed that the reduction of MACE of patients in the observation group was more significant than that of the control group with statistically significant P value of less than 0.05. This result has verified again that Ticagrelor can reduce the incidence of thrombus by effectively inhibiting platelet aggregation and the efficacy is better than Clopidogrel. During the comparison of adverse reactions between patients of both the groups, who took different drugs, the author found that there was no obvious difference between two groups in the incidences of hemorrhage, contusion and gastrointestinal symptoms. But the incidence of respiratory tract adverse reactions of patients in the observation group who took Ticagrelor was higher than that of the control group. Relevant report has pointed out that as Ticagrelor has similar effect with adenosine triphosphate analogues and can stimulate bronchus, it can cause adverse reactions in the respiratory system. But the specific mechanism remains to be further verified [13-16].

The study done by Gennaro Sardella *et al* analyzed basically the Platelet reactivity unit (PRU; mean \pm SD) in patients with diabetes mellitus and ST-segment-elevation myocardial infarction and in those treated with insulin at baseline after ticagrelor (17 pts) and prasugrel (15 pts) loading dose [17]. Our study have concluded that the application effect of Ticagrelor can provide relevant data support during the treatment of patient with STEMI and DM. These findings provide clinical evidence for the adenosine and cAMP on the biological effect in patients with ACS. It will be sincerely appreciated if readers can select the essence of this study and put forward valuable suggestions. While the study done by Gennaro Sardella *et al* [17] admitted that they did not observe a different timing of the onset of action between prasugrel and ticagrelor in patients with diabetes mellitus treated with insulin or not

treated. The main limitation of the study is the focus on antiplatelet measures of efficacy with no ability to assess effects on clinical outcomes.

The study done by Deepak L. Bhatt et al [18] indirectly favors the conclusion of our study, but there are many technical differences in the data collection, sampling, and interpretation of the samples. We have analyzed the following parameters and drawn the conclusion and results on these parameters such as Comparison of CK-MB and cTnI between the groups, Comparison of MACE Incidence after PCI between the groups, Comparison of Adverse Reactions Incidence between Groups after PCI and Mortality rate after Kaplan-Meier analysis.

The study which had been by Deepak L. Bhatt et al have analyzed the results based on the following parameters such as ischemic event rates in patients with and without diabetes, efficacy in patients with versus without diabetes, efficacy in patients with treated diabetes and bleeding. Moreover, for the comparison of ticagrelor, we have taken the clopidogrel as the control drug for the analysis. They have taken the placebo for the comparison, so tectonically the study is been different with our study.

The study done by Dimitrios Alexopoulos et al [19] in 2015 have also analyzed that the patients with insulin-treated DM treated with prasugrel post PCI have higher PR, than patients without DM or non insulin-treated diabetic patients treated with this drug. Ticagrelor treated patients have overall lower PR than patients on prasugrel, independent of DM status or insulin treatment, however the study had been done to compare between the ticagrelor and prasugrel.

6 Conclusion

In summary, the application effect of Ticagrelor can provide relevant data support during the treatment of patient with STEMI and DM. These findings provide clinical evidence for the adenosine and cAMP on the biological effect in patients with ACS. It will be sincerely appreciated if readers can select the essence of this study and put forward valuable suggestions.

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