REPORT

Impact of drug combination of clopidogrel and pantoprazole In the prognosis of patients with transient ischemic attack

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Abstract: The study aimed to investigate the impact of clopidogrel combined with proton pump inhibitors (PPI) pantoprazole treatment on the prognosis of patients with transient ischemic attack (TIA). A total of 478 cases of TIA patients treated with clopidogrel were randomly assigned half to clopidogrel combined with pantoprazole treatment and the control groups (clopidogrel treatment alone) from January 2012 to January 20l4. The platelet aggregation before and after treatment and cerebrovascular events incidence within 90 days were compared and analyzed. Multivariate analysis was used to estimate the incidence of cerebrovascular events within 90 days. The platelet aggregation rate before treatment was 73.2±6.1% in the treatment group, 74.1±8.8% in the control group. The platelet aggregation rate after treatment was 38.1±10.7% in the treatment group, 36.8±9.7% in the control group. The platelet aggregation before and after treatments between the two groups had not significant difference (P>0.05). The incidence of cerebrovascular events within 90 days (11.7% in the treatment group, 9.6% in the control group) between the two groups had not significant difference (P>0.05). Multivariate analysis showed that the incidence of cerebrovascular events within 90 day was associated with hypertension (P=0.008), diabetes (P=0.000), hyperlipidemia (P=0.002) and ABCD2 score >3 points (P=0.000). Clopidogrel combined with pantoprazole treatment had no significant effect on the prognosis of TIA patients.

Keywords: Pantoprazole, clopidogrel, transient ischemic attack.

INTRODUCTION

Transient ischemic attack (TIA) is a class of common clinical ischemic cerebrovascular disease. Because of the higher risk of ischemic cerebrovascular disease, myocardial infarction and other vascular events in the early stage, TIA become one of the hot research spot for the secondary prevention of ischemic cerebrovascular disease. Finding effective treatments to reduce the incidence of vascular events after TIA has significant clinical and social significance. Antiplatelet was one of the most basic medication for TIA therapy. Clopidogrel is a class of thienopyridine derivative, which can effectively block the binding of platelet adenosine diphosphate and receptor after the body's metabolism by cytochrome P450 oxidase, thereby inhibiting platelet aggregation, and playing the role of preventing the occurrence of ischemic stroke in TIA patients. Clopidogrel is also drug currently recommended by domestic and abroad guidelines (Furie *et al*., 2011; Pan *et al*., 2012). Clopidogrel was preferred drug for medium or high-risk groups with ESSEN score more than three points in clinical (Diener *et al*., 2005). However, long-term clopidogrel treatment can easily lead to increased risk of upper gastrointestinal bleeding, which offset the benefits of reducing recurrent stroke to some extent. Therefore, the joint use of proton pump inhibitors (PPIs) was often performed to reduce the risk of bleeding in clinical (Abraham *et al*., 2010). Pantoprazole is widely used in clinical (Ferreiro *et al*., 2011). But recent studies have found that PPIs also required cytochrome P450 metabolism in the body, thereby reduced the effect of antiplatelet by clopidogrel. Past researches in coronary heart disease found that PPI and clopidogrel combination will affect the efficacy of antiplatelet (Ho *et al*., 2009), but there are different results (O'Donoghue *et al*., 2009; Siller-Matula *et al*., 2009), still more controversial about this aspect existed (Mehta *et al*., 2011; Depta and Bhatt, 2012; Scott *et al*., 2014). This study provides new evidence based medicine for clinicians through investigate the impact of clopidogrel combined with PPI pantoprazole treatment on the prognosis of TIA patients.

MATERIALS AND METHODS

Cases

500 cases patients with TIA consecutively admitted to neurology department of our hospital during January 2012 and January 20l4. This study was conducted according to the declaration of Helsinki and was conducted with approval from the Ethics Committee in Nanjing Medical University. Written informed consent was got from all participants.

Inclusion criteria: Meet the definition of the TIA in "secondary prevention of ischemic stroke or transient ischemic attack" of American Standards Association

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(ASA) in 2011; those treated with clopidogrel for more than 90 days after the onset. Case exclusion criteria: new-onset patients with cerebral infarction after admission by MRI; platelet count $<80\times10^9$ /L; coagulation dysfunction; patients with severe liver and kidney diseases; history of peptic ulcer bleeding; cancer patients and patients taking clopidogrel or PPIs within one month before the onset of the disease. These patients were randomly and equally divided into two groups: Treatment group and control group. The baseline data (age, sex, smoking history, coronary heart disease, hypertension, diabetes, previous history of cerebral infarction, blood lipids, fibrinogen and other biochemical markers) needed to be collected after being selection.

Treatment

Treatment group: clopidogrel was firstly given 300 mg, and followed by maintained dose of 75 mg/day. Simultaneously, 40mg/day of pantoprazole was given for more than 90 days. Control group: Clopidogrel was firstly given 300mg and followed by maintained dose of 75 mg/day for more than 90 days. The patients in the two groups were treated with lipid adjustment, glucose and stabilizing blood pressure treatments at the same time.

Observation indicators

Platelet aggregation: adenosine diphosphate was used as inducers, aggregometer was used to detect the platelet aggregation rates within 14 days before and after administration. The incidence of cerebrovascular events within 90 days (ischemic stroke, brain hemorrhage) was monitored by follow-up record.

STATISTICAL ANALYSIS

Data were statistically analyzed using SPSS16.0 statistical software. Enumeration data were analyzed using chi-square test, and measurement data were analyzed using *t* test. Enumeration data between groups were further performed multiple regression correlation analysis.

RESULTS

General information

A total of 500 cases of patients were selected, 342 were performed CYP2C19 genetic testing. Seventy-seven cases in the treatment group and 81 cases in control group had not genetically tested. Two ml of EDTA anticoagulated blood was obtained from patients in the second day after admission, then the blood was detected using the microarray hybridization method in radio-immunity center in our hospital. The kit was bought from Baio biological technology co., LTD in Shanghai. There were 636 and 681 loci were detected in the two allelic genes, and the result of both the two loci were heterozygosis mutation or any of them was homozygous mutation could imply poor metabolism. Of which, CYP2C19 genetic testing of 22 cases were slow metabolizers with the existence of clopidogrel resistance (Tsantes *et al*., 2013), so the treatment drug was replaced by Aspirin, the 22 cases were removed from the study subjects. 13 cases in the treatment group and 9 cases in control group. The treatment group had 237 cases, the control group had 241 cases. No significant difference of baseline data was detected between the two groups ($P>0.05$, table 1).

Platelet aggregation

In the treatment group, the platelet aggregation rate before treatment was 73.2±6.1%, while after treatment was 38.1 ±10.7%, significant difference was found between before and after treatment ($P<0.01$). The platelet aggregation rate of the control group before treatment was 74.1±8.8%, while that after treatment was 36.8±9.7%, a significant difference was detected ($P<0.01$). The difference of platelet aggregation rate for the two groups before treatment had not statistical difference ($P=0.195$), the differences of platelet aggregation rate after treatment was not statistically significant ($P=0.165$, table 2).

Cerebrovascular event rate

32 cases were lost during follow-up, most of them because the phone number was incorrect, or number changed, also some patients or their families did not coordinate. The lost follow-up proportion was 6.4 percent. Of which, the control group had 19 patients (59.4%), the treatment group had 13 cases (40.6%). One case in the control group died due to lung infection. Three cases of patients in the control group, 2 cases of patients in the treatment group quit the experiment because of gastrointestinal bleeding resulting in stopping clopidogrel combined with PPI drug treatment. 47 cases had cerebrovascular events within 90 days, the rate was 10.7% (47/440). 26 cases had cerebrovascular events within 90 days in the treatment group, the rate was 11.7% (26/222). 21 cases in the control group had cerebrovascular events within 90 days, the rate was 9.6% (21/218). The difference was not statistically significance ($P=0.57$). 233 TIA patients had ABCD2 score >3 points, a total of 35 cases occurred cerebrovascular events within 90 days, the rate was 15.0%. Of which, 20 cases of 113 cases in the treatment group had cerebrovascular events within 90 days, the rate was 17.7%; while 15 cases of 120 cases in the control group had cerebrovascular events within 90 days, the rate was 12.5%; the difference was not statistically significant ($P=0.35$).

Related factor analysis of cerebrovascular events

Univariate analysis was performed to gender, age, hypertension, diabetes, coronary heart disease, hyperlipidemia, fibrinogen, platelet aggregation rate when admission, PPI taking, ABCD2 score >3 points, respectively. It was found that the diabetic ($P<0.01$), hypertension ($P=0.045$), hyperlipidemia ($P=0.005$), ABCD2 score >3 points ($P<0.01$) between the two groups was significantly different (table 3). The statistically

Table 1: Baseline Data of treatment group and control group.

	Treatment group	Control group
Cases	237	241
Gender (Male/Female)	140/97	149/92
Mean age (years old)	69.5±10.2	68.1±8.8
Smoking	34 (14.3%)	42 (17.4%)
History of cerebral infarction	39 (16.5%)	35 (14.5%)
Hypertension	199 (84.0%)	207 (85.9%)
High cholesterol	39 (16.5%)	38 (15.8%)
Diabetes	61 (25.7%)	58 (24.1%)
Coronary heart disease	88 (37.1%)	85 (35.3%)
Fibrinogen	3.17±0.84	3.07±0.82

Table 2: Comparisons of the platelet aggregation rate between the two groups.

	Cases	Before treatment	After treatment
Treatment group	237	73.2±6.1%*	38.1±10.7%**
Control group	241	74.1±8.8%	36.8±9.7%

*Compared with the control group before treatment, *P*=0.195.
**Compared with the control group after treatment, *P*=0.165.

Table 3: Related factor univariate analysis of cerebrovascular events within 90 days.

	P value
Gender	0.273
Age	0.833
Hypertension	0.045
Diabetes	<0.001
Coronary heart disease	0.501
Hyperlipidemia	0.005
Fibrinogen	0.425
Admission platelet aggregation	0.795
Taking PPI	0.445
ABCD2 score >3	<0.001
Smoking	0.666

Table 4: Logistic regression analysis of related factors for 90 days cerebrovascular events.

Parameters	Regression coefficients	P	RR	95% CI of RR
Hypertension	6.994	0.008	0.130	0.28, 0.589
Diabetes	19.127	0.000	0.225	0.115, 0.439
Hyperlipidemia	9.827	0.002	0.307	0.147, 0.642
ABCD2	15.707	0.000	0.236	0.115, 0.482

significant univariate analysis of risk factors was substituted into multivariate logistic regression analysis (table 4). The results showed that cerebrovascular events within 90 days was associated with hypertension, diabetes, hyperlipidemia and ABCD2 score >3 points (*P*=0.008, 0.000, 0.002, 0.000).

DISCUSSION

Different mechanism effects of clopidogrel on different anti-platelet of PPI depended on different inhibition intensities of PPI to CYP450 isoenzyme. Inhibition intensity comparisons were: lansoprazole > omeprazole > esomeprazole > pantoprazole > rabeprazole (Li *et al*., 2004; Sibbing *et al*., 2009). Although rabeprazole had a unique way of non-enzymatic degradation, its degradation products rabeprazole sulfide had a strong ability to inhibit CYP2C19. In this experiment, treatment of clopidogrel for 14 days could significantly reduce platelet aggregation rate whether PPI was used or not. No significant difference of platelet aggregation rate was detected between the two groups neither before treatment nor after 14 days of treatment, suggesting that PPI had not obvious influence for anti-platelet effect of clopidogrel in a short

time. The perhaps reasons of that pantoprazole did not affect the antiplatelet therapy of clopidogrel may be due to: 1) low affinity of pantoprazole in CYP450 metabolic processes, especially lowest affinity to CYP2C19 isoenzyme, even pantoprazole may not inhibit the cytochrome P450 isoenzyme CYP2C19, so the inhibition of clopidogrel was the weakest, eventually it did not affect the antiplatelet effect of clopidogrel (Juurlink *et al*., 2009); 2) in addition to metabolism of CYP450 isoenzymes (phase I metabolism), pantoprazole had a unique sulfated (phase II) metabolic bypass. When there were other drugs in phase I metabolism, it can play the non-interactions roles with other drugs because it did not compete with metabolizing enzymes through the phase II metabolism (Li *et al*., 2004; Blume *et al*., 2006), which did not affect the anti-platelet effect of clopidogrel.

Wu *et al*. (2007) made a systematic review for the five major authoritative database included 51 studies about the risk of stroke in the early and late transient ischemic attack (TIA). In the random effect models, the risk of 2, 30 and 90 days stroke after TIA were 3.15%, 8.10% and 9.12%. The comparisons of research reports about stroke development between the positive and negative diagnosis, treatment indicated that the risk of stroke in early TIA was higher, the risk within 2, 30 or 90 days were 9.19%, 13.14% and 17.13%. At present, it was considered that factor with ABCD2 scores >3 was cerebral infarction risk factor, the risk of cerebral infarction within 7 days was significantly increased (Johnston *et al*., 2007; Chatzikonstantinou *et al*., 2013; Wolf *et al*., 2014). In this experiment, the cerebrovascular event rate within 90 days was 10.7%, the cerebrovascular event rate within 90 days of patients with ABCD2 >3 scores was 15.0%, which was basically consistent with the literature. Relevant literature believed that the recurrence of cerebral infarction was related with platelet aggregation (Htun *et al*., 2006; Zhou *et al*., 2013), but platelet aggregation rate in this experiment was data measured at the onset of TIA, which can-not represent the level of recurrence of cerebral infarction. In this experiment, the cerebral infarction recurrence rate of treatment group taking pantoprazole did not increased, multivariate analysis also prompted that the recurrence of cerebral infarction was irrelevant with taking pantoprazole. This PPI patients who must select to take pantoprazole may be reduce the impact on antiplatelet drug efficacy.

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CONFLICTS OF INTEREST

All authors declared that they had no conflicts of interest regarding this paper.

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