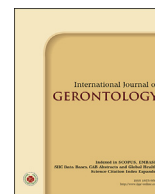


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Original Article

Thromboelastography evaluation of low response to clopidogrel in patients with acute coronary syndrome

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SUMMARY

Background: This study aims to measure platelet aggregation with thromboelastography (TEG) and observe low response to clopidogrel in patients with acute coronary syndrome (ACS) receiving dual antiplatelet therapy.

Methods: TEG was used to measure platelet aggregation in 167 hospitalized patients with ACS. Low response to clopidogrel and aspirin refer to adenosine diphosphate (ADP)-induced platelet aggregation $\geq 70\%$ and arachidonic acid (AA)-induced platelet aggregation $> 50\%$, respectively.

Results: Low response to clopidogrel was observed in 50 patients (29.9%) and 16 patients (9.6%) showed poor response to both clopidogrel and aspirin. The differences in gender, smoking history and total cholesterol (TC) on admission were statistically significant between patients with low and normal response to Clopidogrel ($P < .05$). The multivariate Logistic regression analysis showed that low response to aspirin and daily smoking 10 or less cigarettes were the risk factors of low response to Clopidogrel (the odds ratios were 1.047, $P = .000$ and 2.987, $P = .007$).

Conclusion: Partial ACS patients receiving standard antiplatelet therapy exhibited low response to clopidogrel, which was not affected by the age, combined therapy, or administration method of Clopidogrel, and the patients with low response to aspirin and daily smoking 10 or less cigarettes were more susceptible to low response to clopidogrel.

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1. Introduction

Platelet aggregation and activation play important roles in plaque rupture and thrombosis in patients with acute coronary syndrome (ACS).¹ Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor, and the subsequent binding of fibrinogen to glycoprotein (GP) IIb/IIIa due to conformational change in GPIIb/IIIa, thereby irreversibly inhibiting platelet aggregation.² CURE³ and PCI-CURE⁴ have confirmed that the combination of clopidogrel and aspirin is more effective than aspirin alone at reducing the incidence of early and

long-term serious cardiovascular events in patients with ACS undergoing percutaneous coronary intervention (PCI). Therefore, dual antiplatelet therapy with aspirin and clopidogrel has been regarded as important treatment for ACS.^{5,6} However, according to literature at home and abroad, 4–44% of patients who receive standard dual antiplatelet treatment occurred ischemic events during their follow-up, and this phenomenon is known as the antiplatelet drug low responsiveness (ADLR).^{7–11} Currently, “cardiovascular events occurred after standardized antiplatelet therapy” is the clinical diagnostic criterion of ADLR, but this standard is not clear and cannot predict the occurrence of ADLR in advance, which can make judgments only until ischemic events occur. So, detecting the platelet function can become an ideal indicator toward ADLR. In this study, we observed the incidence of low response to clopidogrel in patients with ACS receiving dual antiplatelet therapy through detecting platelet aggregation with thromboelastography (TEG), and explored the possible contributing factors.

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2. Materials and methods

2.1. Subjects

A total of 167 hospitalized patients with ACS, all Chinese yellow race, including 109 males and 58 females aged 43–88 years with mean age of (64.6 ± 9.9) years. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Capital Medical University. Written informed consent was obtained from all participants. Were selected in Department of Cardiology, Beijing Tiantan Hospital between June 2009 and June 2010. There were 121 cases of angina and 46 cases of recent myocardial infarction; 33 patients had history of old myocardial infarction and 35 patients underwent PCI or coronary artery bypass grafting (CABG), 95 patients orally administrated aspirin 100 mg/d for a long period, and 12 patients orally administrated clopidogrel 75 mg/d for a long period, among who 11 patients were also administrated DAPT. Coronary angiography was performed in 129 patients after admission. Exclusion criteria: (1) acute or chronic hematological disorders, platelets $<100 \times 10^9/L$ or $>450 \times 10^9/L$; (2) moderate or severe anemia, hemoglobin <90 g/L; (3) severe heart failure (NYHA class IV); (4) complicated by severe diseases, such as cancer, liver and kidney failure, serum creatinine >221 $\mu\text{mol/L}$; (5) oral administration of anticoagulants or other antiplatelet agents (warfarin or ticlopidine, etc); (6) allergy to aspirin or clopidogrel (Fig. 1).

The diagnosis of unstable angina met with the diagnosis and treatment guidelines of unstable angina and non-ST segment elevation myocardial infarction in China (2007).¹²

The diagnosis of acute myocardial infarction met with the diagnosis and treatment guidelines of acute myocardial infarction in China (2001).¹³

2.2. Treatment of the patients

Route of administration: If a patient, who was admitted for chest pain, chest tightness, or others symptoms such as dizziness or palpitations, and diagnosed as unstable angina when combined with other auxiliary examination results such as risk factors, medical history, symptoms, ECG, or cardiac enzymes, had been orally administrated long-term anti-platelet drugs, the maintenance dosage was retained (aspirin 100 mg/d and clopidogrel 75 mg/d). Otherwise, this patient (was not applied such therapy and needed the intervention as soon as possible) was administrated the loading dose (aspirin 300 mg and/or clopidogrel 300 mg), followed by the maintenance dosage. If the patient can be performed elective interventional therapy, maintenance dosage was then applied; patients diagnosed as acute myocardial infarction and had been orally administrated long-term anti-platelet drugs, should be continued the maintenance dosage, otherwise, the maintenance dosage was applied after the load dosage. **Drug Specifications:** Aspirin enteric-coated tablet, 100 mg/tablet, Bayer HealthCare; PLAVIX, 75 mg/tablet, Sanofi Pharmaceutical Co.

Data collection: The following data of subjects were recorded, including age, gender, smoking history, medication history and other risk factors for coronary artery disease such as hypertension or diabetes.

General Laboratory tests: On the second day after admission, blood samples were collected from elbow vein and delivered to clinical laboratory to perform blood routine test and detect Fibrinogen, glycated hemoglobin, serum lipid and glucose.

Platelet function detection: Elbow venous blood was drawn from patients receiving maintenance dose of clopidogrel after five consecutive days and patients receiving loading dose on the second day. Samples were stored in blood collection tubes with sodium citrate (2.7 ml blood) or heparin (3 ml blood) to measure platelet

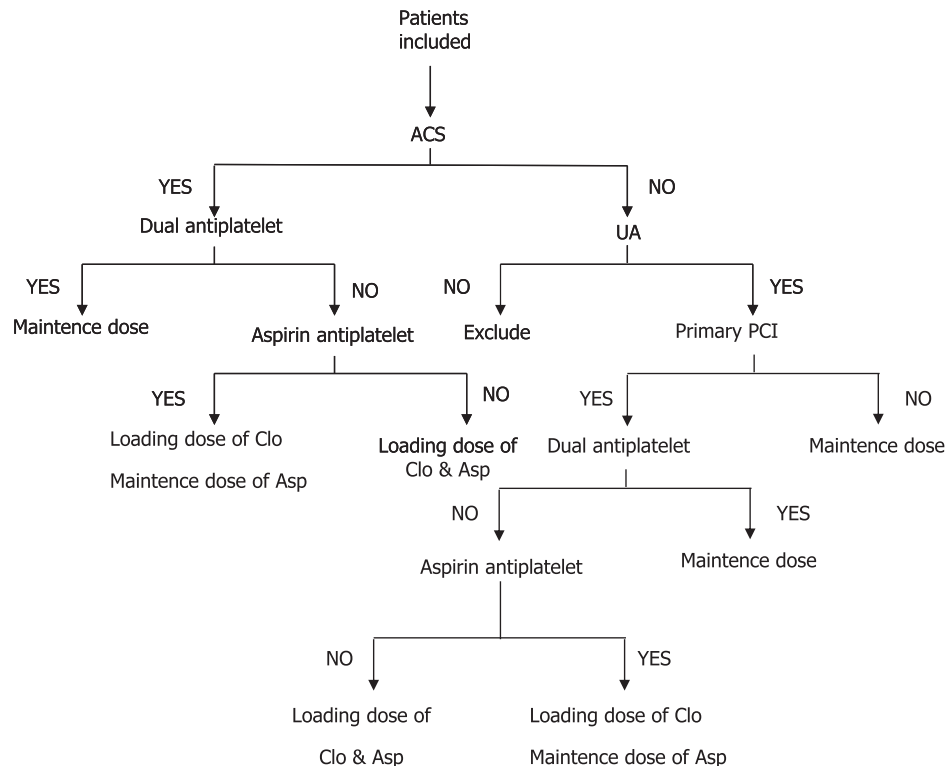


Fig. 1. A flowchart for the participants' enrollment in this study.

inhibition within 2 h. TEG analyzer (TEG 5000, Haemoscope Corporation, USA) was used to measure inhibition of ADP- or arachidonic acid (AA)-induced platelet aggregation by clopidogrel or aspirin. Platelet aggregation = 100%- platelet inhibition.

Evaluation criteria: Low response to clopidogrel and aspirin refer to ADP (2 μmol/L)-induced platelet aggregation ≥ 70% and AA (1 mmol/L)-induced platelet aggregation > 50%, respectively.^{14,15}

2.3. Statistical analysis

Data was analyzed with statistical software package SPSS13.0 (SPSS Inc., Chicago). The measurement data were expressed as mean ± SD, and after performed the Normality test, the independent-sample *t*-test (normally distributed data) or the rank sum test (non-normally distributed data) was used for the comparison between two groups; the count data were expressed as percentage (%), and the χ^2 test was used for the comparison between two groups. Relevant clinical risk factors or confounders for low response to Clopidogrel (dependent variable) in current work were analyzed by using multivariate Logistic regression analysis, with baseline age, gender, medical histories and potential medications use entered in models. All analysis was two-tailed, with *P* < .05 considered as statistically significant.

3. Results

3.1. Low response to clopidogrel

Of 167 subjects with ACS, low response to clopidogrel was observed in 50 patients (29.9%), including 23 patients elder than 65 years and 27 patients younger than 65 years with corresponding incidence of 28.8% and 31.0%. The difference in age was not statistically significant (*P* > .05). There existed no statistically significant difference in the reactivity of clopidogrel among the patients with previous myocardial infarction or revascularization (*P* > .05). The incidence of low response to clopidogrel was not distinctly different between maintenance-dose (35 cases, 31.3%) group and loading-dose group (15 cases, 27.3%, *P* > .05). There were 23 cases of AA-induced platelet aggregation > 50%, including 16 patients (9.6%) who exhibited poor response to both clopidogrel and aspirin. The incidence of aspirin resistance was significantly different between clopidogrel low-responders and normal-responders (*P* < .01). Of aspirin-resistant patients, 16 cases (69.6%) were observed with low response to clopidogrel, while 23.6% (34 cases) of aspirin-sensitive patients showed clopidogrel resistance.

3.2. Possible factors contributing to low clopidogrel response

Clinical data and laboratory test results of patients with low or normal response to clopidogrel were summarized in Tables 1 and 2. The differences in age, hypertension, diabetes, drug combination, fasting blood-glucose (FBG), glycated hemoglobin, platelet count and fibrinogen between two groups were not statistically significant (*P* > .05). Patients with low clopidogrel response showed increasing tendency of serum lipid profile and decreasing hemoglobin level; however, no significant difference was observed between clopidogrel low-responders and normal-responders (*P* > .05). The differences in gender, smoking history and total cholesterol (TC) were statistically significant between two groups (*P* < .05). Low clopidogrel response was more observed in patients who were female or had no or short smoking history (fewer smoking index), or higher TC.

Table 1 Comparison of clinical data between clopidogrel low-responders and normal-responders [case, (%)].

Group case	Low aspirin response	Female	Old people (≥65 years)	Smoking history	Recent MI	Previous MI	Previous PCI/CABG	Hypertension	Diabetes	Long-termoral administration of clopidogrel	Long-termoral administration of aspirin	Load doae of clopidogrel	Load doae of aspirin	Statins	β receptor blocker	Calcium channel blockers	ACEI/ARB
Low clopidogrel response 50	16 (32.0)	23 (46.0)	23 (46.0)	19 (38.0)	12 (24.0)	10 (20.0)	11 (22.0)	37 (74.0)	23 (46.0)	3 (6.0)	32 (64.0)	15 (30.0)	13 (26.0)	46 (92.0)	36 (72.0)	20 (40.0)	38 (76.0)
Normal clopidogrel response 117	7 (6.0)	35 (29.9)	57 (48.7)	69 (59.0)	34 (29.1)	23 (19.7)	24 (20.5)	89 (76.1)	51 (43.6)	9 (7.7)	63 (53.8)	40 (34.2)	40 (34.2)	107 (91.5)	96 (82.1)	41 (35.0)	86 (73.5)
χ^2 value	19.97	4.00	0.10	6.18	0.45	0.00	0.05	0.08	0.08	0.15	1.47	0.28	1.08	0.00	2.14	0.37	0.11
<i>P</i> value	.00	.04	.75	.01	.50	.96	.83	.78	.77	.70	.23	.60	.30	1.00	.14	.54	.74

Table 2
Comparison of clinical data and laboratory test results between clopidogrel low-responders and normal-responders ($\bar{x} \pm s$).

Group Case	Age (years)	Smoking history (years)	Smoking index (cigarette-years)	Hemoglobin (g/L)	Platelet count ($\times 10^9/L$)	Fibrinogen (g/L)	FBG (mmol/L)	Glycated hemoglobin (%)	Lipoprotein (mmol/L)	Triglyceride (mmol/L)	TC (mmol/L)	High density lipoprotein cholesterol (HDL-C) (mmol/L)	Low density lipoprotein cholesterol (LDL-C) (mmol/L)
Low clopidogrel response 50	65.3 \pm 9.7	12.5 \pm 17.9	195.9 \pm 339.7	130.4 \pm 15.0	217.1 \pm 51.5	3.53 \pm 1.12	6.15 \pm 2.11	6.8 \pm 1.6	23.6 \pm 13.9	1.68 \pm 0.78	4.59 \pm 1.17	1.08 \pm 0.25	2.81 \pm 0.93
Normal clopidogrel response 117	64.3 \pm 10.0	19.1 \pm 18.3	342.6 \pm 389.2	136.0 \pm 16.4	213.9 \pm 55.4	3.47 \pm 1.04	6.39 \pm 2.43	6.8 \pm 1.4	21.8 \pm 22.3	1.67 \pm 0.85	4.23 \pm 0.92	1.07 \pm 0.25	2.57 \pm 0.77
t/Z value	-0.58	-2.25	-2.64	1.84	-0.31	-0.30	-0.43	0.18	-1.36	-0.54	-2.07	-0.04	-1.69
P	.56	.03	0.01	.07	.76	.77	.67	.99	.17	.59	.04	.97	.09

3.3. Multivariate logistic regression analysis of low response to clopidogrel in ACS patients

A logistic regression analysis evaluated the impact of age, female, diabetes, history of myocardial infarction, hypertension, smoking status, total cholesterol, AA-induced platelet aggregation rate, and use of calcium antagonists, angiotensin-converting enzyme inhibitors, beta blockers, and statins on low post-treatment platelet aggregation; low response to aspirin and daily smoking 10 or less cigarettes were the risk factors of low response to Clopidogrel, the odds ratio was 1.047 (95%CI: 1.028–1.066), $p < .001$ and 2.987 (95%CI: 1.356–6.580), $p = .007$.

4. Discussion

The incidence of low clopidogrel response reported at home and abroad is 4–44%, which may varies with experimental method, instrument, reagent concentration, blood collection time and clinical status of patients.^{7–11} In this study, the incidence of low clopidogrel response was 29.9% in patients with ACS, corresponding to 28.8% and 31.0% in patients elder than 65 years and younger than 65 years, respectively. Poor response to clopidogrel was observed in 31.3% of patients receiving maintenance dose and 27.3% of patients receiving loading dose ($P > .05$). These results suggest that age and route of administration do not affect clopidogrel responsiveness. Previous history of myocardial infarction, revascularization, or long-term oral anti-platelet agent also did not affect the response to clopidogrel.

At present, the mechanism of low clopidogrel response remains unclear, which may involves platelet receptor gene polymorphisms,¹⁶ low aspirin response,¹⁷ poor insulin response,¹⁸ interaction with statins^{19–21} and individual variability, etc.

Lev et al.¹⁷ performed control study on low response to aspirin and clopidogrel in 150 patients undergoing PCI, and demonstrated that half of the aspirin-resistant patients were also resistant to clopidogrel and only 20% of aspirin-sensitive patients were resistant to clopidogrel, which was consistent with our finding that 69.6% of aspirin-resistant patients (16 cases) showed clopidogrel resistance and only 23.6% (34 cases) of aspirin-sensitive patients were resistant to clopidogrel. Lev speculated it might correlate with enhanced effect of ADP-mediated pathway in aspirin-resistant patients; overweight, female, diabetic or insulin-resistant patients were more observed with clopidogrel and aspirin resistance due to high expression of GPIIb/IIIa and P-selectin, thus to inhibit the effect of clopidogrel. We confirmed that more female patients exhibited low clopidogrel response but did not found the difference between patients with or without diabetes.

Moreover, the difference in lipid metabolism in our study was characterized by higher TC level in clopidogrel low-responders than that in normal-responders. High TC and LDL-C levels and low HDL-C level are identified as risk factors for coronary heart disease. However, we only observed the effect of TC on clopidogrel responsiveness, which might be associated with use of statins in the majority of subjects (91.6%).

Currently, clopidogrel is known to be metabolized to its active metabolite by cytochrome P450 enzymes, including CYP3A4. Therefore, most lipophilic statins that are metabolized by CYP3A4 may influence the antiplatelet effect of clopidogrel. However, we did not found the difference in use of statins between clopidogrel low-responders and normal-responders. It has been reported that atorvastatin and simvastatin, but not pravastatin, can dose-dependently reduce the antiplatelet effect of clopidogrel.¹⁹ In contrast, Kim et al. observed 233 patients undergoing PCI for stable angina pectoris for 12 weeks and showed no impact of atorvastatin and fluvastatin on the antiplatelet effect of clopidogrel.²⁰ A cohort

study that enrolled 13001 patients undergoing coronary stent implantation revealed the interaction between statins and clopidogrel, but the use of statins did not correlated with increased incidence of major adverse cardiac event (MACE) in patients taking clopidogrel postoperatively.²¹ In our research, 88.0% of clopidogrel low-responders and 87.2% of normal-responders received lipophilic statins, and no adverse effects of statins on clopidogrel activity were observed.

Individual variability in response to clopidogrel may be related to smoking. Clopidogrel is an inactive prodrug that requires hepatic bioactivation via several cytochrome P450 enzymes (including CYP3A4 and CYP1A2) to inhibit platelet aggregation.²² Polycyclic aromatic hydrocarbons in cigarette are potent inducers of CYP isoenzyme 1A2, thus enhance the inhibitory effect of clopidogrel on platelet aggregation in smokers.²³ Desai et al.²⁴ found that among the patients orally receiving clopidogrel, patients smoking more than 10 cigarettes had significantly decreased incidence of MACE compared with non-smokers. In our research, low response to clopidogrel was less observed in patients with longer smoking history (more smoking index), indicating that smoking can increase antiplatelet effect of clopidogrel, and daily smoking 10 or less cigarettes is also an important risk factor, consistent with Edem¹¹ and Bliden.²⁵

Study limitations: because this study used post-hoc analysis, it cannot rule out in advance the factors that may affect the hepatic metabolism of clopidogrel, such as proton pump inhibitors or caffeine, which may interfere with the results. In addition, studies have found that smoking-enhanced response to clopidogrel only exists in CteH patients carrying the YP450 isozyme 1A2 genotype, but this article did not test such related genes, so it can't carry out further analysis toward such phenomenon. Finally, the sample size included in this study was small, so it may result in the difference of some possible factors to be reduced. To solve these problems, large-sample strictly-controlled prospective studies should be needed in the future.

In conclusion, part of patients with ACS receiving standard dose of clopidogrel showed inadequate platelet inhibition, defined as low response to clopidogrel. Regardless of age, drug combination and the route of administration, and the patients with daily smoking 10 or less cigarettes or low response to aspirin will be prone to the occurrence of low response to Clopidogrel. Therefore, platelet function assay facilitates the identification of clopidogrel low-responders among these patients and the application of personalized antiplatelet therapy.

Conflicts of interest

All of the authors declare that they have no conflicts of interest regarding this paper.

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