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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

* Corresponding author. Department of Gerontology, Beijing Tiantan Hospital, Capital Medical University, No 6 Tiantanxili, Dongcheng District, Beijing, 100050, China. 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 vellow race, including 109 males and 58 females aged 43-88 vears 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 µmol/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.

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