High On-Treatment Platelet Reactivity to Adenosine Diphosphate Predicts Ischemic Events of Minor Stroke and Transient Ischemic Attack

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Background: This study aimed to evaluate the relationship between thromboelastography adenosine diphosphate maximum amplitude (TEG-ADP_{MA}) and recurrent ischemic events in patients with minor ischemic stroke or high-risk transient ischemic attack (TIA). *Methods:* A total of 265 patients received dual antiplatelet therapy were consecutively enrolled. High on-treatment platelet reactivity (HTPR) to ADP was assessed by TEG-ADP_{MA} and detected the CYP2C19 genotype; recurrent ischemic events were followed up for 90 days after onset. The difference of recurrent ischemic events was analyzed with or without HTPR to ADP by the Kaplan–Meier, and further to determine the difference of recurrent ischemic events in each group according to TEG-ADP_{MA}-based tertile distribution. *Results:* A total of 23 (8.6%) patients had recurrent ischemic events. TEG-ADP_{MA} greater than or equal to 48 mm had good predictive value. Whether these patients were divided into 2 groups or 3 groups, the HTPR to ADP group had higher risk of recurrent ischemic events than the normal on-treatment platelet reactivity to ADP group by the Kaplan–Meier (all, $P < .05$). The tertile distribution map showed that the results of recurrent ischemic events were statistically significant in the third tertile group compared with the other two groups (all, $P < .03$); also, the third tertile group had a higher rate of carriers of at least 1 CYP2C19 reduced-function allele than the other two groups ($P < .05$). *Conclusions:* In patients with minor ischemic stroke and high-risk TIA, the TEG-ADP_{MA} could predict recurrent ischemic events and has auxiliary effect on clinical decision-making. **Key Words:** Minor stroke—transient ischemic attack—thromboelastography—adenosine diphosphate—maximum amplitude—recurrent ischemic events.

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Introduction

Adenosine diphosphate (ADP) receptor antagonist-clopidogrel reduced the rate of recurrent ischemic events in patients with minor ischemic stroke and high-risk transient ischemic attack (TIA).[1,2] To these patients, a large number of ischemic events were still occurred continuously on the basis of regularly using clopidogrel was called high on-treatment platelet reactivity to adenosine diphosphate (HTPR to ADP).[3]

Previous studies have shown that HTPR to ADP measured by thromboelastography adenosine diphosphate maximum amplitude (TEG-ADP_{MA}) was associated with recurrent ischemic events in patients after percutaneous coronary intervention (PCI) stenting.[4] Patients were grouped according to the degree of platelet inhibition by clopidogrel, and showed that patients with lower levels of inhibition had higher risk of recurrent ischemic events.[5,6] But related research was less in patients with minor ischemic stroke or high-risk TIA.

In the Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events trial, patients received dual antiplatelet therapy for a total of 21 days, then continued clopidogrel alone from 22 to 90 days; the incidence of ischemic events was 8.1%.[7] In this study, we evaluated if TEG-ADP_{MA} could predict HTPR to ADP in patients with minor ischemic stroke or high-risk TIA prospectively, and could further predict the relationship between TEG-ADP_{MA} and recurrent ischemic events.

Methods

Study Design

In brief, this was a single-center, prospective study of patients with minor ischemic stroke or high-risk TIA who were continuously enrolled within 24 hours after the onset and received 300 mg of clopidogrel on day 1, followed by a dose of 75 mg per day on days 2-90, combined with aspirin at a dose of 100 mg per day on days 1-21. Patients accepted aspirin and clopidogrel at least 7 days before TEG testing. Recurrent ischemic events of patients were followed up for 90 days after the onset.

Patient Population

From January 2014 to September 2014, patients with minor ischemic stroke or high-risk TIA receiving inpatient treatment at the cerebral vascular disease center of Beijing Tiantan Hospital affiliated with Capital Medical University were continuously enrolled. A total of 278 patients met the following inclusion criteria: age 40 years or older, diagnosis of an acute minor ischemic stroke (National Institutes of Health Stroke Scale [NIHSS] ≤ 5),[8,9] or high-risk TIA ($ABCD^2 \geq 4$)[10,11]; patients with cardiac embolism were excluded according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[12] The exclusion criteria were as follows: hemorrhagic stroke; other central nervous system (CNS) conditions potentially causing the symptoms (vascular malformations, etc.); isolated symptoms without acute infarction by brain computed tomography (CT) or magnetic resonance imaging (MRI); a total NIHSS score greater than 5; clear indications for anticoagulant therapy; aspirin or clopidogrel contraindications; history of intracranial hemorrhage; history of long-term antiplatelet agents or nonsteroidal antiinflammatory drugs; heparin or oral anticoagulant therapy within 10 days before admission; gastrointestinal bleeding or major surgery within 3 months before admission; hospitalization within 3 months, planning possible revascularization (angioplasty); and minor ischemic stroke or high-risk TIA caused by angiography or surgery. No patients received thrombolytic therapy on admission.

Measurement of TEG-ADP_{MA}

Patients were enrolled within 24 hours after the onset and received 300 mg of clopidogrel on day 1, followed by a dose of 75 mg per day on days 2 through 90, combined with aspirin at a dose of 100 mg per day on days 1 through 21. At least 7 days of dual anti-platelet therapy, platelet aggregation inhibition reached steady state. Morning fasting venous blood samples were collected in blood collection tubes containing 3.2% sodium citrate and heparin potassium, and were tested within 2 hours.

The TEG 5000 Thrombelastograph (Haemonetics, Braintree, USA) measured TEG-ADP_{MA} value; qualitative and quantitative measurement of the physical properties of the clot was provided by an automatic analysis software of the TEG coagulation analyzer. TEG technology was briefly described as the oscillating cup comprising blood sample suspended into a fixed metal probe, and the metal probe and the oscillating cup were connected by a blood clot. The intensity of blood clots was determined by measuring the amplitude of rotation of the metal probe, and the 2 parts were proportional to the relationship. The maximum amplitude represented the maximum blood clot strength, which was expressed as TEG-ADP_{MA} parameter.[13,14]

HTPR to ADP was defined as TEG-ADP_{MA} greater than or equal to 48 mm after antiplatelet therapy according to manufacturer's instructions.[4] Patients with a maximum blood clot strength lower than this boundary value were considered to have normal on-treatment platelet reactivity to ADP (NTPR to ADP).

TEG Quality Control

Three sets of TEG 5000 Thrombelastograph Hemostasis Analyzer system were used to perform TEG testing. Before TEG testing, quality control testing was carried out for each Hemostasis Analyzer system; the Hemostasis Analyzer system could be applied to TEG testing only through the quality control testing.