Analysis of thrombelastogram-guided medication in patients with coronary heart disease after percutaneous coronary intervention

YINGBO LI1, HONGJIN CHANG2, LINA NI1, PENG XUE1, CAIXIA LI3, LIN YUAN1, HAILING CUI1 and CHENGYONG YU1

1Department of Clinical Laboratory, Weihai Central Hospital, Weihai, Shandong 264400; 2Department of Blood Transfusion, Affiliated Hospital of Jining Medical University, Jining, Shandong 272000; 3Department of Medical Administration, Weihai Central Hospital, Weihai, Shandong 264400, P.R. China

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Abstract. Effects of thrombelastogram-guided (TEG-guided) clopidogrel and aspirin on major adverse cardiovascular events (MACE) after percutaneous coronary intervention (PCI) were investigated. A retrospective analysis was performed on 203 patients undergoing PCI interventional therapy in the Cardiovascular Medicine of Weihai Central Hospital from February 2015 to September 2016. The patients were treated with clopidogrel and aspirin for anti-thrombus therapy. Among them, 104 patients who had TEG detection of anticoagulant effects for guiding medication were the experimental group, and 99 patients without TEG detection for guiding medication the control group. The coagulation function and the platelet inhibition rate of patients after medication were evaluated and compared between the two groups. The incidence of MACE and bleeding events of patients was counted during three months of follow-up. Patients in the experimental group had higher R (coagulation reaction time) value and K (blood clot formation time) value than those in the control group after treatment (P<0.05), and lower MA (maximum amplitude) value than those in the control group (P<0.05). Patients in the experimental group had higher postoperative platelet inhibition rate than those in the control group (P<0.05). Patients in the experimental group had higher incidence of MACE and bleeding events than those in the control group (P<0.05). Coronary heart disease (CHD) patients after PCI with the TEG-guided dose adjustment of clopidogrel have more satisfactory treatment effects than patients without the TEG guidance. TEG makes the treatment of patients more targeted and is worthy of promotion.

Introduction

Thrombelastogram (TEG), first applied in the 1940s, is used to detect the bleeding risk during surgery and evaluate the efficacy of blood product infusion, which is widely used in heart and other operations (1,2). TEG detection of solidification changes in blood is clinically effective for understanding patients’ platelet function, which is helpful for antiplatelet therapy (3). Coronary heart disease (CHD) is caused by myocardial ischemia, hypoxia or necrosis due to vascular cavity obstruction or stenosis as a result of atherosclerosis in coronary artery blood vessels. As the first choice for the treatment of CHD, percutaneous coronary intervention (PCI) is currently widely used in clinical practice (4,5). However, the mechanical rotation and expansion of blood vessels during the operation leads to the rupture of coronary plaques and the mass release of tissue factors, resulting in platelet aggregation and thrombosis. Therefore, regular anti-thrombus therapy should be implemented after operation to prevent thrombosis (6).

Currently, clopidogrel combined with aspirin for anti-platelet therapy is a clinically routine treatment regimen for preventing thrombosis after PCI. However, due to the different drug metabolism genotypes of clopidogrel and aspirin, as well as diabetes mellitus, calcification or acute coronary syndrome, routine treatment is not effective in preventing thrombosis in some patients. The risk of thrombosis will be increased if the drug adjustment could not be made in time (7,8). Therefore, it is of great clinical significance to effectively prevent thrombosis after PCI. There are studies reporting that clopidogrel with double maintenance dose (150 mg, 1 time/day) or double loading dose (600 mg) helps to better improve the coagulation status of patients after PCI, thereby reducing the incidence of major adverse cardiovascular events (MACE) (9,10). A study reported that TEG could be used to guide the clinical medication by evaluating platelet function in CHD patients after PCI, thereby promoting the recovery of patients. In that study, TEG was used to adjust the use of different drugs, but the efficacy of
TEG-guided medication and no TEG-guided medication was not compared (11).

Therefore, in this study, the antiplatelet effect of clopidogrel with maintenance dose with the individualized guidance was studied in order to investigate the application value of TEG in CHD patients after PCI.

**Materials and methods**

**General information.** A retrospective analysis was performed on 203 patients undergoing PCI interventional therapy in the Cardiovascular Medicine of Weihai Central Hospital (Weihai, China) from February 2015 to September 2016, including 121 males and 82 females, with an average age of 55.7±2.3 years and an average BMI of 25.3±3.1 kg/m². All patients were treated with clopidogrel and aspirin for anti-thrombus therapy. Among them, 104 patients with the TEG detection of anticoagulant effects for guiding medication were in experimental group, and 99 patients without the TEG detection for guiding medication in control group. There were no significant differences between the two groups in sex, age, preoperative coagulation function and other aspects (Table I).

This study was approved by the Ethics Committee of Weihai Central Hospital (Weihai, China). Patients who participated in this research had complete clinical data. The signed informed consents were obtained from the patients or the guardians.

**Inclusion and exclusion criteria.** Inclusion criteria were: Patients diagnosed with CHD. Exclusion criteria were: Patients
who had taken anti-thrombus drugs recently, with tumors or severe liver and kidney diseases, who are allergic to clopidogrel and aspirin, with the past history of peptic hemorrhage and cerebral hemorrhage, and patients who did not cooperate with the examination were excluded. All subjects signed an informed consent form and cooperated with medical staff to complete relevant medical treatment.

Experimental instruments and drugs. The TEG 5000 coagulation analyzer was purchased from Haemonetics Management Co., Ltd. (Shanghai, China). Clopidogrel (SFDA approval number: H31022653) was purchased from Shanghai Fudan Fuhua Pharmaceutical Co., Ltd. (Shanghai, China). Aspirin (SFDA approval number: H32024219) was purchased from Nanjing Pharmaceutical Factory Co., Ltd. (Nanjing, China).

Experimental methods. At 1 day before PCI, all patients were orally administered with routine 300 mg of load quantity aspirin and 300 mg of clopidogrel. During the operation, patients in both groups were treated with 3.8% sodium citrate anticoagulation. In the experimental group, the TEG detection was performed with the coagulation analyzer. After operation, patients in the control group were given routine 75 mg/day clopidogrel and 100 mg/day aspirin. Medication adjustment was performed on patients in the experimental group based on their TEG detection results. More than half of the patients in the experimental group had >50% platelet aggregation rate. When the platelet aggregation rate was >50%, aspirin was increased to 300 mg and clopidogrel was adjusted to double loading dose. The TEG detection was performed again on patients in the two groups on the next day after operation. Their coagulation function was evaluated, and their platelet inhibition rates were compared, with the platelet inhibition evaluation standard as previously described (12). All patients were followed up by telephone or clinic after discharge, in order to know if they had MACE (including recurrent angina, myocardial infarction, identified stent thrombosis and cardiac death) and bleeding events (including eye, nose, gingival, skin, brain, gastrointestinal and urinary system bleeding) within three months.

Statistical methods. SPSS19.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. The Chi-square test was used for enumeration data. Measurement data were expressed as mean ± SD, and tested by t-test. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of postoperative TEG detection of coagulation function of patients between two groups. Patients in the experimental group had higher R (coagulation reaction time) value and K (blood clot formation time) value than those in the control group after treatment (P<0.05), and lower MA (maximum amplitude) value than those in the control group (P<0.01) (Table II and Fig. 1).

Comparison of postoperative platelet inhibition and platelet count of patients between two groups.

In the experimental group, the ineffective rate and poor effect rate of the platelet inhibition were 0 and 4.81%, respectively, significantly lower than 7.07 and 15.15% in the control group (P<0.05). There was no significant difference in the general effect rate (P>0.05). The good effect rate of patients in the experimental group was 64.42%, significantly higher than 46.46% in the control group (P<0.05) (Tables III and IV, and Fig. 2).

Comparison of MACE occurrence of patients within three months between two groups. The numbers of patients with
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recurrent angina, myocardial infarction, stent thrombosis and cardiogenic death in the experimental group were 3, 2, 0, and 1, respectively. Whereas in the control group they were 9, 7, 5 and 4, respectively. The total incidence of MACE in the experimental group was 5.77%, significantly lower than 25.25% in the control group, with a statistically significant difference (P<0.05) (Table V and Fig. 3).

Comparison of occurrence of bleeding events of patients between two groups. There was 1 patient with gingival bleeding and 1 patient with skin bleeding in the experimental group; 1 patient with eye and nose bleeding, 4 patients with gingival bleeding, 4 patients with skin bleeding and 2 patients with gastrointestinal bleeding in the control group. The total incidence of bleeding was 19.2% in the experimental group, and 11.11% in the control group. There was a significant difference in the incidence of bleeding events between the two groups (P<0.05) (Table VI).

Discussion

CHD, a common disease in heart medicine, has a serious impact on patients’ health and quality of life (13). There is a study (14) showing that the pathogenic factors of CHD are complicated, for which age, hypertension and diabetes mellitus can be independent risk factors. It has been reported (15) that CHD patients usually have a high coagulation tendency, especially after PCI. Their coagulation status and platelet activity are affected. At present, clopidogrel combined with aspirin is a routine treatment after PCI. However, even if it is a conventional treatment, due to different degrees of tolerance to

Table IV. Platelet counts before and after surgery in two groups (x10^9/l).

| Time          | Experimental group (n=104) | Control group (n=99) | t value | P-value |
|---------------|----------------------------|----------------------|---------|---------|
| Before surgery| 213.62±12.37               | 214.25±13.01         | 0.354   | 0.754   |
| After surgery | 126.58±7.59                | 176.65±6.31          | 50.98   | <0.001  |

Table V. Comparison of MACE occurrence of patients within three months between two groups [n (%)].

| Factors                  | Experimental group (n=104) | Control group (n=99) | χ^2     | P-value |
|--------------------------|----------------------------|----------------------|---------|---------|
| Recurrent angina         | 3 (2.88)                   | 9 (9.09)             | -       | -       |
| Myocardial infarction    | 2 (1.92)                   | 7 (7.07)             | -       | -       |
| Stent thrombosis         | 0 (0.00)                   | 5 (5.05)             | -       | -       |
| Cardiogenic death        | 1 (0.96)                   | 4 (4.04)             | -       | -       |
| Total incidence          | 6 (5.77)                   | 25 (25.25)           | 14.88   | <0.001  |

Table VI. Comparison of occurrence of bleeding events of patients between two groups [n (%)].

| Bleeding site            | Experimental group (n=104) | Control group (n=99) | χ^2     | P-value |
|--------------------------|----------------------------|----------------------|---------|---------|
| Eye and nose             | 0                          | 1                    | -       | -       |
| Gingival                 | 1                          | 4                    | -       | -       |
| Skin                     | 1                          | 4                    | -       | -       |
| Brain                    | 0                          | 0                    | -       | -       |
| Gastrointestinal         | 0                          | 2                    | -       | -       |
| Urinary system           | 0                          | 0                    | -       | -       |
| Total incidence          | 2 (1.92)                   | 11 (11.11)           | 7.144   | <0.050  |
drugs and different efficacy in different patients, some patients may have MACE (16). TEG is an instrument that obtains blood coagulation patterns and related parameters. Through TEG analysis, the coagulation function and platelet changes of patients are reflected in a more comprehensive way (17). Currently, TEG is widely used in the detection of coagulation function in patients after PCI to improve the efficacy and reduce the risk of thrombosis and other complications by guiding the selection and dose adjustment of anticoagulant drugs (18). Previous studies (19,20) reported that TEG can evaluate the platelet function of patients after PCI, but there are few studies on whether to use TEG to guide patients in medication and the comparison of the efficacy between TEG-guided medication and no TEG-guided medication. Therefore, in this study, the antiplatelet effect of individual-guided clopidogrel with maintenance dose was studied to investigate the application value of TEG in CHD patients after PCI.

In this study, TEG was used to analyze and compare the coagulation function of patients between the two groups. The results showed that patients in the experimental group with TEG-guided medication adjustment had higher R value and K value than those in the control group, and lower MA value than those in the control group. The function of coagulation factor can be reflected by R value, K value and MA value. When R value and K value are increased and MA value is decreased, coagulation factor and platelet coagulation activity are both decreased (21). It is indicated that the overall coagulation function of patients was better in the experimental group than that in the control group. Then, the platelet inhibition and platelet count of patients were compared between the two groups. The results showed that the ineffective rate and poor effect rate of patients in the experimental group were 0% and 4.81%, respectively, significantly lower than the 7.07% and 15.15% in the control group. There was no significant difference in the general effect rate (P>0.05). The good effect rate of patients in the experimental group was 64.42%, significantly higher than the 46.46% in the control group. There was no significant difference in preoperative platelet count between the two groups, but the platelet count in the experimental group was significantly lower than that in the control group. It is suggested that the platelet inhibitory effect on patients is better in the experimental group than that in the control group, indicating that the TEG-guided adjustment of anticoagulant drugs is beneficial to improve patients' coagulation function and platelet inhibition.

In the study of Gurbel et al (22), it is reported that the TEG determination of the coagulation function and platelet inhibition after PCI is used to adjust the dosage of anticoagulant drugs in patients with low response to aspirin and clopidogrel. There is no stent thrombosis during the 2-year follow-up, but some patients in the control group have it. This confirms our conclusion. After that, the incidence of MACE and bleeding events of patients was compared between the two groups. The results showed that the total incidence of MACE in the experimental group was 5.77%, significantly lower than the 25.25% in the control group, with a statistically significant difference (P<0.05). The total incidence of bleeding was 1.92% in the experimental group, and 11.11% in the control group. There was a significant difference in the incidence of bleeding events between the two groups (P<0.05).

It is indicated that the individual-guided anticoagulant drugs after PCI through TEG detection is beneficial to reduce the incidence of MACE and bleeding events. There is a study confirming (23) that optimizing anticoagulant therapy after TEG detection can reduce the postoperative incidence and fatality rate of MACE as well as bleeding events in patients undergoing PCI.

In summary, CHD patients after PCI with the TEG-guided dose adjustment of clopidogrel have better treatment effects than patients without the TEG guidance. TEG makes the treatment of patients more targeted and is worthy of promotion. However, due to the small sample size and limited time in this study, the side effects of long-term high doses of antithrombotic drugs were not investigated. The safety of TEG detection after PCI remains to be studied.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YL wrote the manuscript. YL and HoC recorded and analyzed coagulation function index. LN and PX analyzed the general data of patients. CL, LY and HaC were responsible for treatment of patients. CY helped with statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Weihai Central Hospital (Weihai, China). Patients who participated in this research had complete clinical data. The signed informed consents were obtained from the patients or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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