The change in platelet count in patients with acute coronary syndrome 6 months after coronary stent implantation

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After coronary stent implantation, patients with acute coronary syndrome commonly take clopidogrel, and few patients develop severe thrombocytopenia related to clopidogrel. However, we found in our clinical practice that platelet counts of most patients decrease slightly after taking clopidogrel for 6 months. To address this discrepancy, we studied the change in platelet count after coronary stent implantation in patients with acute coronary syndrome. Ninety-five patients were selected for this study, and their prestent platelet counts were compared with those 6 months after stent implantation. All patients had low/intermediate-risk non-ST segment elevation myocardial infarction/unstable angina and underwent delayed coronary interventional treatment. No patient suffered from thrombocytopenia ($<100\times10^9$/l) during the 6-month observation period. Six months after stent implantation, platelet counts significantly decreased in the majority of patients (73/95, 76.9%) and increased only in the minority of patients (22/95, 23.1%). A multivariate analysis showed that the change in platelet count was positively correlated with the change in leukocyte and fibrinogen value, and negatively correlated with number of stents. The platelet count decreased in the majority of patients after stent implantation, which may be caused by the removal of stress factors or stent-related platelet consumption. Clopidogrel may partly prevent stent-related platelet consumption. *Blood Coagul Fibrinolysis* 26:661–664

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Introduction

Acute coronary syndrome includes ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) and unstable angina. Early or delayed percutaneous coronary stent implantation can significantly improve outcomes [1]. After stent implantation, clopidogrel and aspirin are recommended for at least 1 year to prevent stent thrombosis; however, a minority of patients develop severe thrombocytopenia [2].

There are two known mechanisms for clopidogrel-induced thrombocytopenia. One is thrombotic thrombocytopenic purpura (TTP). The incidence of clopidogrel-induced TTP ranges from one out of 8500 to one out of 26 000 [3]. From 1998 to 2011, 197 cases of clopidogrel-related TTP were reported to the U.S. Foods and Drugs Administartion (FDA), and most patients recovered after withdrawal of clopidogrel and treatment with plasmapheresis therapy [3]. A second mechanism is immune thrombocytopenia (ITP), due to clopidogrel-related platelet autoreactive antibodies. Clopidogrel-induced ITP occurs at a lower incidence, and the thrombocytopenia resolves by withdrawal of clopidogrel and administration of immunoglobulin and steroids [4,5]. In our clinical practice, however, we have found that most patients with coronary stent implantation develop a mild decrease in their platelet count when assessed 6 months after taking clopidogrel. The mechanisms described above cannot completely explain this phenomenon because these two mechanisms rarely occur and typically cause more severe thrombocytopenia.

In order to address this discrepancy, we studied the change in platelet count after coronary stent implantation in intermediate/low-risk patients with acute coronary syndrome in relation to clopidogrel.

Materials and methods

Patients

Consecutive patients admitted with low/intermediate NSTEMI/UA were enrolled in this study on the basis of the following inclusion and exclusion criteria. Eligibility criteria included ischemic symptoms lasting more than 10 min within 24 h of presentation, combined with high-risk features such as ischemic ST-segment ECG changes (ST depression $\geq$0.5 mm, transient ST elevation of 0.5–1.0 mm lasting $\geq$10 min) and/or positive cardiac biomarkers (troponin I or T and/or creatine kinase-myocardial-brain isoenzyme higher than the upper limit of normal) within 24 h of hospital admission. The low or intermediate risk is defined as less than 140 by the Grace risk score at admission [1]. Patients with the following diseases were excluded: STEMI and high-risk NSTEMI/

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UA (Grace risk score >140), haematological diseases (such as myelodysplastic syndrome, megaloblastic anaemia, aplastic anaemia, paroxysmal nocturnal haemoglobinuria), platelet count less than 100×10^9/l before stent implantation, splenomegaly, autoimmune diseases and infections (such as pneumonia). The study was approved by our institutional ethics committee, and either written or oral informed consent was obtained from all patients.

Sampling and treatments in hospital

Blood samples were obtained from patients on hospital admission for tests including the complete blood count (CBC), liver and kidney function, coagulation profile, folic acid and B12 levels. Thrombocytopenia was defined as platelet count less than 100×10^9/l. To exclude pseudothrombocytopenia, peripheral blood smears were evaluated for the presence of platelet aggregates. All patients received aspirin 100 mg orally (p.o.) daily, clopidogrel 75 mg p.o. daily, nadroparin calcium 4100 IU subcutaneously daily and a lipid-lowering medication. Patients were also treated for comorbidities such as hypertension, diabetes mellitus, peripheral vascular disease and congestive heart failure. Patients underwent coronary angiography and coronary stent implantation 72–96 h after the treatment described above. After stent implantation, patients were treated with clopidogrel 75 mg p.o. daily and aspirin 100 mg p.o. daily for 1 year.

Follow-up

During follow-up, it was recommended that patients stop taking clopidogrel if he or she had bleeding or thrombocytopenia ($<100 \times 10^9$/l). Six months after coronary stent implantation, blood samples were obtained from patients for the following tests: CBC, peripheral blood smear, liver and kidney function, coagulation profile, folic acid and B12 levels. Patients also underwent coronary angiography to observe whether there was stent thrombosis.

Statistical analysis

According to platelet count at admission, patients were divided into platelet less than 200×10^9/l group and platelet at least 200×10^9/l group. On the basis of the change in platelet count (drop from prestent to 6 months after stent implantation), patients were then further divided into prespecified decreased and increased groups. The decreased group was further subdivided into mild ($\leq 19 \times 10^9$/l), moderate (20 to 49×10^9/l) or major ($50–200 \times 10^9$/l) decrease group, and increase group into mild ($\leq 19 \times 10^9$/l), moderate ($20–49 \times 10^9$/l) or major ($20–200 \times 10^9$/l) increase group. Firstly, the CBC, liver and kidney function, and coagulation profile were compared on admission and 6 months after stent implantation. Continuous variables are presented as medians with standard deviation; categorical variables are expressed as percentages. Continuous variables following a Gaussian distribution were compared with the paired *t*-test, while those not meeting the Gaussian distribution were compared with the Wilcoxon rank sum test. Secondly, multivariate analysis was used to identify factors that were associated with changes in platelet count. Multivariate analysis was performed using multiple regression analysis. The dependent variable is the change in platelet count (change from present to 6 months after stent implantation); covariates entered into the model included baseline characteristics (age, sex, diabetes, hypertension), invasive procedures (the number of stents) and presenting features that included fibrinogen, activated partial thromboplastin time (aPTT), prothrombin time (PT), leukocyte count, platelet count, alanine aminotransferase, aspartate aminotransferase, albumin, immunoglobulin, creatinine and blood urea nitrogen. Other covariates included the change in leukocyte, fibrinogen, aPTT and PT, all of which were defined as the change from prestent to 6 months after stent implantation. A value of P less than 0.05 was considered statistically significant for all tests. All analyses were performed with SPSS software version 13 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 95 patients with low/intermediate-risk NSTEMI/unstable angina were enrolled in this study on the basis of the inclusion and exclusion above from May 2010 to February 2013. Patient characteristics are summarized in Table 1. No patient had bleeding or thrombocytopenia during 6 months, so no patient stopped taking clopidogrel. There were no documented cases of TTP or ITP in this patient cohort. All patients underwent coronary angiography and no one developed stent thrombosis. Change in platelet count 6 months after stenting compared with prestent, platelet counts decreased in the majority of patients (76.9%) 6 months poststenting with a major decrease in 23.2% of cases, a moderate decrease in 24.2% of cases and a mild decrease in 29.5% of cases. Notably, the platelet counts 6 months after stenting were all above 100×10^9/l. No platelet aggregates were found on peripheral blood smears of all patients, excluding pseudothrombocytopenia. Platelet counts increased in only 23.1% cases (composed of a moderate increase in 12.6% of cases and a mild increase of 10.5% of cases) (Tables 2 and 3).

Table 1 Patients' characteristics

Variable	
No. of patients	95
Age (years)	56 (36–78)
Male sex, %	83.2
Diabetes mellitus, %	24.2
Hypertension, %	54.7
Stent numbers, %	
1	29.5
2	29.5
3	24.2
4	16.8

Table 2 The change in platelet count and other tests before and after stenting

Variable	Prestenting	Six months after stenting	*P*
Plt ($x10^9$/l)	221.36 ± 64.90	195.28 ± 53.64	<0.001
Leu ($x10^9$/l)	7.11 ± 2.08	6.32 ± 1.49	<0.001
PT (s)	11.31 ± 0.80	10.95 ± 0.80	<0.001
aPTT (s)	33.93 ± 10.66	31.68 ± 3.81	0.002
Fg (mg/dl)	323.12 ± 107.49	282.00 ± 67.83	<0.001
ALT (U/l)	42.29 ± 49.41	24.14 ± 10.88	<0.001
AST (U/l)	35.29 ± 41.28	22.08 ± 6.676	0.003

ALT, alanine aminotransferase; aPTT, partial thromboplastin time; AST, aspartate aminotransferase; Fg, fibrinogen; Leu, leukocyte; Plt, platelet; PT, prothrombin time.

Change in other tests 6 months after stenting

Compared with prestent, the leukocyte count, alanine aminotransferase, aspartate aminotransferase, aPTT and PT significantly decreased 6 months after stent implantation (Table 2). Leucocyte counts 6 months after stent implantation were all above 4×10^9/l. Other tests results such as haemoglobin, immunoglobulin, albumin, folic acid and B12 levels were not statistically different.

Prestent leukocyte count in the platelet more than 200×10^9/l group was significantly higher than that in platelet less than 200×10^9/l group (7.87 ± 2.25 versus $6.23 \pm 1.0 \times 10^9$/l, $P < 0.001$), whereas there were no significant differences between two groups in prestent fibrin, alanine aminotransferase, aspartate aminotransferase or the rate of comorbidities such as hypertension and diabetes.

Factors affecting change in platelet count

Multivariate analysis showed that the change in platelet count was positively correlated with the change in leukocyte and fibrinogen, and negatively with number of stents (Table 4).

Discussion

This study showed that platelet counts declined in the majority of patients (76.9%) from prestent to 6 months after stent implantation. However, the platelet counts of all patients remained above 100×10^9/l, and no patient stopped antiplatelet therapy because of bleeding or thrombocytopenia. Platelet count decline is common in the patients with coronary stent implantation.

Table 3 Change in platelet count

	($n = 95$) %
Major decrease ($50-200 \times 10^9$/l)	23.2
Moderate decrease ($20-49 \times 10^9$/l)	24.2
Mild decrease ($\leq 19 \times 10^9$/l)	29.5
Mild increase ($\leq 19 \times 10^9$/l)	10.5
Moderate increase ($20-49 \times 10^9$/l)	12.6
Major increase ($50-200 \times 10^9$/l)	0

Change in platelet count was defined as platelet count change from prestent to 6 months after stenting.

Table 4 Multivariate regression analysis for risk factors of change in platelet count

	Beta	*P*
Change in leukocyte count	0.407	<0.001
Change in fibrinogen value	0.260	0.005
Stent number	−0.192	0.032

Change in platelet count was defined as platelet count change from prestent to 6 months after stenting. Change in leukocyte count was defined as leucocyte count change from prestent to 6 months after stenting. Change in fibrinogen value was defined as fibrinogen value change from prestent to 6 months after stenting.

Decline in platelet counts can be due to decreased platelet production, splenic sequestration, accelerated platelet destruction or consumption. In this study, platelet, leukocyte and erythrocyte counts are within the normal range 6 months after stent implantation. Patients were excluded if they had prior haematological disorders, and CBC values were within normal range after stent implantation, excluding a platelet production problem. There were no medications that affected bone marrow suppression and patients had normal VB12 and folate levels. All patients had normal liver function and patients with splenomegaly and autoimmune disease were excluded, so increased sequestration and destruction are unlikely causes.

A multivariate analysis showed that a decrease in platelet count was significantly and positively related to a decrease in leukocyte count. Prestent leukocyte values were significantly higher in the patients who had platelet counts at least 200×10^9, compared with patients with platelet counts less than 200×10^9/l. Because an increase in leukocyte and platelet counts is often caused by stress such as myocardial necrosis or inflammation and pain in patients with acute coronary syndrome [6,7], we hypothesized that leukocyte and platelet count declined 6 months after stent implantation when stress factors disappeared.

We chose low/intermediate-risk NSTEMI/unstable angina patients for this study only, and the limitations of the study are that we do not have preadmission 'baseline', or more severe patients (STEMI) to compare the effects of acute stress response on platelet count.

The multivariate analysis showed that a change in platelet counts was significantly and positively related to a change in fibrinogen values. Namely, as fibrinogen values decreased, platelet counts also declined. Fibrinogen is an acute phase reactant and will increase with stress such as inflammation. We hypothesized that fibrinogen and platelet count declined 6 months after stent implantation when stress factors disappeared. Considering the finding that aPTT and PT were significantly shortened 6 months after stent implantation, it was possible that there was also a hypercoagulability that consumed fibrinogen and platelets and led to their decrease. Because factor VIII was not tested in this experiment, it is not clear whether a shortened aPTT was due to the increase of factor VIII.

For patients with stent implantation, it is the stent that injures endothelium and leads to hypercoagulability. Theoretically, the more stents a patient had, the more serious the damage to the endothelium would be, and the more obviously the platelet count would decrease. However, the multivariate analysis showed that change in platelet count was significantly and negatively correlated with the number of stents placed. That is, the more stents a patient had, the less decline the platelet count would be. The use of clopidogrel seems to explain this difference.

Stent implantation might impose damage to endothelium, which leads to activation and consumption of platelets. Clopidogrel competitively binds the P2Y12 ADP receptor [8], inhibits platelet activation and might reduce platelet consumption. Furthermore, more damaged endothelial cells may produce more interleukin-6 (IL-6) that contributes to thrombopoiesis [9,10]. The combination of clopidogrel and IL-6 may account for the smaller decline of platelet count in the patients with more stents.

In conclusion, platelet count decreased in the majority of patients with acute coronary syndrome 6 months after stent implantation. The reasons may include removal of stress factors and accelerated platelet consumption caused by stent-related hypercoagulability. Stent-related platelet consumption may be prevented partly by clopidogrel. This observation warrants further investigation.

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Conflicts of interest

There are no conflicts of interest.

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