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Preoperative platelet function predicts perioperative bleeding complications in ticagrelor-treated cardiac surgery patients: a prospective observational study

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Abstract

Background: Treatment with $P2Y_{12}$ receptor antagonists increases the risk for perioperative bleeding, but there is individual variation in the antiplatelet effect and time to offset of this effect. We investigated whether preoperative platelet function predicts the risk of bleeding complications in ticagrelor-treated cardiac surgery patients.

Methods: Ninety patients with ticagrelor treatment within <5 days of surgery were included in a prospective observational study. Preoperative platelet aggregation was assessed with impedance aggregometry using adenosine diphosphate (ADP), arachidonic acid (AA), and thrombin receptor-activating peptide (TRAP) as initiators. Severe bleeding complications were registered using a new universal definition of perioperative bleeding. The accuracy of aggregability tests for predicting severe bleeding was assessed using receiver operating characteristic (ROC) curves, which also identified optimal cut-off values with respect to sensitivity and specificity, based on Youden's index.

Results: The median time from the last ticagrelor dose to surgery was 35 (range 4–108) h. The accuracy of platelet function tests to predict severe bleeding was highest for ADP [area under the ROC curve 0.73 (95% confidence interval 0.63–0.84, $P<0.001$); TRAP 0.61 (0.49–0.74); AA 0.53 (0.40–0.66)]. The optimal cut-off for ADP-induced aggregation was 22 U. In subjects with ADP-induced aggregation below the cut-off value, 24/38 (61%) developed severe bleeding compared with 8/52 (14%) when aggregation was at or above the cut-off value ($P<0.001$). The positive and negative predictive values for this cut-off value were 63 and 85%, respectively.

Conclusions: Preoperative ADP-induced platelet aggregability predicts the risk for severe bleeding complications in ticagrelor-treated cardiac surgery patients.

Key words: acute coronary syndrome; blood platelets; cardiovascular surgery; haemorrhage; platelet function tests

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Editor's key points

- Dual antiplatelet therapy (DAPT) increases risk of bleeding in cardiac surgery, but there is significant individual variation.
- Platelet aggregation was used to predict risk of bleeding in an observational study of 90 subjects treated before surgery with ticagrelor and aspirin.
- Preoperative platelet function testing was able to predict severe bleeding with reasonable sensitivity and specificity in DAPT patients.

Dual antiplatelet therapy (DAPT) with acetylsalicylic acid and a $P2Y_{12}$ receptor antagonist reduces the risk of thrombotic events in patients with acute coronary syndrome (ACS), but increases the risk of perioperative bleeding complications if acute or urgent surgery is necessary.[1 2] Current international guidelines recommend discontinuation of the $P2Y_{12}$ inhibitors ticagrelor and clopidogrel at least 5 days before surgery and 7 days before surgery for prasugrel.[3 4] However, a significant proportion (30–50%) of patients on DAPT who undergo coronary artery bypass grafting (CABG) are operated on after a shorter discontinuation time.[1 2 5 6]

The recommended discontinuation times are based on the pharmacodynamic and pharmacokinetic properties of the $P2Y_{12}$ inhibitors[7] and experience from CABG subgroups in randomized trials.[6 8 9] However, there is individual variation in the magnitude and duration of the antiplatelet effect of the $P2Y_{12}$ inhibitors.[7 10] An individualized assessment based on platelet function immediately before operation might thus be preferable to time since discontinuation to predict the risk for bleeding complications. This approach is endorsed in the latest European revascularization guidelines, which state that platelet function testing should be used to guide antiplatelet therapy interruption, rather than arbitrary use of a specified period of delay in patients undergoing CABG surgery.[3] However, this statement is based on limited data,[11 12] as indicated by a C level of evidence. Evidence in support of this approach has so far been published only for thienopyridine-treated CABG patients;[5 13] no data are available for patients treated with the new, more efficient platelet inhibitor, ticagrelor, which is preferred over clopidogrel for most ACS patients according to current guidelines in the USA and Europe.[14 15]

We designed a prospective observational study to test the hypothesis that preoperative platelet function testing can be used to predict the risk for major bleeding complications in ticagrelor-treated cardiac surgery patients when ticagrelor is discontinued <5 days before surgery.

Methods

Subjects

Ninety cardiac surgery patients [mean age 68 (SD 9), range (46–82) yr, 80% men] with ACS treated with acetylsalicylic acid and ticagrelor were included in the study from October 2012 to April 2015. In all patients, ticagrelor was discontinued <5 days before surgery, but acetylsalicylic acid was not stopped. Subject characteristics are presented in Table 1. The decision to operate despite ongoing or recently discontinued ticagrelor treatment was made by a heart team, including a senior cardiac surgeon and a senior cardiologist, according to guidelines.[15] All subjects apart from two underwent CABG. These two patients had ACS treated with acute coronary stenting but required subsequent urgent valve surgery because of mitral regurgitation. The study was approved by the regional research ethics committee and was performed in accordance with the 1975 Declaration of Helsinki after written informed consent.

Clinical management

Subjects were operated on according to our standard protocol with cardiopulmonary bypass. Before cannulation, heparin (350 IU kg^{-1}) was given and supplemented as required to maintain an activated clotting time of >480 s. The standard uncoated extracorporeal circuit was primed with 1 litre of Ringer-acetate (Fresenius-Kabi, Uppsala, Sweden), 0.2 litre of mannitol (150 mg/ml) (Fresenius-Kabi) and 10 000 IU of heparin. Cardiopulmonary bypass was performed with a phosphorylcholine-coated hollow-fibre membrane oxygenator (Sorin INSPIRE; Sorin, Mirandola, Italy) using standard non-pulsatile cardiopulmonary bypass technique with normothermia or mild hypothermia. Haematocrit was kept >20%, and a standard blood flow of 2.4 litre min^{-1} m^{-2} was maintained. Cardioprotection was achieved with cold blood cardioplegia. After decannulation, heparin was neutralized with protamine sulphate (1 mg protamine per 100 IU heparin). All subjects received bolus doses of 2 g tranexamic acid both at induction of anaesthesia and after skin closure; aprotinin was not used.

Bleeding and transfusions

Postoperative bleeding volume was defined as the total amount of chest tube drainage during the first 12 h after surgery or until re-exploration for bleeding. After surgery, the decision to transfuse red blood cells (RBCs) was based on clinical and haemodynamic status or signs of low oxygen delivery with mixed venous saturation <55%, or both, according to our institutional guidelines.[16] Haemoglobin <70 g $litre^{-1}$ was an absolute indication for RBC transfusion; with ongoing significant bleeding, a haemoglobin of 100 g $litre^{-1}$ was the aim. Plasma was transfused for ongoing significant bleeding (>200 ml h^{-1}) and prolonged coagulation time on thromboelastometry, in the absence of signs of a sustained effect of heparin on thromboelastometry or activated clotting time. Platelets were transfused for ongoing significant bleeding (>200 ml h^{-1}) and for low platelet count (<100×10^9 $litre^{-1}$) or suspected platelet dysfunction (i.e. ongoing or recently stopped antiplatelet therapy), or both. Both platelet concentrates produced by apheresis from one donor and from buffy coats from four regular blood donors were used. The final decision to transfuse or not was always at the discretion of the responsible physician.

Bleeding complications were defined according to the universal definition of perioperative bleeding (UDPB) in adult cardiac surgery.[17] Severe bleeding occurred when one or more of these six criteria were met: chest drain loss >1000 ml in the first 12 h after surgery; delayed sternal closure; need for surgical re-exploration because of bleeding or tamponade; use of recombinant factor VIIa; transfusion of ≥5 units of RBCs within 24 h of chest closure; or transfusion of ≥5 units of plasma within 24 h of chest closure.

Platelet function testing

Whole blood samples were collected immediately before surgery (after induction of anaesthesia) and analysed using Multiplate whole blood aggregometry (Roche Diagnostics, Risch-Rotkreuz,