Does Platelet Reactivity Predict Bleeding in Patients Needing Urgent Coronary Artery Bypass Grafting During Dual Antiplatelet Therapy?

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Background. **Up to 15% of patients require coronary artery bypass grafting (CABG) during dual antiplatelet therapy. Available evidence suggests an association between platelet reactivity and CABG-related bleeding. However, platelet reactivity cutoffs for bleeding remain elusive. We sought to explore the association between platelet reactivity and bleeding.**

Methods. **Patients on aspirin and a $P2Y_{12}$ receptor inhibitor within 48 hours before isolated CABG (n = 149) were enrolled in this prospective study. Blood was drawn 2 to 4 hours preoperatively and platelet reactivity assessed by light transmittance aggregometry (LTA), vasodilator-stimulated phosphoprotein (VASP) assay, Multiplate analyzer and Innovance PFA2Y. The primary endpoint was calculated red blood cell loss computed as follows: (blood volume × preoperative hematocrit × 0.91) – (blood volume × hematocrit × 0.91 on postoperative day 5) + (mL of transfused red blood cells × 0.59).**

Results. **Preoperative platelet reactivity was low [median (interquartile range): LTA: 20 (9–28)%; VASP-PRI: 39 (15–73)%; Multiplate adenosine phosphate test: 16 (12–22) U*min]. Innovance PFA2Y ≥300 seconds, 72%. Median (IQR) red blood cell loss in patients in first the LTA tertile was 1,449 (1,020 to 1,754) mL compared with 1,107 (858 to 1,512) mL and 1,075 (811 to 1,269) mL in those in the second and third tertiles, respectively ($p < 0.004$). Bleeding Academic Research Consortium (BARC)-4 bleeding differed between tertiles (62% versus 46% versus 36%; $p = 0.037$). In a multivariable linear regression model, aspirin dose ≥300 mg, cardiopulmonary bypass time, EuroSCORE, and tertile distribution of platelet reactivity were significantly associated with red blood cell loss.**

Conclusions. **A gradual decrease in red blood cell loss and BARC-4 bleeding occurs with increasing platelet reactivity in patients on antiplatelet therapy undergoing CABG. Our findings support current guidelines to determine time of surgery based on an objective measurement of platelet function (Platelet Inhibition and Bleeding in Patients Undergoing Emergent Cardiac Surgery; clinicaltrials.gov NCT01468597).**

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Three to 15% of patients presenting with acute coronary syndrome undergo coronary artery bypass grafting (CABG) during dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor [1, 2]. Although preoperative $P2Y_{12}$ receptor inhibitor therapy has been associated with a reduction in the risk of ischemic event occurrences, recent exposure has been associated with an increased relative risk of death and reoperation by about 50 and 200%, respectively. The latter observations are mainly attributed to excessive bleeding [3]. Furthermore, blood transfusion was associated with a dose-dependent increase in morbidity and mortality after CABG [4]. To avoid excessive bleeding, current guidelines recommend a standardized 5 days preoperative period of withdrawal of clopidogrel and ticagrelor and a 7 days withdrawal of prasugrel, unless there is high ischemic risk [5].

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The Timing Based on Platelet Function Strategy to Reduce Clopidogrel Associated Bleeding Related to CABG (TARGET-CABG) study prospectively demonstrated that a platelet function measurement-based strategy to time CABG in clopidogrel-treated patients was associated with the same amount of bleeding that occurred in clopidogrel-naive patients and with a 50% shorter preoperative waiting period than recommended in the guidelines [6]. In patients who require urgent CABG during DAPT, current guidelines recommend to time surgery based on tests of platelet function [5, 7]. However, the optimal platelet function assay and a validated cutoff of platelet reactivity predicting bleeding remain elusive [7]. Although the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI) and Study of Platelet Inhibition and Patient Outcomes (PLATO) trial results suggested that CABG-related bleeding increased with greater $P2Y_{12}$ receptor inhibition, studies evaluating the relationship between measured platelet reactivity and CABG-related bleeding in patients on aspirin and new $P2Y_{12}$ receptor inhibitors are lacking [8, 9]. Thus, the aim of the current study was to evaluate whether or not on-treatment platelet reactivity as assessed by light transmittance aggregometry (LTA) was associated with on-pump CABG-related bleeding in patients recently exposed to DAPT. Furthermore, we also sought to assess the utility of other platelet function tests and the correlation between platelet function tests.

Patients and Methods

After institutional review board approval (Medical University of Graz, Austria; EK: 21 to 202 ex 09/10), all patients with recent exposure to DAPT undergoing urgent or emergent CABG with or without concomitant valve replacement were screened between October 2010 and September 2013 for eligibility for this prospective observational study. After obtaining written informed consent, patients were enrolled in the study if they received aspirin (100 to 500 mg/day) and a $P2Y_{12}$ receptor inhibitor within 48 hours preoperatively. Patients on chronic dialysis, on concomitant oral anticoagulants and patients unable to consent were excluded. Patients undergoing off-pump CABG or concomitant valve replacement and patients without platelet function data were excluded from final analysis.

Patient Management

DAPT was discontinued once an indication for CABG was established. As per institutional protocol, glycoprotein IIb or IIIa inhibitors were stopped preoperatively for at least 4 hours and 8 hours in patients with normal renal function and a glomerular filtration rate $\leq$30 mL/min, respectively. The perioperative care of the patients was at the discretion of the attending physicians, who were blinded to platelet function data. Surgery was performed by the individual cardiac surgeon on duty. Anticoagulation was established by an initial loading dose of 300 IU/kg unfractionated heparin to obtain an activated clotting time $\geq$400 seconds that was maintained during cardiopulmonary bypass (CPB) by supplemental administration. On completion of CPB, anticoagulation was reversed by protamine chloride in a 1:1 ratio; additional protamine was given as needed to achieve an activated clotting time <140 seconds. All patients received tranexamic acid. The perioperative transfusion trigger was set to a hematocrit of 20% on CPB and 25% thereafter, unless active bleeding or low cardiac output suggested a need to increase this level. Platelets were administered in abnormal postpump bleeding based on clinical judgment [10]. Thrombelastometry (ROTEM, Tem Innovations GmbH, Munich, Germany) was used to guide fresh frozen plasma, Prothromplex (Baxter Healthcare GmbH, Vienna Austria), and Haemocomplettan (CSL Behring GmbH, Vienna Austria) administration to target the normal range of clotting time and clot strength in tissue factor activated (EXTEM), heparinase-containing (HEPTEM) and fibrin-based (FIBTEM) thrombelasotmetry. As per institutional protocol rethoracotomy was performed in case of hemodynamic instability, cardiac tamponade, and chest tube drainage of 1,000 mL after excluding or correcting residual heparin or dilutional coagulopathy. Patients received 325 mg aspirin intravenously 6 hours postoperatively and 100 mg/day thereafter unless contraindicated by active bleeding. One-year mortality was assessed by telephone interview.

Platelet Function Testing

Blood samples were obtained by venipuncture within 2 to 4 hours preoperatively and platelet reactivity was assessed by the following:

- Chronolog 700 Lumi-Aggregometer (Chronolog Corp., Havertown, PA) using 5 μM adenosine phosphate (ADP) to stimulate platelet aggregation in platelet-rich plasma [11]
- Flow cytometric vasodilator-stimulated phosphoprotein (VASP)-phosphorylation assay (Biocytex, Marseille, France) [11]
- Multiplate analyzer (Roche Diagnostics GmbH, Vienna, Austria) using the ADP test [12]
- Innovance PFA2Y (Siemens Healthcare, Marburg, Germany) using the P2Y cartridge in whole blood as described previously [13].

Study Endpoints

The primary endpoint was the calculated perioperative red blood cell (RBC) loss that has been used previously to assess bleeding in patients undergoing cardiac surgery and was calculated as follows: (blood volume × preoperative hematocrit × 0.91) – (blood volume × hematocrit × 0.91 on postoperative day 5) + (mL of transfused RBCs × 0.59). A factor of 0.91 was applied to correct hematocrit of peripheral blood sampling and the factor 0.59 accounts for the average hematocrit of RBC units [14].