BJA

British Journal of Anaesthesia, 117 (6): 749–57 (2016)

doi: 10.1093/bja/aew357
Clinical Practice

CLINICAL PRACTICE

Prospective observational study of the effect of dual antiplatelet therapy with tranexamic acid treatment on platelet function and bleeding after cardiac surgery

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Abstract

Background. The bleeding impact of dual antiplatelet therapy (DAPT), aspirin and clopidogrel, maintained until coronary artery bypass graft surgery (CABG), is still a matter of debate. The lack of preoperative antiplatelet activity measurement and heterogeneity of antifibrinolytic protocols in prior studies make the conclusions questionable. The aim of this prospective study was to determine, after preoperative antiplatelet activity measurement, if the maintenance of DAPT until CABG increases bleeding in patients treated with tranexamic acid (TA).

Methods. This observational study included 150 consecutive patients, 89 treated with aspirin and 61 treated with DAPT, undergoing a first-time planned on-pump CABG with TA treatment. Antiplatelet activity was measured with platelet aggregation tests and quantification of VASP phosphorylation. Postoperative bleeding at 24 h was recorded and propensity score analysis was performed.

Results. Based on VASP assay, 54% of patients showed high on-clopidogrel platelet activity inhibition. Postoperative bleeding at 24 h increased by 22% in the DAPT group, compared with the aspirin group (680 [95% CI: 360-1670] *vs* 558 [95%CI: 267-1270] ml, $P < 0.01$), consistent with increased blood transfusion (21% vs 7%, $P = 0.01$); a higher incidence of mediastinitis did not reach statistical significance (15% vs 4%, $P = 0.05$). Bleeding correlated with the extent of clopidogrel antiplatelet effect, with the best correlation for the VASP assay.

Conclusions. Maintenance of DAPT until the day of CABG in patients treated with TA, increased postoperative bleeding at 24 h in parallel with preoperative antiplatelet activity induced by clopidogrel.

Key words: antifibrinolytic agents; blood loss; clopidogrel; coronary artery bypass; mediastinitis.

Editorial decision August 28, 2016; **Accepted:** September 30, 2016

Editor's key points

- The impact of dual antiplatelet therapy (DAPT) on bleeding after cardiac surgery in patients treated with antifibrinolytic drugs is unclear.
- Preoperative platelet function and bleeding in the first 24 h after cardiac surgery was determined in a prospective observational study of 150 consecutive patients in a single centre.
- Bleeding was somewhat greater in patients receiving tranexamic acid and treated preoperatively with DAPT compared with aspirin alone, which correlated with degree of preoperative antiplatelet effect.

The benefit of dual antiplatelet therapy (DAPT), such as clopidogrel combined with aspirin, is well-established in the treatment of both acute coronary syndrome and ischaemic cardiomyopathy.[1] Aspirin maintenance during surgery does not increase the postoperative bleeding in coronary artery bypass grafting (CABG) patients,[2] but continuation of DAPT until CABG is a matter of debate. Several studies and meta-analyses have tried to address this question,[1 3–6] and guidelines have been published.[6–8] Nevertheless, conclusions are questionable because of major methodological concerns. The most important bias is lack of preoperative platelet activity measurement, even though a large inter-individual variability in response to clopidogrel is well known.[9–11] In one retrospective study that assessed platelet activity, patients undergoing off-pump or on-pump CABG[9] were combined, even though cardio-pulmonary bypass (CPB) is known to impact postoperative bleeding.[12]

While intraoperative treatment with anti-fibrinolytic agents can reduce perioperative bleeding in cardiac surgery,[13 14] in most studies neither antifibrinolytic agents nor standardized infusion protocols were used, increasing study heterogeneity.[9 15 16] With aprotinin, postoperative bleeding was not increased when DAPT was maintained until the day of surgery.[14] Since withdrawal of aprotinin from the market, tranexamic acid (TA) is currently recommended in cardiac surgery despite being less efficacious.[7] In addition, TA might partially reverse the effect of platelet activity inhibition by DAPT.[17]

The present study was designed to compare postoperative bleeding at 24 h after maintenance of DAPT *vs* aspirin alone, in patients undergoing on-pump elective primary CABG and receiving TA infusion. Systematic preoperative platelet activity measurements were performed in each patient to distinguish clopidogrel good-responders and poor-responders.

Methods

Patients

The ICARE study (ClinicalTrial.gov: NCT01216150) is a prospective observational trial conducted at a large academic hospital from December 2009 to November 2010, when maintenance of DAPT until the day of surgery was usual in our institution. We performed an observational study to assess impact of DAPT on postoperative bleeding by propensity score analysis using boosted regression trees. No additional blood sample was required for this study, and measurements performed are routine for all patients undergoing cardiac surgery. As preoperative antiplatelet activity was measured in residual blood samples (<5 ml), waived informed consent was approved by the ethical committee. However, verbal and written information was given to patients.

During the study period, all patients undergoing elective isolated first-time CABG were enrolled.[14] We excluded patients in whom mechanical support or intra-aortic balloon pump was required, as their antithrombotic therapy management differs during the postoperative period. We also excluded all patients who did not receive aspirin until surgery, those who had been preoperatively exposed to antiplatelet glycoprotein IIb/IIIa inhibitors, and those with a history of haematological disease that can interfere with coagulation or platelet functions. Patients treated with DAPT and in whom clopidogrel was stopped > 10 days before surgery were included in the aspirin group. In case of clopidogrel discontinuation < 10 days before surgery, patients were excluded to rule out a potential residual effect of clopidogrel. Low molecular weight heparin (LMWH) was systematically discontinued 12 h before surgery.

Intraoperative management

Patients enrolled in this study were pre-treated with TA (Exacyl®, Sanofi-Aventis, Paris, France) i.v. bolus and infusion at 10 mg kg^{-1} for 20 min after induction of anaesthesia, followed by continuous i.v. infusion of 2 mg kg^{-1} h^{-1} until the end of surgery, according a standardized protocol.[18] In case of renal dysfunction, continuous infusion was adapted as follows: 1.5 mg kg^{-1} h^{-1} for serum creatinine 140-290 μmol L^{-1}, 1 mg kg^{-1} h^{-1} for serum creatinine 291-580 μmol L^{-1}, 0.5 mg kg^{-1} h^{-1} for serum creatinine > 581 μmol L^{-1}.

As described,[14] before aortic cannulation, an initial loading dose of heparin was directly administrated by the surgeon into the right atrium, to obtain a whole-blood-activated clotting time > 400 sec measured using a micro-coagulation analyzer (HemochronJr II, Inter- national Technidyne Corporation, Edison, NJ). After discontinuation of cardiopulmonary bypass, heparin was neutralized by protamine sulfate (0.008–0.01 mg IU^{-1} of total heparin dose). Intraoperative cell salvage was used systematically (Electa, Dideco, Mirandola, Italy).

Postoperative anti-thrombotic therapy

Early postoperative antithrombotic therapy consisted of an i.v. bolus of 100 mg aspirin given 6 h after the arrival in the intensive care unit (ICU).[14] Initial prophylactic anticoagulation was started 6 h after the end of the surgical procedure, with unfractioned heparin continuously infused at 100 IU kg^{-1} day^{-1}, switched to once daily administration of enoxaparin 40 mg the day after surgery. Transfusion was a decision left to the clinical team, and written guidelines are used in our department. In case of persistent bleeding only, platelet transfusion was administered without any blood clot formation in operating room and/or when platelet count was < 80,000 μl^{-1}. No preventive transfusion was given. Based on recommendations of the Society of Thoracic Surgeons and the Society of Cardiovascular Anaesthesiologists,[19] red blood cell transfusion was recommended in our institution in case of haemoglobin < 7 g dl^{-1}, fresh frozen plasma transfusion in case of serious bleeding with prothrombin time less than 50%, and fibrinogen for plasma concentration less than 2 g dl^{-1}.

Preoperative platelet reactivity assessment

Preoperative platelet function inhibition was measured in each patient. Platelet aggregation tests and flow cytometric assays with vasodilator-stimulated phosphoprotein (VASP) were performed.[20 21] Aggregation studies were performed within 3 h of blood collection; test results were known retrospectively at the