Thrombosis Research 136 (2015) 519–525

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Preoperative platelet aggregation predicts perioperative blood loss and rethoracotomy for bleeding in patients receiving dual antiplatelet treatment prior to coronary surgery

Dariusz Plicner [a], Piotr Mazur [a,b,*], Hubert Hymczak [a], Jarosław Stoliński [a], Radosław Litwinowicz [a,b], Rafał Drwiła [a,b], Anetta Undas [a,b]

[a] John Paul II Hospital, Krakow, Poland
[b] Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland

ARTICLE INFO

Article history:
Received 21 February 2015
Received in revised form 13 April 2015
Accepted 28 April 2015
Available online 5 May 2015

Keywords:
Coronary artery bypass grafting
CABG
Bleeding
Transfusions
Clopidogrel
Platelet aggregation

ABSTRACT

Introduction: Patients scheduled for coronary artery bypass graft surgery (CABG) are commonly treated with clopidogrel. We sought to assess the relation between preoperative platelet aggregation and bleeds in CABG patients on clopidogrel.

Material and methods: In a case-control study, we compared 52 consecutive patients undergoing isolated CABG on aspirin and clopidogrel 75 mg/d versus 50 controls on aspirin monotherapy. Platelet aggregation induced by 10 μmol/l adenosine di-phosphate (ADP) in platelet-rich plasma was measured in subjects on clopidogrel within 5 days prior to surgery. ADP-induced aggregation of ≥50% was used to define subjects with satisfactory inhibition of platelet reactivity.

Results: In 29 patients with preoperative ADP-induced aggregation ≥50%, compared with 23 subjects with aggregation <50%, lower chest-tube drainage volumes (after 6 h, $p = 0.002$; and 12 h, $p = 0.001$) and fewer rethoracotomies were observed ($p = 0.03$). The former group was characterized with lower transfusion rates of packed red blood cells ($p = 0.009$), platelet concentrate ($p = 0.04$) and fresh frozen plasma ($p = 0.001$). Patients with ADP-induced aggregation ≥50% did not differ from untreated controls regarding the postoperative drainage, transfusions and rethoracotomy. The incidence of thromboembolic events and death during perioperative period were similar in all groups. Multivariate logistic regression identified ADP-induced aggregation <50% as the only independent predictor of rethoracotomy (OR = 2.94 [1.12-7.75], $p = 0.029$).

Conclusions: Patients on aspirin and clopidogrel <5 days before CABG who had preoperative ADP-induced platelet aggregation ≥50% have bleeding risk similar to those receiving aspirin monotherapy. Reduced platelet reactivity to ADP can predict postoperative bleeding in CABG patients on dual antiplatelet therapy.

1. Introduction

Dual antiplatelet therapy (DAPT) involving aspirin and clopidogrel is common among patients who require coronary artery by-pass grafting (CABG). The benefits and safety of preoperative clopidogrel use before CABG have been extensively investigated. Two clinical trials (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events [CURE] and Acute Catheterization and Urgent Intervention Triage strategy [ACUITY]) demonstrated a cardiovascular events risk reduction and increased major bleeding risk among urgent CABG patients operated on clopidogrel [1,2]. Interestingly, only the patients who received clopidogrel ≤ 5 days from CABG had increased risk of both major bleeding and ischemic events [1,2]. Berger et al. reported increased risk of bleeding-related complications in DAPT patients undergoing CABG when the last dose of clopidogrel was taken ≤ 4 days before surgery [3]. Recently, Miceli and colleagues demonstrated in 926 CABG patients that DAPT with clopidogrel continued until the surgery is associated with elevated risk of myocardial infarction (MI) and bleeding compliations [4]. Similar results were presented by Firanescu et al. in a randomized trial [5], however platelet reactivity was not assessed in any of these studies.

Several methods of platelet function testing are available, including point-of-care tests like VerifyNow, Multiplate, or Plateletworks.

Abbreviations: ADP, adenosine di-phosphate; APTT, activated partial thromboplastin time; BMI, body mass index; CABG, Coronary artery bypass grafting; CK-MB, creatine kinase MB fraction; CPB, cardiopulmonary bypass; DAPT, dual antiplatelet therapy; FFP, fresh frozen plasma; Hb, hemoglobin; HPA, high platelet aggregation; INR, international normalized ratio; LPA, low platelet aggregation; LTA, light transmission aggregometry; MI, myocardial infarction; PCI, percutaneous coronary intervention; PMI, perioperative myocardial infarction; PRBC, packed red blood cells; STS, Society of Thoracic Surgeons.

* Corresponding author at: Institute of Cardiology Jagiellonian University Medical College, 80 Pradnicka St., 31-202 Krakow, Poland. Tel.: +48 12 6143075; fax: +48 12 4233900.
E-mail address: piotr.k.mazur@gmail.com (P. Mazur).

http://dx.doi.org/10.1016/j.thromres.2015.04.037
0049-3848/

However, it is the light transmission aggregometry (LTA) induced by adenosine di-phosphate (ADP), that is considered the gold standard to evaluate platelet function [6]. In patients treated with clopidogrel, the results of various platelet function tests are correlated, but not interchangeable [7]. Bleeding after cardiac surgery remains one of the most feared complications, affecting mortality and morbidity [8]. Also perioperative blood-product transfusions increase postoperative morbidity in patients undergoing CABG [9].

In 2004 Chen et al. reported that platelet inhibition by clopidogrel, documented by LTA, is a predictor of perioperative bleeding and transfusion requirement in 45 CABG patients exposed to clopidogrel 6 days preoperatively, while point-of-care tests (PFA-100 and Plateletworks) did not predict bleeding [10]. Recently Yu et al. have demonstrated that the results of VerifyNow tests do not predict transfusion requirements in CABG patients [11]. Dalén et al. reported that platelet aggregation measured with the Plateletworks system does not correlate with postoperative blood loss after CABG [12].

The 2014 European Society of Cardiology and European Association for Cardiothoracic Surgery guidelines on myocardial revascularization support the 5 day clopidogrel withdrawal period before CABG, however, they indicate 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 (class IIa recommendation, level of evidence C) [13]. Although the 5-day washout period is supported by strong data [14], these indications are invalid if the patient is at high ischemic risk – who despite clopidogrel use should undergo CABG irrespectively of discontinuation period [13,15].

Platelet function testing may be beneficial in reducing the gap between clopidogrel therapy interruption and CABG, by helping the surgeon identify the time-point when there is no significant platelet inhibition anymore, or by yielding information on increased risk of procedure-related bleeding [16]. We hypothesized that in patients on DAPT with clopidogrel, who undergo CABG less than 5 days after clopidogrel exposure, preoperative ADP-induced platelet aggregation measured by LTA predicts procedure-related bleeding and rethoracotomy, postoperative chest-tube output, peri- and post-procedural transfusion of blood products, prolonged stay on intensive care unit and mortality.

2. Material and Methods

2.1. Patients

From May 2012 to June 2013 in a case-control study we recruited 52 consecutive coronary artery disease patients who received DAPT with clopidogrel 75 mg and low-dose aspirin once daily and underwent primary, isolated elective or urgent CABG within 5 days from clopidogrel exposure. The control group comprised 50 consecutive CABG patients, who did not receive clopidogrel preoperatively. The patients were recruited at the same time. All patients continued aspirin 75-150 mg/d until the day of CABG. We excluded individuals with a history of any cardiac surgery, those with renal dysfunction (serum creatinine >177 μmol/l), those receiving vitamin K antagonists or other oral anticoagulants, known cancer, signs of acute infections, known hemorrhagic diathesis. Individuals receiving prasugrel or ticagrelor, as well as patients with clopidogrel discontinuation period >5 days or those who received a loading dose prior to urgent cathererization preceding CABG, were ineligible. Bleeding risk was assessed using the Papworth Bleeding Risk Score [17].

2.2. Coronary Artery Bypass Grafting Procedure

Fasting period had to be as long as 12 h preoperatively in elective cases, in urgent cases the patient had to be fasting for at least 8 h. Oral medications were administered for the last time on the morning of CABG (except for oral hypoglycemic and antiplatelet agents). All patients underwent standardized anaesthesia and received median sternotomy. Cardiopulmonary by-pass (CPB) was performed at moderate hypothermia (oesophageal temperature, 32 °C) using a nonpulsatile roller pump (Jostra Medizintechnik AG, Hirrlingen, Germany) and a 40 μm arterial blood filter (Jostra Medizintechnik AG, Hirrlingen, Germany), with blood flow at 2.0-2.4 l/min/m^2 and mean arterial pressure at 40-60 mmHg. Cardiac arrest was achieved by intermittent (administered at approximately 20 minutes intervals) antegrade warm blood or cold crystalloid cardioplegia. Anticoagulation was achieved by administration of heparin (500 IU/kg) before the onset of CPB, and monitored using of the activated clotting time, which had to be above 400 seconds during CPB. At the end of CPB anticoagulation was reversed by protamine to obtain a normal activated clotting time (normal reference range: 90-120 seconds). Meticulous surgical hemostasis was aimed at during all procedures. Operations were performed by 9 experienced surgeons. The "cell-savers" were not used in any of the cases. During CPB packed red blood cells (PRBC) transfusion was indicated when hemoglobin (Hb) value was lower than 7.5 g/dl (normal reference range for Hb: 12-16 g/dl). During the procedure, platelet concentrate (PC) was transfused just after protamine administration in all patients with total platelets count less than 100×10^3/μl or if the perioperative bleeding was assessed to be severe by the surgeon together with the anesthesiologist. After CABG, the patients were transferred to the intensive care unit for postoperative ventilation. Patients were extubated according to the standard criteria. None of the patients received aminocapronic acid, aprotinin or desmopressin acetate. Tranexamic acid was administered in two doses (20 mg/kg i.v. after sternotomy, and 20 mg/kg i.v. after the end of CPB) in all cases. No "auto-transfusions" (requiring patients' blood withdrawal by the anesthesiologist prior to heparinization) were performed in any of the cases.

2.3. Postoperative Management

The volume of post-operative drainage was measured after 6 h and 12 h. The drained blood was not reinfused. Total number of transfused blood products units, as well as the number of transfused units during the operation, first 6 postoperative hours and between 6th and 12th postoperative hours, were recorded. PRBC transfusion was administered when Hb level dropped to <7.0 g/dl. PC was transfused if there was an ongoing bleeding >200 ml/h and platelet count was below 100×10^3/μl; fresh frozen plasma (FFP) was transfused when there was an ongoing bleeding. Rethoracotomy was indicated if the total drainage exceeded 400 ml during the first hour or when it was more than 200 ml/h during 5 consecutive hours.

2.4. Outcomes

The primary clinical outcomes in this study were: postoperative chest tube drainage during first 6 postoperative hours and after 12 h, blood products transfusions in the operating room, during first 6 postoperative hours and between 6th and 12th postoperative hours, major perioperative blood loss and reoperations for bleeding. The secondary outcomes were: perioperative myocardial infarction (PMI), intensive care unit length of stay, and in-hospital cardiovascular death. PMI (within 24 hours after CABG) was defined as the serum creatine kinase MB fraction (CK-MB) level greater than or equal to 5 times the upper limit of normal, and new Q waves had to be present, or CK-MB value had to be greater than or equal to 10 times the upper limit of normal (with or without Q waves) and no symptoms were required. CK-MB values were measured at 6, 12, 18, and 24 hours after CABG. The upper normal value of CK-MB is 17 U/l. Major perioperative blood loss was defined as a need for transfusion of a total of ≥4 PRBC units during the surgery before the patient left the operating room. In-hospital cardiovascular death was defined as death due to cardiovascular diseases, occurring during the same hospitalization. Additional retrospective analysis was performed using the universal definition for perioperative