Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

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

Original article

Impact of preoperative dual antiplatelet therapy on bleeding complications in patients with acute coronary syndromes who undergo urgent coronary artery bypass grafting

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ARTICLE INFO

Article history:
Received 16 November 2015
Received in revised form 5 February 2016
Accepted 12 February 2016
Available online xxx

Keywords:
Bleeding
Coronary artery bypass grafting
Platelet inhibitors
Coronary heart disease

ABSTRACT

Background: A 5- to 7-day washout period before coronary artery bypass grafting (CABG) is recommended for patients who have recently received a thienopyridine derivative; however, data supporting this guideline recommendation are lacking in Japanese patients.
Methods: Urgent isolated CABG was performed in 130 consecutive patients with acute coronary syndromes (ACS) (101 men; mean age, 69 years). Urgent CABG was defined as operation performed within 5 days after coronary angiography. All patients continued to receive aspirin 100 mg/day. The subjects were retrospectively divided into 2 groups: 30 patients with preoperative thienopyridine (clopidogrel in 15 patients, ticlopidine in 15) exposure within 5 days [dual antiplatelet therapy (DAPT) group] and 100 patients without exposure [single antiplatelet therapy (SAPT) group].
Results: Although the DAPT group had a higher proportion of patients who received perioperative platelet transfusions than the SAPT group (50% vs. 18%, $p < 0.001$), intraoperative bleeding (median, 1100 ml; interquartile range, 620–1440 vs. 920 ml; 500–1100) and total drain output within 48 h after surgery (577 ± 262 vs. 543 ± 277 ml) were similar. CABG-related major bleeding, which was defined as type 4 or 5 bleeding according to the Bleeding Academic Research Consortium definitions, occurred in a significantly higher proportion of patients in the DAPT group than in the SAPT group (20% vs. 3%, $p = 0.005$). This difference in major bleeding was driven mainly by the higher rate of transfusion of $\geq$5 U red blood cells within a 48-h period in the DAPT group (13% vs. 1%, $p = 0.01$). There was no significant difference in the 30-day composite endpoint including death, myocardial (re)infarction, ischemic stroke, and refractory angina between the DAPT group and SAPT group (17% vs. 19%).
Conclusions: Preoperative DAPT increases the risk of CABG-related major bleeding in Japanese patients with ACS undergoing urgent CABG.

Introduction

Dual antiplatelet therapy (DAPT) with aspirin and oral adenosine diphosphate (ADP)-receptor antagonists such as thienopyridine derivatives reduces thrombotic events more effectively than single antiplatelet therapy (SAPT) with aspirin alone in patients with acute coronary syndromes (ACS) and those who have undergone percutaneous coronary intervention (PCI) [1,2]. The benefits of DAPT in patients with recent ACS are similar regardless of whether the patient receives medical therapy or undergoes thrombolysis or revascularization by either PCI or coronary artery bypass grafting (CABG) [3]. Recent guidelines recommend that clopidogrel or ticagrelor in addition to aspirin should be administered to all patients with non-ST-segment elevation ACS without contraindications who are treated by either an early invasive or ischemia-guided strategy [4]. However, 10–15% of patients admitted with ACS undergo CABG during the initial hospitalization [5]. An increased risk of perioperative bleeding has

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http://dx.doi.org/10.1016/j.jjcc.2016.02.013
0914-5087/

been reported in patients who received DAPT within 5 days of surgery [6]. While interruption of antithrombotic drugs prior to CABG surgery may increase the thromboembolic risk, continuation may increase the risk of bleeding. Unfortunately, it is unclear which antiplatelet agent to use or when it should be discontinued [7]. Consequently, the challenge is to optimize the timing of surgery to minimize the risk of potentially fatal ischemic events before CABG and at the same time reduce the incidence of serious surgical bleeding. A 5- to 7-day washout period before CABG is recommended for patients receiving thienopyridine in the Japanese guidelines for ST-segment elevation myocardial infarction (STEMI); however, these guidelines are notably based on non-Japanese evidence. The aim of the present study is to evaluate whether recent exposure to DAPT before urgent CABG is associated with an increased risk of bleeding complications in Japanese patients with ACS.

Materials and methods

Patients

We retrospectively studied 152 consecutive patients with ACS including STEMI and non-ST-segment elevation ACS, who underwent urgent CABG using either on-pump or off-pump procedures at Yokohama City University Medical Center between June 2005 and April 2012. Twenty-two patients were excluded because they had undergone redo CABG, surgical ventricular restoration, or other concomitant surgical procedures, such as valve repair or replacement, or if they had recently received cilostazol, novel oral anticoagulants, or thrombolytic agents before surgery. The remaining 130 patients with ACS who underwent urgent isolated CABG were included in the analysis. Urgent CABG was defined as operation performed within 5 days after coronary angiography. The study protocol was approved by the ethics committee of Yokohama City University. Written comprehensive informed consent was obtained from all patients.

Antithrombotic agents

All patients continued to receive aspirin 100 mg/day. Because ticlopidine was the only thienopyridine derivative approved in Japan until September 2007, subjects treated between June 2005 and September 2007 received ticlopidine 200 mg/day. After clopidogrel was approved in Japan for use in patients with ACS in October 2007, a 300-mg loading dose of clopidogrel followed by 75 mg/day was prescribed. Other ADP-receptor antagonists and glycoprotein IIb/IIIa inhibitors were not available in Japan during the study period. Whether or not patients received thienopyridine derivatives before coronary angiography was left to the discretion of the attending cardiologist. All study patients received intravenous unfractionated heparin as the anticoagulant therapy. Warfarin reversal with vitamin K was performed and heparin bridging was started at the time of ACS admission in all 6 patients receiving warfarin. Intraoperative heparin was used in all patients during the procedure to maintain a target activated clotting time of more than 400 s. At the end of surgery, heparin reversal with protamine was performed. Oral anticoagulants were prescribed only in patients with saphenous vein bypass grafts, atrial fibrillation, or intracardiac thrombus after surgery. Treatment with a thienopyridine derivative was not resumed in any patient after surgery.

Operative techniques and transfusion

In our hospital, the indications for and timing of revascularization are discussed and determined by the "Heart Team," consisting of cardiologists and cardiac surgeons, who base their decisions mainly on the findings of coronary angiography. Patients considered at high risk for recurrent ischemic events underwent emergent CABG with or without intra-aortic balloon pumping (IABP). CABG was performed through a full sternotomy incision, using general surgical and cardioprotective techniques and endotracheal anesthesia. Whether CABG was performed on-pump or off-pump was left to the discretion of the attending surgeon. All patients were monitored and treated in the intensive care unit (ICU) after CABG. Transfusions of allogeneic blood components were given at the discretion of the attending anesthesiologist or surgeon. The indications for allogeneic transfusion were based on routine laboratory measurements of activated partial thromboplastin time, activated clotting time, and international normalized ratio of prothrombin time, as well as on fibrinogen, hemoglobin, and hematocrit levels. Furthermore, the use of allogeneic blood products was influenced by the patients' hemodynamic and physiological data, as well as blood loss volume.

Clinical outcomes

Intraoperative and postoperative bleeding volumes were evaluated retrospectively. Postoperative bleeding was defined as the total amount of chest tube drainage within 48 h after surgery. CABG-related major bleeding was defined as type 4 or 5 bleeding according to the Bleeding Academic Research Consortium definitions [8] and included perioperative intracranial bleeding; reoperation for bleeding; transfusion of $\geq$5 U red blood cells within a 48 h period; or a chest tube output of $\geq$2 L within a 24-h period; and fatal bleeding. Reoperation for bleeding was defined as the return to the operating room necessitated by bleeding or cardiac tamponade. Transfusion requirements were estimated on the basis of the total amount of packed red blood cells, platelet concentrates, and fresh frozen plasma transfused intraoperatively as well as within 48 h after surgery. We also analyzed the relation between recent exposure to DAPT and composite ischemic events, including death, myocardial (re)infarction (including CABG-related myocardial infarction), ischemic stroke, and refractory angina within 30 days after admission. CABG-related myocardial infarction was defined as an elevation in the plasma level of creatine kinase-myocardial band to more than 10 times the upper level of normal during the first 72 h after CABG in accordance with the criteria of the universal definition of myocardial infarction (type 5) [9]. Ischemic stroke was a combined outcome including transient ischemic attack or cerebrovascular infarction. Refractory angina was diagnosed on the basis of chest pain associated with electrocardiographic evidence of ischemia unable to be controlled by a combination of medical therapy.

Statistical analysis

Categorical variables are reported as percentages and were compared by the chi-square test. Continuous variables were reported as mean $\pm$ SD or as medians (interquartile range) and were compared with the use of Student's *t*-test or Mann–Whitney *U*-test. Values of $p < 0.05$ were considered to indicate statistical significance. All statistical analyses were performed with SPSS19 (SPSS, Inc., Chicago, IL, USA).

Results

We studied 130 patients with ACS who underwent urgent isolated CABG (101 men; mean age, 69 years). The subjects were retrospectively divided into 2 groups: 30 patients who had received aspirin and a thienopyridine derivative within 5 days before CABG were assigned to the DAPT group (clopidogrel in 15 patients, ticlopidine in 15), and 100 patients who had received

Please cite this article in press as: Nagashima Z, et al. Impact of preoperative dual antiplatelet therapy on bleeding complications in patients with acute coronary syndromes who undergo urgent coronary artery bypass grafting. J Cardiol (2016), http://dx.doi.org/10.1016/j.jjcc.2016.02.013