Individualized strategy for clopidogrel suspension in patients undergoing off-pump coronary surgery for acute coronary syndrome: A case-control study

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Objective: An increasing number of patients presenting for urgent coronary surgery have been exposed to clopidogrel, which constitutes a risk of bleeding and related events. Based on the wide variability in clopidogrel response and platelet function recovery after cessation, we evaluated the role of point-of-care platelet function testing to define the optimal time for off-pump coronary artery bypass graft (CABG) surgery in a case-control study.

Methods: Three equally matched groups (300 patients in total) undergoing isolated off-pump CABG for acute coronary syndrome were compared. Group A were treated with clopidogrel and prospectively underwent a strategy guided by platelet function testing. Outcomes were compared with 2 propensity score matched groups: group B underwent CABG after the currently recommended 5 days without clopidogrel; group C were never exposed to clopidogrel.

Results: Patients in group A had reduced postoperative bleeding compared with those in group B (523 $\pm$ 202 mL vs 851 $\pm$ 605 mL; $P < .001$) and a lower number of units packed red blood cells (PRBCs) transfused during the postoperative hospital stay (1.2 $\pm$ 1.6 units vs 1.9 $\pm$ 1.8 units; $P = .004$). Postoperative bleeding and the number of units of PRBCs transfused were similar in group A and group C. There was no difference in blood-derived products and platelet consumption, mortality, or the need for reoperation among the groups. Patients in group A waited 3.6 $\pm$ 1.7 days for surgery. The strategy used for group A saved 280 days of hospital stay in total.

Conclusions: The strategy guided by platelet function testing for off-pump CABG offers improved guidance for optimal timing of CABG in patients treated with clopidogrel. This strategy significantly reduces postoperative bleeding and blood consumption, and has a shorter waiting time for surgery than current clinical practice. (J Thorac Cardiovasc Surg 2014;148:1299-306)

ACD

The current 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines for percutaneous coronary intervention (PCI) recommend the administration of a loading dose of clopidogrel in patients undergoing PCI (class I indication) and dual antiplatelet therapy ideally for up to 12 months with additional aspirin after PCI with stents for acute coronary syndrome (ACS) or non-ACS (class I indication).[1] Recently, 2012 ACCF/AHA guidelines for the management of unstable angina/non-ST-elevation myocardial infarction suggested aspirin and clopidogrel for convalescent and long-term therapy for patients treated medically (class I indication).[2] As a consequence, an increasing number of patients who present for cardiac surgery are receiving antiplatelet treatment with clopidogrel and are at risk of bleeding and bleeding-related complications.

The pharmacokinetics and pharmacodynamics of clopidogrel indicate that platelet inhibition decreases gradually to pretreatment levels ~1 week after treatment is terminated.[3] Accordingly, current ACC/AHA guidelines recommend stopping clopidogrel at least 5 days before surgery in elective patients referred for coronary artery bypass graft (CABG) surgery to reduce bleeding, usage of blood products, and related complications.[4,5] Data from the CRUSADE initiative reported that an increasing proportion of patients who need urgent surgery for ACS are exposed to clopidogrel and may be at risk for cardiac events while awaiting surgery after therapy withdrawal.[6] The optimal management of these patients is unclear and has been matter of debate in recent years.

Most studies advise against surgery within 24 hours after discontinuation of clopidogrel, if the patient is stable, to avoid the significant risk of major bleeding complications.[4,7]

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Abbreviations and Acronyms

ACCF = American College of Cardiology Foundation
ACS = acute coronary syndrome
ACT = activated clotting time
AHA = American Heart Association
CABG = coronary artery bypass graft
CI = confidence interval
CT = closure time
FFP = fresh frozen plasma
INR = Internationalized normalized ratio
OR = odds ratio
PCI = percutaneous coronary intervention
PRBC = packed red blood cells
SCAI = Society for Cardiovascular Angiography and Interventions

However, data on bleeding risk if CABG is performed between 24 hours and 5 days after clopidogrel cessation are conflicting. Some studies suggested that a 3-day delay could suffice to avoid bleeding risk and obtain safe outcomes.[7-10] In contrast, other investigators reported a significantly increased bleeding risk if CABG is performed within 5 days of clopidogrel cessation.[11,12] These different results can likely be attributed to the considerable intra- and interindividual variability of clopidogrel-induced antiplatelet response; some individuals have suboptimal platelet inhibition despite an adequate dosage of clopidogrel, whereas others have delayed recovery of platelet function after clopidogrel cessation.[3]

This study evaluated the possibility of reducing postoperative blood loss and blood product consumption in patients treated with clopidogrel undergoing urgent CABG for ACS. We hypothesized that individualized point-of-care platelet function testing could provide a useful guide to optimal timing for surgery after discontinuation of antiplatelet therapy.

METHODS

This case-control study was designed according to the STROBE (Strengthening the Reporting of Observational Study Epidemiology) statement. The protocol was approved by the institutional ethics committee. All patients were enrolled prospectively and provided written informed consent. For the control patients, selected retrospectively, the institutional review board approved the use of the database for research; hence, the need for individual patient consent was waived for this study. All patients had preliminarily granted permission for the use of their medical records for research purposes.

Patient Population and Study Groups

From October 2012 to February 2013, 100 consecutive patients (group A) scheduled for CABG surgery for ACS at the Department of Cardiac Surgery of University Federico II in Naples, who were under clopidogrel treatment (single therapy or combined with aspirin 100; 325 mg/d) and met the inclusion criteria, were prospectively enrolled in the study. The exclusion criteria are listed in Table 1. Clopidogrel was suspended once the indication for CABG was established and the waiting time for surgery was guided by a point-of-care platelet function test. According to guidelines, aspirin was not discontinued before surgery.[4,5]

Group A was compared with 2 control groups based on 1:1:1 matching (100 patients in each group). These patients underwent CABG surgery between January and September 2012. Group B consisted of 100 patients who underwent CABG for ACS, were taking a daily oral dose of clopidogrel (75 mg/d) alone or in addition to aspirin (100-325 mg/d) preoperatively, and were managed in accordance with current guidelines; clopidogrel was suspended 5 days before surgery, whereas aspirin was continued.[4,5] Group C consisted of 100 controls who underwent elective CABG and were not taking thienopyridine therapy. Group B and group C were collected retrospectively from our institutional database To obtain 3 homogeneous groups and eliminate confounding bias caused by unequal distribution of clinical and demographic characteristics among groups, patient selection was performed by propensity score matching.

The main clinical and demographic characteristics of the patients are described in Table 2. Group A and group B were homogeneous for age, sex, clinical history, clinical presentation, medical therapy, preoperative risk factors, coronary lesions, surgical procedures, and risk factors for bleeding. Group C was mainly different for clinical presentation, preoperative risk factors, medical therapy, overall risk factors for bleeding and, therefore, was highly significant as control.

All surgical procedures were performed off-pump by the same group of experienced surgeons through a median sternotomy. The surgical technique was similar for all patients. The left thoracic artery was the conduit of choice. The right thoracic artery and the radial artery were used whenever indicated. Thoracic arteries were harvested in skeletonized fashion. Before anastomosis, patients received 150 IU heparin/kg body weight to obtain a kaolin activated clotting time (ACT) of longer than 400 seconds. Protamine sulfate was administered to reverse the heparin effect with the goal of normalizing the ACT. A cell salvage device was used during the surgery in all cases and salvaged blood was reinfused. Perioperative management was according to our institutional standards and was similar in all patients. Dual antiplatelet therapy with aspirin 100 mg and clopidogrel 75 mg was started when postoperative chest tube drainage was less than 50 mL/h for 2 consecutive hours and was continued daily.[13]

Complete blood count and a coagulation panel, including prothrombin time, partial thromboplastin time, thrombin time, and blood fibrinogen concentrations, were analyzed preoperatively immediately on arrival at the intensive care unit and every 6 hours of the first 2 postoperative days or more frequently if required. To recognize heparin rebound or inadequate heparin neutralization, ACT was analyzed immediately on arrival at the intensive care unit, every 3 hours for the first 12 hours, and every 6 hours thereafter. Further evaluations of the ACT followed the administration of protamine sulfate given with the goal of normalizing the ACT. Chest tube drainage was registered at 6, 12, 24, and 36 postoperative hours. Blood loss volume per patient was assessed after the first 36 postoperative hours (shed blood was never reinfused). Postoperative transfusion rates and quantities were recorded for the principal blood product types, including packed red blood cells (PRBCs), platelets, fresh frozen plasma (FFP), and cryoprecipitate. Factor VII or other agents were not used routinely.

Transfusion of blood products and management of postoperative bleeding were determined by following an institutional algorithm. PRBCs were transfused when the patient's blood hemoglobin level was less than 6 g/dL for patients younger than 65 years or of less than 7 g/dL for patients older than 65 years. When the hemoglobin level was between 7 and 10 g/dL, PRBCs were transfused in cases of bleeding with symptoms of hypovolemia, decreased oxygen saturation in mixed venous blood unrelated to systemic oxygenation, and when signs of myocardial ischemia ere present.[14] Postoperative bleeding was managed as follows: (1) preliminary