Clopidogrel Treatment Before Coronary Artery Bypass Graft Surgery Increases Postoperative Morbidity and Blood Product Requirements

Farzan Filsoufi, MD,* Parwis B. Rahmanian, MD,* Javier G. Castillo, MD,* Ronald A. Kahn, MD,† Gregory Fischer, MD,† and David H. Adams, MD*

Objectives: **An increasing number of patients are referred for coronary artery bypass graft surgery while treated with clopidogrel. This agent inhibits the platelet P2Y12 adenosine-5′-diphosphate (ADP) receptor, which results in an inhibition of platelet aggregation. The aim of this study was to determine the effect of preoperative clopidogrel treatment on postoperative bleeding, mortality, and morbidity in patients after coronary artery bypass graft surgery.**

Design: **Retrospective cohort study.**

Setting: **University hospital (single institution).**

Participants: **One hundred forty-four patients who underwent isolated coronary artery bypass graft surgery.**

Interventions: **Seventy-two patients who received clopidogrel during the preoperative period formed the study group. Seventy-two patients (matched based on age, sex, and preoperative risk profile) served as the control group.**

Measurements and Main Results: **Clopidogrel-treated patients received significantly more platelet (4.4 ± 5.7 *v* 1.3 ± 3.2 U, $p < 0.001$) and red blood cell (5.1 ± 4.2 *v* 2.6 ± 2.6 U, $p < 0.001$) transfusions compared with the control group. All-cause mortality and morbidity were significantly higher in clopidogrel-treated patients (n = 7, 9% *v* n = 1, 1%; $p = 0.031$). In addition, the lengths of stay in the intensive care unit and the hospital were significantly longer in these patients (2.5 ± 2.7 *v* 1.4 ± 0.9 days, $p = 0.002$; 9.9 ± 11 *v* 6 ± 2.5 days, $p = 0.003$). Despite an increased morbidity in the clopidogrel group, the midterm survival was similar between the 2 groups (1-year and 5-year survival 97% ± 2% and 95.7% ± 3% *v* 100% ± 0% and 87% ± 10%, respectively; $p = 0.885$).**

Conclusions: **Preoperative clopidogrel is associated with increased transfusion requirement after coronary artery bypass graft surgery. The present data suggest that all-cause mortality and major morbidity may also increase in these patients. In clopidogrel-treated patients, coronary artery bypass graft surgery should be delayed in the absence of specific medical indications as recommended by recent American Heart Association guidelines.**

KEY WORDS: coronary artery bypass graft surgery, clopidogrel, bleeding, mortality, morbidity

PERCUTANEOUS CORONARY INTERVENTION (PCI) has become the preferred therapeutic approach in many patients with severe coronary artery disease. Periprocedural and 1-month treatments with clopidogrel are administered after PCI with bare metal stents to reduce the risk of early stent thrombosis.[1] More recently, the new-generation drug-eluting stents were introduced into clinical practice to reduce the rate of in-stent restenosis. However, it has been suggested that they are associated with a higher rate of late stent thrombosis. In patients who have received a drug-eluting stent, it is recommended to continue treatment with clopidogrel for at least 1 year.[1] The administration of a loading dose of clopidogrel is also beneficial in patients with a non–ST-elevation acute coronary syndrome (NSTE ACS). In the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events trial, it has been shown that patients who received aspirin and clopidogrel within 24 hours of onset of NSTE ACS had an improved outcome with a reduced rate of a composite of mortality and cardiovascular morbidity (9.3%) compared with patients with only aspirin (11.4%, $p < 0.001$).[2]

Currently, an increasing number of patients are referred for coronary artery bypass graft (CABG) surgery while they are treated with clopidogrel. The potential impact of this preoperative treatment on surgical outcome has not been investigated completely. A few studies have suggested that CABG surgery in patients receiving clopidogrel is associated with increased postoperative blood loss and blood products requirements[3,4]; however, the impact of clopidogrel treatment before CABG surgery on postoperative mortality and morbidity remains largely unknown.[5,6]

Herein, the authors report their experience in a recent cohort of patients who underwent CABG surgery and were treated with clopidogrel preoperatively, with an emphasis on bleeding complications, transfusion requirements, hospital outcome, and late survival. The authors particularly analyzed postoperative morbidities that may be related directly to bleeding complications and blood transfusions.

METHODS

The authors conducted a retrospective study among 2,725 consecutive patients who underwent isolated CABG procedures at the authors' institution between January 1998 and December 2005. The protocol was approved by the local institutional review board and complied with the Health Insurance Portability and Accountability Act regulations and the ethical guidelines of the 1975 declaration of Helsinki, as revised in 2000. The approval included a waiver of informed consent.

Clinical variables were prospectively entered into the New York State Department of Health (NYSDH, State Cardiac Advisory Committee) data registry. The NYSDH data registry represents a mandatory verified peer-reviewed data-collection system including all adult cardiac surgery procedures in the state New York and records and analyzes data in a strictly supervised and widely reported fashion. Patient demographics and risk factors, operative information, and postoperative outcome data were retrospectively analyzed. Additional information was obtained from patient charts when necessary. Follow-up survival information was obtained by crossmatching patients' social security numbers with the Web-based social security death index. Table 1 summarizes preoperative variables included in this study and their definition as indicated.

A total of 72 patients with clopidogrel treatment at the time of surgery were identified and served as the study group. This included patients in whom clopidogrel was discontinued within 72 hours of

*From the Departments of *Cardiothoracic Surgery and †Anesthesiology, Mount Sinai School of Medicine, New York, NY.*

Address reprint requests to Farzan Filsoufi, MD, Department of Cardiothoracic Surgery, Mount Sinai School of Medicine, 1190 Fifth Avenue, Box 1028, New York, NY, 10029. E-mail: Farzan.filsoufi@mountsinai.org

1053-0770/08/2201-0012$34.00/0

doi:10.1053/j.jvca.2007.10.009

Table 1. Variables Included in this Study

Variables
Age
Sex
Preoperative variables
Weight (kg)
Height (cm)
Body Mass Index (kg/m^2)
Diabetes mellitus requiring medication
Hypertension
Preoperative renal insufficiency (creatinine >2.5 mg/dL or dialysis)
Prior cerebrovascular accident
Peripheral vascular disease
Chronic obstructive pulmonary disease
Hepatic failure (Liver disease and bilirubin >2 mg/dL and albumin <3.5 g/dL)
Prior myocardial infarction
Prior cardiac surgery
Congestive heart failure (NYHA class III and IV)
Active endocarditis
Ejection fraction (%)
Urgent operation (requiring operation during current hospitalization)
Emergent operation (refractory unrelenting cardiac compromise requiring emergency operation)
Preoperative intra-aortic balloon pump
Intraoperative variables
Type of procedure (conventional CABG, off-pump CABG)
Cardiopulmonary bypass time
Cross clamp time (X-clamp time)
Number of grafts
Postoperative variables
Hospital mortality
Renal failure (Creatinine >2.5 mg/dL more than 7 days or dialysis)
Respiratory failure (prolonged ventilator therapy (>72 h), reintubation or tracheostomy)
Stroke (new permanent neurological event)
Postoperative myocardial infarction
Bleeding requiring reoperation
Deep sternal wound infection
Unplanned reoperation
Gastrointestinal complication
Length of hospital stay

Abbreviations: CABG, coronary artery bypass grafting; NYHA, New York Heart Association.

surgery. To create an appropriate comparison group, patients without clopidogrel treatment who underwent isolated CABG surgery during the same timeframe were selected if age, sex, ejection fraction, and predicted mortality by EuroSCORE were within the same range as the clopidogrel cases. SAS software (SAS Institute Inc, Cary, NC) was used to create a random sample. Using this technique, 72 patients without clopidogrel treatment at the time of surgery with similar demographics and risk profile were identified and served as the control group.

Outcome measures for this study included hospital mortality, postoperative bleeding and major complications (respiratory failure, renal failure, deep sternal wound infection, stroke, and gastrointestinal complications), time on ventilator, length of stay in the intensive care unit, and hospital and late survival. Hospital mortality was defined as death after the procedure before patient discharge regardless of the duration of hospitalization. Patients who died after discharge from the hospital but within 30 days after the procedure were also considered as hospital deaths. Bleeding was assessed by chest-tube output within 48 hours after surgery, transfusion requirements, and the need for reoperation. Respiratory failure was defined as prolonged ventilator therapy (>72 hours) or the need for reintubation or tracheostomy. Renal failure was defined as creatinine >2.5 mg/dL for more than 7 postoperative days or the need for dialysis. Stroke was defined as a new permanent neurologic event occurring peri- or postoperatively. The definition of these complications was based on the NYSDH data-registry definitions.

All procedures were performed by using standard anesthetic and surgical techniques adapted to the individual procedures. Anesthesia was induced with midazolam, 40 to 60 μg/kg, and fentanyl, 20 μg/kg. After induction, anesthesia was maintained with isoflurane. A small skin incision and a full sternotomy were performed in all patients. Twenty-six percent (n = 38) of procedures were performed without the use of cardiopulmonary bypass (CPB) (off-pump coronary artery bypass). The remaining 74% (n = 106) procedures were performed by using CPB.

After systemic heparinization obtained an activated coagulation time of at least 400 seconds, CPB was established between the ascending aorta and the right atrium by using a 2-stage cannula. During CPB, a minimum flow of 2.2 L/min/m^2 and a perfusion pressure of >60 mmHg were maintained in all patients. After aortic cross-clamp and cardioplegic arrest, distal anastomoses were performed first followed by proximal anastomoses using the single cross-clamp technique. Aortic cross-clamp was released thereafter, and patients were weaned from CPB after a short reperfusion.

Off-pump CABG surgery was performed based on the surgeon's preferences. However, this technique was favored in elderly patients, particularly those with significant comorbidities such as renal dysfunction. In patients undergoing off-pump coronary artery bypass, heparin was administered to achieve an activated coagulation time of 300 seconds. Coronary stabilizer and cardiac positioning devices were used to improve the exposure of the coronary arteries and to facilitate the distal anastomoses under beating-heart conditions. Intracoronary shunts were inserted to avoid myocardial ischemia during the construction of the distal anastomoses. Proximal anatomoses were created using a side-bite clamp. Protamine was administered based on the heparin level after the completion of the coronary anastomoses.

Antifibrinolytic therapy consisted of ε-aminocaproic acid in 138 (96%) patients, whereas aprotinin was administered in only 6 (4%) patients; all the latter were clopidogrel recipients. A loading dose of ε-aminocaproic acid (150 mg/kg) was administered for 30 minutes followed by a continuous infusion of 15 mg/kg/min. No ε-aminocaproic acid was added to the CPB circuit prime. The infusion was continued until the end of surgery. Aprotinin was administered at a loading dose of 2,000,000 KIU intravenously for a 30-minute period. After completion of the loading dose, a maintenance dose of 500,000 KIU was started and continued until the surgical procedure was finished. In addition 2,000,000 KIU were added to the CPB circuit prime. The decision regarding the administration of ε-aminocaproic acid or aprotinin was based on the individual cardiac surgeon's and anesthesiologist's preference.

Postoperatively, all patients were transferred to the intensive care unit. Patients were weaned from the ventilator when hemodynamic stability was achieved, no major postoperative bleeding (chest tube output <100 mL/h), no signs of tamponade, and no evidence for hemothorax in chest x-ray occurred, and adequate consciousness was obtained.

Red blood cell transfusions and the administration of blood products such as platelets, fresh frozen plasma, and cryoprecipitate were based on individual physician's preference. The authors did not use a specific bleeding management algorithm in this study.

Normally distributed continuous variables are presented as mean ± standard deviation and otherwise as median ± interquartile range. Categoric variables are shown as the percentage of the sample. A