Impact of clopidogrel use on mortality and major bleeding in patients undergoing coronary artery bypass surgery

Nahum Nesher¹*, Steve K. Singh², Hosam F. Fawzy², Jeri Y. Sever³, Bernard E. Goldman⁴, Gideon N. Cohen⁵, Claude Lafamme⁶, Stephen E. Freams⁷

¹Division of Cardiac and Vascular Surgery, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Suite H410, Toronto, Ontario, M4N 3M5, Canada
²Division of Cardiac Surgery, St. Michael’s Hospital, University of Toronto, Toronto, Canada
³Anesthesia and Transfusion Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada

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Abstract

Patients who received clopidogrel prior to coronary bypass surgery are at increased risk for bleeding that must be balanced with risk of ongoing ischemia if coronary artery bypass grafting is delayed. This study aimed to evaluate the impact of clopidogrel on mortality and major bleeding in patients undergoing urgent coronary bypass surgery. We reviewed 451 consecutive patients who underwent urgent isolated coronary bypass surgery; 262 had not received clopidogrel, whereas 189 received clopidogrel ≤5 days preoperative. The primary endpoint was in-hospital death, massive transfusion or massive blood loss. Patient characteristics were almost similar between groups. There was no difference in in-hospital death or massive bleeding indices between groups (clopidogrel: 7% vs. no clopidogrel: 6%, P = 0.9). No difference was observed even after adjusting for the date of stopping clopidogrel preoperatively. Multivariate regression analysis showed that clopidogrel or the duration it was stopped preoperatively did not predict adverse outcomes. Significant independent predictors included preoperative renal dysfunction, hemoglobin level and peripheral vascular disease. clopidogrel, or the time it was stopped prior to surgery, was not a risk factor for in-hospital death, massive bleeding, or other poor early outcomes in patients undergoing urgent coronary artery bypass surgery.

Keywords: Clopidogrel; Bleeding; Coronary artery bypass surgery; Mortality

1. Introduction

Clopidogrel is a potent antagonist of platelet adenosine diphosphate (ADP)-receptors. It achieves significant inhibition of platelet aggregation within 2–5 h after typical oral doses [1]. Since clopidogrel is often given before angiography and percutaneous coronary interventions (PCIs), patients may be referred for surgery with the additional handicap of an irreversible platelet inhibition that lasts about 5–7 days [2]. The multi-national GRACE registry showed that 7% of non-ST elevation myocardial infarctions (NSTEMI) and 4% of STEMI patients receive coronary artery bypass grafting (CABG) surgery during their hospital admission [3]. Most of these patients receive clopidogrel upon first presentation of their acute coronary syndrome in the emergency department to reduce morbidity and mortality from ongoing ischemia [3]. Many patients are also receiving long-term clopidogrel with or without aspirin for secondary prevention of coronary or cerebrovascular ischemic events, many of whom may require surgical coronary revascularization [4].

Studies have shown that treatment with clopidogrel before CABG is associated with increased postoperative bleeding, transfusion, re-exploration rates, overall lengthier hospital stays and increased mortality [5]. Thus, the cardiac surgical team is often reluctant to operate on these patients given the increased bleeding risk.

The primary objective of this study was to examine bleeding indices, morbidity and mortality in a large series of patients undergoing urgent CABG, with contemporary cardiac surgical practices, as a function of clopidogrel use. Our secondary objective was to determine if the timing that clopidogrel was stopped prior to surgery influenced clinical outcomes.

2. Materials and methods

Institutional ethics approval was granted to perform a retrospective review of 451 consecutive patients undergoing isolated CABG surgery on an urgent basis at our institution, between April 2005 and January 2008. Ethics Board waived the need for individual patient consent requirement due to the nature of the study design. Demographic,
preoperative, operative characteristics and in-hospital outcomes were collected prospectively in an institutional database. Charts for patient deaths were individually retrieved and reviewed to ascertain, whether bleeding was the cause for death. Of the 451 patients who underwent urgent isolated CABG, 262 (58%) did not receive clopidogrel prior to surgery, while the remaining 189 (42%) received clopidogrel ≤5 days prior to CABG.

2.1. Operative technique

Patients were standardized in their anesthesia, induced with fentanyl and midazolam and maintained with propofol and isoflurane. All were ventilated with preset standard ventilator parameters. The alpha-stat acid base management was adopted when cardiopulmonary bypass (CPB) was applied. Heparin (300 U/kg) was administered to maintain the activated clotting time >480 s. During CPB, the body temperature was allowed to drift to 32–34 °C. Cardiac arrest was induced and maintained with antegrade cold or tepid blood cardioplegia. Intraoperative heparin monitoring was performed by standard activated clotting time (Hemochron 8). Protamine was administered to reverse heparin according to standard practice (1 mg/1 mg heparin given before and during CPB). Full dose Trasylol (Aprotinin™, Bayer) was administered before and during the operation in all patients who had received clopidogrel prior to CABG in order to minimize postoperative bleeding. Anti-fibrinolytic therapy was used for all other urgent patients in the non-clopidogrel group; however, this was primarily tranexamic acid (Cyclocapron™).

Postoperatively all patients received aspirin (325 mg daily) and low molecular weight heparin (2500 U daily) 12 h after surgery.

2.2. Endpoints

The primary endpoint was the composite endpoint of death, massive transfusion or blood loss. Death was defined as 30-day mortality. Massive transfusion was defined as a transfusion of 10 U of red cells or greater, which represented two standard deviations (S.D.) above the mean number of red blood cells transfused for isolated cardiac surgery in our institution. Excessive blood loss was defined as >2 l of chest tube loss in the first 24 h, which corresponded to 2 S.D. above the mean for 24 h chest tube loss following isolated coronary surgery in our institution.

2.3. Statistical analyses

Categorical patient variables were compared using the χ²-test or Fisher’s exact test where appropriate and are reported as percentages. The mean±S.D. of continuous variables were compared using Student t-tests for normally distributed variables and Wilcoxon rank test was used for variables that had non-parametric distribution. One-way analysis of variance was used to ascertain the impact of the day clopidogrel was stopped on clinical outcomes. Independent predictors of our primary and secondary outcomes were determined using multivariable logistic regression analysis. Models were constructed in a clinically relevant, parsimonious manner with subsequent elimination of non-significant determinants (P>0.1). Significance was assumed for P<0.05. SAS version 8.2 statistical software (Cary, NC) was used.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

3. Results

3.1. Patient characteristics

Between April 2005 and January 2008, 451 cases, or 60% of all isolated CABG procedures, were performed on an urgent basis. Of these, 262 (52%) were patients who did not receive clopidogrel prior to CABG, or received a dose >5 days prior. There were 189 patients (48%), who received clopidogrel ≤5 days prior to CABG.

Patient demographics, preoperative and operative characteristics are listed in Table 1. The patients receiving clopidogrel were significantly more likely to have had a previous myocardial infarction (MI), a previous PCI, or have NYHA class ≥3 symptoms. Despite cross-clamp times being longer in the group receiving clopidogrel, there was no difference in CPB or total operative times.

3.2. Early outcomes

Table 2 lists the early outcomes comparing patients in the clopidogrel vs. the non-clopidogrel groups. There was no difference in mortality [non-clopidogrel: 6 (2%) vs. clopidogrel: 6 (3%), P=0.6]. Detailed chart review of the deaths in both groups found no difference in bleeding as a cause, or significant contributor to death. Outcomes related to MI, bleeding and hospital and intensive care unit (ICU) length of stays were not different between groups. In addition, there was no difference in the primary outcome or other endpoints when the specific discontinuation date of clopidogrel was analyzed (Table 3).

3.3. Predictors of outcomes

The results of multivariable logistic regression are listed in Table 4. The use of clopidogrel, or the timing of its stoppage prior to isolated, urgent CABG, was not a significant independent predictor of the combined endpoint, or other endpoints of interest (mortality, postoperative MI, or chest re-opening). Preoperative renal dysfunction, peripheral vascular disease and lower preoperative hemoglobin were independent predictors of the combined endpoint of 30-day mortality, massive bleeding or massive blood transfusion.

4. Discussion

We report the largest evaluation of clopidogrel use as a function of perioperative outcomes in patients undergoing urgent CABG surgery. Our results indicate that clopidogrel, or the time it was stopped preoperatively, were not significant independent risk factors for excessive bleeding or poor outcome in patients requiring urgent CABG. We hypothesize that routine use of aprotinin along with more
attentive surgical technique may serve to ameliorate the adverse impact of clopidogrel on bleeding in these patients.

Clopidogrel, a thienopyridine antiplatelet agent, inhibits ADP-dependent platelet activation and aggregation has been demonstrated to reduce ischemic events and mortality in patients with coronary and vascular disease [2–4, 6] as well as being shown most potent at reducing cardiovascular death, MI or stroke, in patients presenting with acute coronary syndromes, compared to aspirin treated alone (the clopidogrel in unstable angina to prevent recurrent...
ischemic events) [7]. Subgroup analysis from these trials suggested that patients who underwent surgical revascularization also benefited from clopidogrel [8]. Since publication of these studies, chronic clopidogrel administration in patients with atherosclerotic disease, prior coronary stenting, or both, has become common. Furthermore, the results of the CURE trial strongly suggested adding clopidogrel to aspirin as soon as possible after hospital admission for management of unstable angina and MI without ST-segment elevation, or both. Several recent studies have demonstrated that clopidogrel use (with or without the synergistic antiplatelet effects of aspirin), within four days of CABG significantly increases blood loss, reoperations for bleeding, and transfusion requirements for red blood cells, plasma, and platelets [5, 10–12].

Cardiologists argue that acutely withdrawing clopidogrel in unstable patients prior to urgent CABG may provoke further myocardial ischemia [11]. Surgeons, however, are justifiably concerned of putting patients at risk of perioperative bleeding, mediastinal tamponade, and blood product use (with its attendant risks) [5, 10, 11]. The American College of Cardiology/American Heart Association 2004 guideline update for CABG surgery [13], states that ‘If clinical circumstances permit, clopidogrel should be withheld for five days before performance of CABG surgery’ (class I recommendation, level of evidence: B). This recommendation applies mainly in elective CABG patients; however, the management of unstable patients on clopidogrel remains uncertain. Recent data indicate that as many as 5% of patients presenting with acute coronary syndrome (ACS) may require urgent surgery with clopidogrel [10].

In our study population, clopidogrel was discontinued somewhere between five days and the surgical intervention day. For those patients who did undergo urgent CABG <5 days after clopidogrel was given, the relative risk of major or life-threatening bleeding was found to be equal to the non-treated group. We anticipated that the degree of bleeding would correlate inversely with the number of days since the last clopidogrel exposure; however, the time of stopping clopidogrel had no impact on perioperative bleeding, major morbidity or mortality in our analysis. Since the entire clopidogrel group received aprotinin, we hypothesized that this may be one important feature that might be different inhibitory levels for a clopidogrel at a given dose [1], a fact which might explain our results. However, since neither platelet function data nor clopidogrel
grel plasma levels were available in this study, it is difficult to match the group with respect to thrombotic biology or clopidogrel kinetics, although the majority of the patients received a 300 mg loading dose in the treated group.

Lately, due to a report of negative impact on long-term survival in patients who received aprotinin, the drug has been temporarily withdrawn from the market in some countries, until further evaluation by the authorities [14, 15]. Nevertheless, as we were obliged to convert to tranexamic acid whenever surgery had to be performed, while patients received clopidogrel, we still find the less potent anti-fibrinolitic effective (given in the correct dose).

Irrespective of the mechanism, our data, which represents the largest single center experience on this topic, suggest that clopidogrel used ≤5 days prior to surgery does not adversely impact bleeding or perioperative morbidity and mortality. We suggest that urgent CABG surgery can be performed safely in such patients, with routine aprotinin use, without delay.

References