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Effects of Continuous Administration of Clopidogrel Before Off-Pump Coronary Artery Bypass Grafting in Patients With Acute Coronary Syndrome

— A Propensity Score Analysis —

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Background Clopidogrel has become standard treatment after urgent percutaneous coronary revascularization. Due to its enhanced and irreversible platelet inhibition, patients undergoing urgent surgical revascularization have a higher risk of bleeding complications and transfusions. Therefore, the effect of preoperative continuous administration of clopidogrel on the incidence of hemorrhagic complications in patients undergoing off-pump coronary artery bypass surgery with acute coronary syndrome was evaluated.

Methods and Results From March 2004 to September 2006, 172 patients with acute coronary syndrome underwent isolated off-pump coronary artery bypass surgery; 70 (40.7%) and 102 (59.3%) of these patients did or did not take clopidogrel before surgery respectively. Seventy patients in each group were matched using propensity scores and associations between preoperative continuous administration of clopidogrel and postoperative bleeding, hemostatic reoperation, blood products received, the need for multiple transfusions and early graft patency by coronary computed tomography were assessed. Univariate analysis showed the continuous clopidogrel group had similar levels of postoperative bleeding for 24 h (601.4±312.6 ml vs 637.2±452.4 ml, p=0.616) and rates of reexploration (1.4% vs 1.4%), perioperative blood transfusion (33.3% vs 34.3%, p>0.05) and platelet transfusion (2.9% vs 7.1%, p=0.44) compared with the non-continuous group.

Conclusions Preoperative continuous administration of clopidogrel did not increase the risk of hemorrhagic complications in patients with acute coronary syndrome undergoing isolated off-pump coronary artery bypass surgery. These findings indicate that surgery after clopidogrel treatment in patients with acute coronary syndrome should not be delayed until platelet function returns to normal because they may have a higher risk of recurrent myocardial ischemic events. (*Circ J* 2008; **72:** 626–632)

Key Words: Acute coronary syndrome; Clopidogrel; Coronary artery bypass; Off-pump

The use of platelet aggregation inhibitors, including aspirin, glycoprotein IIb/IIIa inhibitors and clopidogrel, has become a standard management strategy for patients with acute coronary syndrome. In a recent prospective randomized controlled study, clopidogrel significantly reduced the risk of cardiovascular death, myocardial infarction, stroke and other related ischemic events in patients with acute coronary syndrome. Clopidogrel demonstrated benefits incremental to and independent of other therapies, including anticoagulants, angiotensin-converting enzyme inhibitors, β-blockers and lipid-lowering agents! These findings indicate that all patients with acute coronary syndrome should benefit from the favorable effects of clopidogrel, without exception and without delay, if possible during the prehospitalization period.

Clopidogrel treatment may also be beneficial for patients who have not had the opportunity to undergo coronary angiography with subsequent percutaneous coronary intervention (PCI) and who are dependent on thrombolytic therapy, as well as those who require urgent surgical revascularization. Some of these patients will subsequently require urgent or emergent surgical revascularization. Due to the enhanced and irreversible platelet inhibition produced by clopidogrel, which is frequently present in patients requiring coronary artery bypass graft (CABG) surgery, the use of this agent has become a concern[2,3] Patients exposed to clopidogrel have been reported to experience markedly increased postoperative bleeding and transfusion requirements, in addition to a nearly 10-fold increase in reexploration rates after CABG surgery, thus raising the question of the appropriate timing of the cessation of clopidogrel before CABG surgery[2–4]

Bleeding after CABG may be due to inadequate surgical hemostasis, coagulation and/or platelet abnormalities[5] Exposure to cardiopulmonary bypass (CPB) causes dilutional thrombocytopenia, coagulopathy, shear-induced platelet dysfunction, a systemic inflammatory response and activation of plasminogen, and the safety and efficacy of off-pump CABG (OPCAB) have been confirmed[6–15] By eliminating the deleterious effects of CPB, OPCAB surgery has been found to result in a 2-fold reduction in postoperative

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bleeding, lower surgical reexploration rates and a 25% decrease in transfusion requirements.[16,17] Clopidogrel, however, may reduce these advantages of OPCAB surgery by increasing perioperative hemorrhagic complications. Our colleagues recently reported favorable outcomes of the continuous use of clopidogrel in patients undergoing elective surgery for isolated OPCAB, but that study excluded patients with acute coronary syndrome![8] Consequently, the present study was conducted to ascertain the effect of preoperative continuous administration of clopidogrel and aspirin on the incidence of reexploration as a result of hemorrhage, perioperative transfusion requirements, morbidity and mortality in patients undergoing OPCAB, especially due to acute coronary syndrome.

Methods

We searched the cardiac surgery research database at our institution for all patients who underwent isolated OPCAB surgery due to acute coronary syndrome between March 2004 and September 2006. Acute coronary syndrome included the diagnosis of unstable angina or recent myocardial infarction. Patients who underwent mini-lateral thoracotomy, surgical ventricular restoration and other concomitant surgical procedures were excluded, as were patients with recent preoperative exposure to coumadin, platelet glycoprotein inhibitors or thrombolytics. The search identified a total of 172 consecutive eligible patients with acute coronary syndrome, all of whom had been treated by a single experienced OPCAB surgeon (KJY). Preoperative patient characteristics and perioperative outcomes had been collected prospectively during hospitalization and entered into the cardiac surgery research database as part of routine clinical practice. The present study was approved by the Institutional Review Board of Medical College of Yonsei University, which waived the requirement for individual patient consent.

In our center, all patients with unstable angina or recent myocardial infarction receive an oral loading dose of 600 mg clopidogrel and 500 mg aspirin before diagnostic or therapeutic coronary angiography. They are maintained on a daily oral regimen of 75 mg clopidogrel and 100 mg aspirin independent of emergent or non-emergent cases. Patients who continued taking 2 antiplatelet agents until immediately before surgery were classified as the continuous group, whereas patients whose surgery was postponed at least 3 days (mean: 4.3±1.2; median: 4; range: 3–7 days) after discontinuing clopidogrel were classified as the non-continuous group. All patients in both groups continued taking aspirin before surgery. In our institute, OPCAB was performed as soon as possible, especially for patients with unstable angina or recent myocardial infarction. Intraoperative heparin anticoagulation was used in both groups, at an initial dose of 1 mg/kg, with additional dosing administered during the procedure to maintain a target activated clotting time of more than 350 s. At the end of surgery, half heparin reversal with protamine was performed. In almost all patients, clopidogrel and aspirin were resumed 6 h after surgery. A history of gastrointestinal bleeding disorders or peptic ulcer disease was considered an absolute contraindication to immediate postoperative clopidogrel administration. Similarly, those patients with chest tube output greater than 100 ml/h were not considered for immediate postoperative clopidogrel administration. Patients considered at high risk for recurrent ischemic events, according to the attending surgeon's assessment, received postoperative heparin. Factors that led surgeons to prescribe postoperative heparin included technically difficult anastomosis, very small (<1.0 mm) or calcified distal target vessels, severe diffuse atherosclerosis, a history of peripheral or cerebrovascular disease, a history of percutaneous coronary revascularization and diabetes mellitus. However, there were no standardized criteria and the decision to prescribe postoperative heparin was ultimately made according to the surgeon's perception of risk.

Operative Techniques

All patients underwent general endotracheal anesthesia with continuous Swan-Ganz catheter monitoring, transesophageal echocardiography and arterial pressure monitoring. Off-pump coronary artery bypass surgery was performed through a full sternotomy incision with skeletonized harvesting of the left internal thoracic artery. The radial artery was harvested from the non-dominant forearm using a Harmonic scalpel (Ethicon Endosurgery Inc, Cincinnati, OH, USA). The right internal thoracic artery, saphenous vein and/or right gastroepiploic artery were also harvested if necessary. The target arteries were stabilized using an Octopus tissue stabilizer (Medtronic, Minneapolis, MN, USA). In most instances, the left internal thoracic artery was first anastomosed to the left anterior descending artery using intra-coronary shunts. A proximal silastic snare was used to anastomose other coronary arteries. Blood was removed from the sites of arteriotomy using a misted CO_2 blower and irrigation with warm saline.

Hemorrhagic Outcomes

The primary end point was the need for reexploration as a result of bleeding, exclusive of any other cardiac or non-cardiac cause. Reexploration due to hemorrhage was indicated when chest tube drainage exceeded 500 ml in the first hour, 400 ml/h in the first 2 h, 300 ml/h in the first 3 h or 200 ml/h in the first 4 h or in the case of cardiac tamponade. Ultimately, the decision for hemorrhagic reexploration was made by the surgeons, who used a uniform clinical practice. In cases of increased intraoperative bleeding, steps taken to achieve hemostasis included examination for surgical causes of bleeding; administration of protamine for adequate heparin reversal to normalize activated clotting time; and transfusion with packed red blood cells (pRBC). Aprotinin, aminocaproic acid and other hemostatic agents were not routinely used. A cell saver was used to process salvaged blood, and blood collection by cardiotomy suction continued until closure of the sternal wound. Intra- and postoperative transfusion rates and quantities were recorded for principal blood products, including pRBCs, platelets and fresh frozen plasma (FFP). The volume of blood captured and reinfused intraoperatively by a cell salvage device was not evaluated, but intraoperative blood loss was. Allogenic pRBC were transfused when the hematocrit level was less than 25% for patients 65 years of age or older, and when the hematocrit level was less than 21% for patients younger than 65 years of age throughout the present study period. FFP was transfused when the postoperative international normalized ratio was greater than 1.5 with excessive bleeding greater than 200 ml/h for 2 consecutive hours. The criteria for transfusion of platelets were postoperative platelet count less than 50,000/mm^3 with excessive bleeding greater than 200 ml/h for 2 consecutive hours. Additional blood product transfusions were at the discretion of the surgeon, anesthesiologist or intensivist.

Table 1 Patient Demographic and Preoperative Characteristics, Unadjusted and Adjusted for Propensity Score Matching

	Unadjusted			*Adjusted*		
	Continuous (n=70)	*Non-continuous (n=102)*	*p value*	*Continuous (n=70)*	*Non-continuous (n=70)*	*p value*
Age (years)	*63.5±9.6*	*63.4±9.6*	*0.948*	*63.5±9.6*	*63.8±9.1*	*0.864*
Female	*17 (24.3)*	*43 (42.2)*	*0.016*	*17 (24.3)*	*20 (28.6)*	*0.702*
3-vessel disease	*54 (77.1)*	*90 (88.2)*	*0.061*	*54 (77.1)*	*59 (84.3)*	*0.392*
Left main disease	*22 (31.4)*	*38 (37.3)*	*0.515*	*22 (31.4)*	*21 (30.0)*	*1.000*
Recent MI	*22 (31.4)*	*37 (36.3)*	*0.519*	*22 (31.4)*	*22 (31.4)*	*1.000*
s/p PTCA	*16 (22.9)*	*20 (19.6)*	*0.703*	*16 (22.9)*	*18 (25.7)*	*0.844*
Diabetes mellitus	*34 (48.6)*	*53 (52.0)*	*0.756*	*34 (48.6)*	*42 (60.0)*	*0.235*
Hypertension	*41 (58.6)*	*71 (69.6)*	*0.146*	*41 (58.6)*	*44 (62.9)*	*0.729*
Chronic renal failure	*6 (8.6)*	*7 (6.9)*	*0.772*	*6 (8.6)*	*7 (10.0)*	*1.000*
CVA	*6 (8.6)*	*9 (8.8)*	*1.000*	*6 (8.6)*	*8 (11.4)*	*0.799*
PAOD	*16 (22.9)*	*19 (18.6)*	*0.565*	*16 (22.9)*	*15 (21.4)*	*1.000*
LVEF (%)	*51.4±16.5*	*54.6±14.2*	*0.271*	*51.4±16.5*	*52.7±14.7*	*0.634*
BSA	*1.73±0.13*	*1.71±0.20*	*0.678*	*1.73±0.13*	*1.73±0.19*	*0.938*

Values are either mean±SD or number of patients (percentage).
MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CVA, cerebrovascular accident; PAOD, peripheral arterial obstructive disease; LVEF, left ventricular ejection fraction; BSA, body surface area.

Table 2 Operative and Postoperative Data, Unadjusted and Adjusted for Propensity Score Matching

	Unadjusted			*Adjusted*		
	Continuous (n=70)	*Non-continuous (n=102)*	*p value*	*Continuous (n=70)*	*Non-continuous (n=70)*	*p value*
Operation time (min)	*260.3±51.2*	*229.7±54.4*	*0.002*	*260.3±51.2*	*231.9±48.5*	*0.004*
Distal anastomosis (number)	*3.1±0.7*	*3.3±0.8*	*0.265*	*3.1±0.7*	*3.2±0.7*	*0.653*
MV (h)	*15.0±10.7*	*13.7±6.7*	*0.305*	*15.0±10.7*	*14.2±7.1*	*0.600*
ICU stay (h)	*53.0±19.6*	*51.2±22.9*	*0.603*	*53.0±19.6*	*52.8±25.9*	*0.955*
Intraoperative blood loss (ml)	*303.3±149.5*	*265±135.3*	*0.754*	*303.3±149.5*	*273.8±138.6*	*0.842*
Postoperative blood loss (ml)	*601.4±312.6*	*627.0±426.4*	*0.693*	*601.4±312.6*	*637.2±452.4*	*0.616*
Chest tube drain (days)	*4.0±2.5*	*3.8±1.8*	*0.621*	*4.0±2.5*	*3.9±1.8*	*0.784*

Values are mean±SD.
MV, mechanical ventilation; ICU, intensive care unit; Postoperative bleeding, for the first 24 h postoperatively.

Statistical Analysis

Data were computerized and analyzed using SPSS for Windows, version 12.0 (SPSS, Inc, Chicago, IL, USA). Categorical variables were compared using the chi-squared test or Fisher's Exact Test, and continuous variables were compared using Student's t-test or the Mann-Whitney U test, where appropriate. Continuous variables were dichotomized using the median or extreme values over the normal range as the cut-off value. A value of $p \leq 0.05$ by univariate analysis was chosen as the criterion for submitting variables to the model. Goodness of fit was assessed using the Hosmer and Lemeshow chi-squared test. The relative risk, defined as the ratio of incidence of exposed to non-exposed subjects, was used to summarize the strength of the association between risk factors and reexploration for bleeding; the 95% confidence intervals of relative risk were calculated using Miettinen's test-based approach. Unless otherwise stated, results are expressed as mean ± standard deviation (SD) for continuous variables and as percent for categorical variables. Patients in the continuous and non-continuous groups were matched by closest propensity score.

Results

Patient Characteristics and Perioperative Outcomes

Of the 172 patients who underwent isolated OPCAB for acute coronary syndrome, 70 (40.7%) took continuous clopidogrel preoperatively, whereas 102 (59.3%) did not. Of those, sixteen patients required emergent OPCAB just after diagnostic coronary angiography. Because the group of patients who took clopidogrel continuously contained lower percentages of women and patients with triple vessel disease, we used propensity matching scores, matching 70 patients in each group. Demographics and preoperative characteristics, both unadjusted and adjusted for propensity score analysis, are shown in Table 1. After adjustment for propensity score, there were no significant between-group differences in baseline characteristics, indicating that the propensity model had successfully removed the imbalance in the distribution of a number of risk factors. Unadjusted and adjusted perioperative outcomes are shown in Tables 2, 3,4 and 5. Postoperative rates of myocardial infarction, intraaortic balloon pump insertion, coronary spasm, respiratory failure, renal failure and need for hemodialysis, deep sternal infection, need for prolonged ventilation, intensive care unit length of stay and operative mortality did not differ significantly between the 2 groups. The immediate postoperative graft patency rate also did not differ significantly between the 2 groups. Mean operation time, however, was significantly longer for the continuous group (260.3± 51.2 min vs 231.9±48.5 min, p=0.004).

Hemorrhage-Related Reexploration

We found that the reexploration rate as a result of bleeding was identical in the continuous and non-continuous groups (1.4% vs 1.4%, p=1.00) (Table 4). A separate analysis of all patients who received clopidogrel by number of distal anastomoses also showed no significant variations in

Table 3 Postoperative Complications and Operative Mortality, Unadjusted and Adjusted for Propensity Score Matching

	Unadjusted			*Adjusted*		
	Continuous (n=70)	*Non-continuous (n=102)*	*p value*	*Continuous (n=70)*	*Non-continuous (n=70)*	*p value*
Perioperative MI	*1 (1.4)*	*1 (1.0)*	*1.00*	*1 (1.4)*	*1 (1.4)*	*1.00*
IABP insertion	*0 (0)*	*0 (0)*	*1.00*	*0 (0)*	*0 (0)*	*1.00*
Coronary spasm	*1 (1.4)*	*0 (0)*	*0.41*	*1 (1.4)*	*0 (0)*	*0.41*
Respiratory failure	*1 (1.4)*	*0 (0)*	*0.41*	*1 (1.4)*	*0 (0)*	*0.41*
Pneumonia	*0 (0)*	*2 (2.0)*	*0.39*	*0 (0)*	*1 (1.0)*	*0.41*
Renal failure	*0 (0)*	*1 (1.0)*	*0.41*	*0 (0)*	*1 (1.0)*	*0.41*
Hepatic failure	*0 (0)*	*1 (1.0)*	*0.41*	*0 (0)*	*1 (1.0)*	*0.41*
Mediastinitis	*1 (1.4)*	*0 (0)*	*0.41*	*1 (1.4)*	*0 (0)*	*0.41*
Operative mortality	*1 (1.4)*	*0 (0)*	*0.41*	*1 (1.4)*	*0 (0)*	*0.41*

Values are either mean±SD or number of patients (%).
IABP, intraaortic balloon pump. Other abbreviation see in Table 1.

Table 4 Postoperative Bleeding Complications and Transfusion, Unadjusted and Adjusted for Propensity Score Matching

	Unadjusted			*Adjusted*		
	Continuous (n=70)	*Non-continuous (n=102)*	*p value*	*Continuous (n=70)*	*Non-continuous (n=70)*	*p value*
Bleeding complications	*1 (1.4)*	*3 (3.0)*	*1.00*	*1 (1.4)*	*2 (2.9)*	*1.00*
Reexploration	*1 (1.4)*	*1 (1.0)*	*0.95*	*1 (1.4)*	*1 (1.4)*	*1.00*
UGI bleeding	*0 (0)*	*1 (1.0)*	*1.00*	*0 (0)*	*1 (1.4)*	*0.65*
Prolonged drainage	*1 (1.4)*	*1 (1.0)*	*0.95*	*1 (1.4)*	*1 (1.4)*	*1.00*
Hemothorax	*0 (0)*	*1 (1.0)*	*1.00*	*0 (0)*	*1 (1.4)*	*0.65*
Blood transfusion	*23 (33.3)*	*34 (33.3)*	*1.00*	*23 (33.3)*	*24 (34.3)*	*1.00*
pRBC transfusion (U)	*0.4±0.3*	*0.5±0.5*	*0.513*	*0.4±0.3*	*0.5±0.4*	*0.624*
Platelet transfusion	*2 (2.9)*	*6 (5.9)*	*0.48*	*2 (2.9)*	*5 (7.1)*	*0.44*

Values are either mean±SD or number of patients (%).
UGI, upper gastro-intestinal tract; pRBC, packed red blood cell; U, unit.

Table 5 Graft Patency by Multi-Slice CT

	Continuous (n=70)	*Non-continuous (n=102)*	*p value*
Multi-slice CT evaluation[a]	*54 (77.1)*	*88 (86.3)*	*0.88*
Patent graft (%)[b]	*167/168 (99.4)*	*287/290 (99.0)*	*0.92*

Values are either mean±SD or number of patients (%).
[a]Multi-slice computed tomography (CT) was evaluated in 54 patients (77.1%) in continuous group and 88 patients (86.3%) in non-continuous group at the 7th postoperative day.
[b]The 167 grafts (99.4%) were patent in continuous group and 287 grafts (99.0%) were patent in non-continuous group at the 7th postoperative day.

the incidence of hemostatic reexploration (p=0.65, data not shown here).

Allogenic Blood Transfusion

Univariate analysis disclosed that the continuous and non-continuous groups showed similar postoperative blood loss, and similar rates of perioperative blood transfusions (33.3% vs 34.3%, p=1.000) and perioperative platelet transfusions (2.9% vs 7.1%, p=0.441; Table 4). Changes in hemoglobin and platelet counts in both groups are shown in Fig 1. There was a significant between-group difference in hemoglobin on the first day after OPCAB surgery (8.8 vs 9.1 g/dl, p=0.046). However, there was no significant difference in hematocrit level on the first day after OPCAB (25.5 vs 26.3%, p=0.079). There were significant between-group differences in platelet count on the first and second days after OPCAB surgery (p=0.004). For 16 patients who required emergent surgery, dosages of preoperative clopidogrel and aspirin were same with non-emergent OPCAB. Postoperative blood loss for 24 h was 446.4±206.3 ml and 634.5±396.4 ml (p=0.083), and blood transfusions were needed in 8 (50%) and 155 patients (31.6%) (p=0.166) for emergent and non-emergent OPCAB patients, respectively.

Operative Mortality

The operative mortality rate did not differ significantly between the 2 groups (1.4% vs 0%, p=0.41).

Discussion

The clinical applicability of clopidogrel is expanding. For example, the CAPRIE trial – a large, randomized, double-blind, multicenter study involving 19,185 subjects – showed that prophylactic clopidogrel therapy was associated with an almost 9% decrease in the relative risk of myocardial infarction, ischemic stroke or vascular death[19,20] Similarly, the CURE trial, a randomized, double-blind, placebo-controlled study in 12,562 patients presenting within 24 h of the onset of acute coronary symptoms, found that administration of 300 mg clopidogrel in addition to aspirin was associated with a 20% reduction in cardiovascular mortality, myocardial infarction and cerebrovascular accidents[20–22] Clopido-

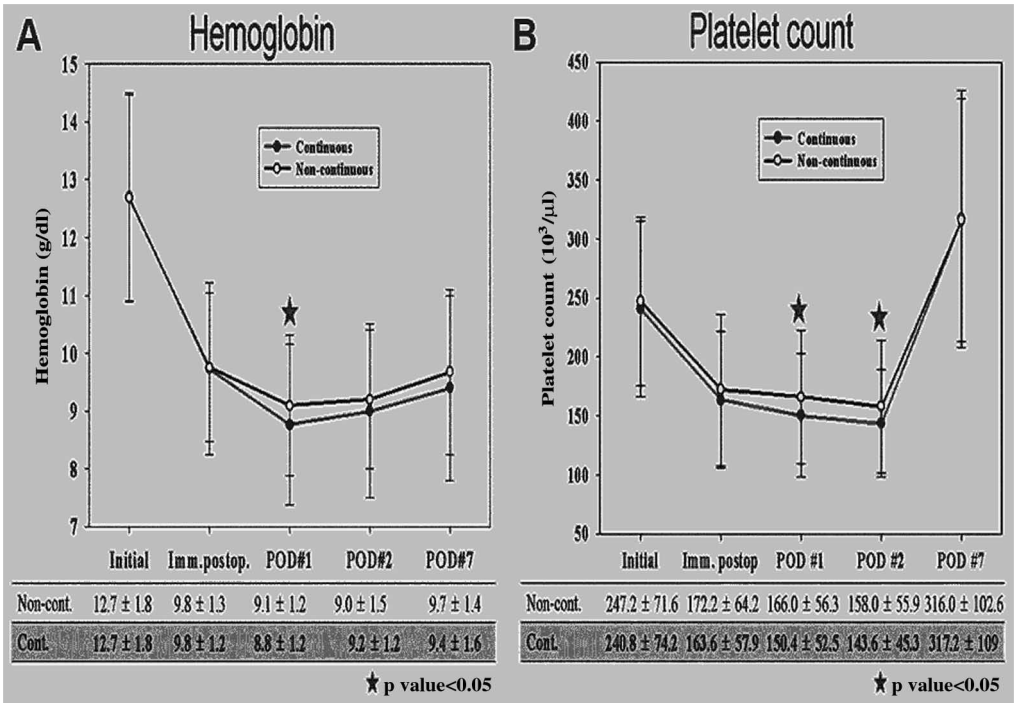

Fig 1. (A) Perioperative change in hemoglobin. There was a significant between-group difference in hemoglobin on the first day after off-pump coronary artery bypass graft (OPCAB) surgery. (B) Perioperative change in platelet count. There were significant between-group differences in platelet count on the first and second days after OPCAB surgery

grel and aspirin acted synergistically, in that clopidogrel inhibits adenosine 5'-diphosphate-induced platelet aggregation, whereas aspirin inhibits cyclooxygenase and reduces thromboxane A2. These findings indicate that all patients with an acute coronary syndrome should benefit from the favorable effects of clopidogrel, without exception and without delay, if possible during the prehospitalization period!

The Clopidogrel for the Reduction of Events During Observation (CREDO) trial evaluated the safety and efficacy of clopidogrel, with or without a loading dose, when given in conjunction with aspirin before PCI. Patients receiving clopidogrel 6 h before intervention exhibited a 35% reduction in mortality, myocardial infarction and urgent target-vessel revascularization[23]

Therefore, as the indications for clopidogrel use expand, an increasing percentage of patients presenting for surgical coronary revascularization do so subject to irreversible platelet inhibition.

Several studies have reported an increased incidence of postoperative bleeding with clopidogrel, along with associated transfusion requirements and the need for surgical reexploration[2–4] For example, patients receiving clopidogrel before CABG were found to be almost 6 times more likely to require surgical reexploration to control hemorrhage and had a 20% increase in pRBC transfusion requirements[3] Similarly, a more recent cohort study involving 59 patients receiving clopidogrel within 7 days of CABG found that this drug was associated with increases in reoperation due to hemorrhage (6.8% vs 0.6%), increased chest tube drainage (817±761 vs 501±427 ml) and average amounts of transfused pRBC (2.6 vs 1.6 units), platelets (0.9 vs 0.2 units) and FFP (0.8 vs 0.3 units)[2] In contrast to many previous reports, we recently found that preoperative clopidogrel and aspirin exposure did not increase perioperative blood loss and blood transfusion requirements in patients undergoing elective OPCAB[18] Almost all cardiac surgeons may be concerned about clopidogrel-induced hemorrhagic complications, especially in patients who need urgent or emergency surgery due to acute coronary syndrome. One study found that, in patients with acute coronary syndrome necessitating urgent surgical revascularization, failure to stop clopidogrel at least 7 days before surgery resulted in unacceptable rates of transfusion and reexploration for bleeding, regardless of whether on- or off-pump surgery was used[24] In the present study, however, we observed that patients in this particular subgroup (ie, those with acute coronary syndrome who were continuously exposed to clopidogrel and subsequently underwent OPCAB surgery) did not have higher risks of operative mortality, reexploration to control hemorrhage, and transfusions of blood products. In addition, sixteen patients who required emergent OPCAB did not have higher risks of more bleeding and transfusions. Thus, we concluded that preoperative clopidogrel administration did not predict reexploration due to hemorrhage or blood product transfusion.

To our knowledge, this report is the first to show that continuous preoperative clopidogrel did not have a deleterious effect on postoperative blood loss, blood product transfusions and reexploration after OPCAB surgery in patients with acute coronary syndrome. These findings have important clinical implications. One of the principal benefits of OPCAB surgery is its lower rate of hemorrhagic sequelae, and it now appears that preoperative clopidogrel administration does not ameliorate the beneficial effects of eliminating CPB[16,17] Therefore, OPCAB surgery may preclude the potential hemorrhagic complications created by clopidogrel administration, even for patients with acute coronary syndrome.

In addition, continuous administration of clopidogrel dur-

ing the preoperative period and immediately after OPCAB surgery might be of benefit by preserving graft patency. Although no studies have been performed using clopidogrel, the effects of the other thienopyridine, ticlopidine, on aorto-coronary bypass graft patency have been examined in a randomized double-blind study.[25] When begun at least 2 days after CABG surgery, ticlopidine improved both immediate and 1-year graft patency. In the present study, multi-slice computed tomography on the seventh postoperative day showed excellent patency rate in both groups (Table 5). Therefore, due to its improved safety profile and comparable efficacy, many institutions, including ours, use clopidogrel immediately after OPCAB to prevent graft occlusion in high-risk patients. Because of the limited number of index events, a sample size larger than those from a single institution is required for clinically meaningful conclusions.

The efficacy of clopidogrel in clinical practice has reached a point where avoiding clopidogrel exposure is not possible. Surgeons regard patients who continuously exposed to clopidogrel preoperatively as having an increased bleeding tendency when they open the sternum from skin to bone marrow or periosteum. Then, how can we get a better outcome for these patients? Intraoperative bleeding may be reduced by meticulously controlling fatty tissue and sternal bone bleeding from the beginning of the surgery. Our results showed that operation time was about 30 min longer in patients continuously exposed to clopidogrel. We think that this 30 min are essential to reduce hemorrhagic complications after OPCAB surgery. More delicate anastomotic techniques and more meticulous hemostasis may decrease hemorrhagic complications and improve immediate and long-term surgical outcomes.

Study Limitations

Limitations of the present study include all those inherent in any retrospective single-institution analysis. All data elements, however, were prospectively entered into a cardiac surgery research database according to prespecified definitions, and data analysis was performed using appropriately risk-adjusted statistical models to adjust for differences in preoperative risk factors. Regrettably, the patient sample size was not large enough to reflect statistically significant differences in mortality, and hence the effect of clopidogrel on operative mortality cannot be stated conclusively. In addition, because our surgical strategies include the performance of coronary artery bypass surgery as soon as possible in patients with acute coronary symptoms, the duration of clopidogrel discontinuation in the Non-continuous group was much shorter than that in other reports. Finally, we did not assess resistance to aspirin or clopidogrel and perioperative platelet function.

Conclusions

We have shown here that preoperative continuous administration of clopidogrel and aspirin did not increase the risk of hemostatic reoperation and the requirements for blood product transfusions during and after OPCAB surgery in patients with acute coronary syndrome. These findings indicate that urgent or emergency surgery after clopidogrel treatment should not be delayed until platelet function returns because these patients may be exposed to the risk of recurrent myocardial ischemic events.

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References

1. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; **345:** 494–502.
2. Hongo R, Ley J, Dick S, Yee RR. The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. *J Am Coll Cardiol* 2002; **40:** 231–237.
3. Yende S, Wunderink RG. Effect of clopidogrel on bleeding after coronary artery bypass surgery. *Crit Care Med* 2001; **29:** 2271–2275.
4. Gansera B, Schmidtler F, Spiliopoulos K, Angelis I, Neumaier-Prauser P, Kemkes BM. Urgent or emergent coronary revascularization using bilateral internal thoracic artery after previous clopidogrel antiplatelet therapy. *Thorac Cardiovasc Surg* 2003; **51:** 185–189.
5. Woodman RC, Harker LA. Bleeding complications associated with cardiopulmonary bypass. *Blood* 2000; **76:** 1680–1697.
6. Holloway DS, Summaria L, Sandesara J, Vagher JP, Alexander JC, Caprini JA. Decreased platelet number and function and increased fibrinolysis contribute to post-operative bleeding in cardiopulmonary bypass patients. *Thromb Haemost* 1988; **59:** 62–67.
7. Harker LA. Bleeding after cardiopulmonary bypass. *N Engl J Med* 1986; **314:** 1446–1448.
8. Mammen EF, Koets MH, Washington BC, Wolk LW, Brown JM, Burdick M, et al. Hemostasis changes during cardiopulmonary bypass surgery. *Semin Thromb Hemost* 1985; **11:** 281–292.
9. Rinder CS, Bohnert J, Rinder HM, Mitchell J, Ault K, Hillman R. Platelet activation and aggregation during cardiopulmonary bypass. *Anesthesiology* 1991; **75:** 388–393.
10. Brasil LA, Gomes WJ, Salomao R, Buffolo E. Inflammatory response after myocardial revascularization with or without cardiopulmonary bypass. *Ann Thorac Surg* 1998; **66:** 56–59.
11. Spiess BD. The contribution of fibrinolysis to post-bypass bleeding. *J Cardiothorac Vasc Anesth* 1991; **5:** 13–17.
12. Mack M, Bachand D, Acuff T, Edgerton J, Prince S, Dewey T, et al. Improved outcomes in coronary artery bypass grafting with beating-heart techniques. *J Thorac Cardiovasc Surg* 2002; **124:** 598–607.
13. Subramanian VA. Less invasive arterial CABG on a beating heart. *Ann Thorac Surg* 1997; **63:** S68–S71.
14. Puskas JD, Wright CE, Ronson RS, Brown WM 3rd, Gott JP, Guyton RA. Off-pump multivessel coronary bypass via sternotomy is safe and effective. *Ann Thorac Surg* 1998; **66:** 1068–1072.
15. Calafiore AM, Angelini GD, Bergsland J, Salerno TA. Minimally invasive coronary artery bypass grafting. *Ann Thorac Surg* 1996; **62:** 1545–1548.
16. Ascione R, Williams S, Lloyd CT, Sundaramoorthi T, Pitsis AA, Angelini GD. Reduced postoperative blood loss and transfusion requirement after beating-heart coronary operations: A prospective randomized study. *J Thorac Cardiovasc Surg* 2001; **121:** 689–696.
17. Nuttall GA, Erchul DT, Haight TJ, Ringhofer SN, Miller TL, Oliver WC, et al. A comparison of bleeding and transfusion in patients who undergo coronary artery bypass grafting via sternotomy with and without cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2003; **17:** 447–451.
18. Shim JK, Choi YS, Oh YJ, Bang SO, Yoo KJ, Kwak YL. Effects of preoperative aspirin and clopidogrel therapy on perioperative blood loss and blood transfusion requirements in patients undergoing off-pump coronary artery bypass graft surgery. *J Thorac Cardiovasc Surg* 2007; **134:** 59–64.
19. Harker LA, Boissel JP, Pilgrim AJ, Gent M. Comparative safety and tolerability of clopidogrel and aspirin: Results from CAPRIE: CAPRIE Steering Committee and Investigators: Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events. *Drug Safety* 1999; **21:** 325–335.
20. Kam PCA, Nethery CM. The thienopyridine derivatives (platelet adenosine diphosphate receptor antagonists): Pharmacology and clinical developments. *Anesthesia* 2002; **58:** 28–35.
21. Mehta SR, Yusuf S; Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Study Investigators. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. *Eur Heart J* 2000; **21:** 2033–2041.

22. Mitka M. Results of CURE trial for acute coronary syndrome. *JAMA* 2001; **285:** 1828–1829.
23. Steinhubl SR, Berger PB, Mann JT, Fry ET, DeLago A, Wilmer C, et al; CREDO Investigators. Clopidogrel for the Reduction of Events During Observation: Early and sustained dual oral anti-platelet therapy following percutaneous coronary intervention: A randomized controlled trial. *JAMA* 2002; **288:** 2411–2420.
24. Genoni M, Tavakoli R, Hofer C, Bertel O, Turina M. Clopidogrel before urgent coronary artery bypass graft. *J Thorac Cardiovasc Surg* 2003; **126:** 288–289.
25. Limet R, David JL, Magotteaux P, Larock MP, Rigo P. Prevention of aorta-coronary bypass graft occlusion: Beneficial effect of ticlopidine on early and late patency rates of venous coronary bypass grafts: A double-blind study. *J Thorac Cardiovasc Surg* 1987; **94:** 773–783.