Surgery for Acquired Cardiovascular Disease

Clopidogrel and bleeding in patients undergoing elective coronary artery bypass grafting

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Objective: In an effort to minimize transfusions in patients undergoing elective coronary artery bypass grafting operations after recent clopidogrel exposure, we studied laboratory tests predictive of platelet dysfunction and used a strict algorithm-driven treatment of bleeding.

Methods: Forty-five patients receiving clopidogrel within 6 days of the operation and 45 control subjects were studied. Prothrombin time, activated partial thromboplastin time, platelet count, and platelet function test results were measured before heparinization, after protamine administration, and then every 2 hours. No transfusions were administered unless a patient met both laboratory and clinical criteria.

Results: Algorithm-driven treatment of bleeding significantly reduced the mean units of all blood components transfused by about one third, as shown by comparison with current control and historical data. Compared with current control subjects, clopidogrel recipients required significantly more transfusions of platelets (9.0 ± 1.7 vs 1.2 ± 0.5 U; P = .0001) and packed red blood cells (4.3 ± 0.6 vs 2.3 ± 0.5 U; P = .01) and required longer periods of controlled ventilation (12.4 ± 1.3 vs 8.6 ± 0.8 hours; P = .02). Preoperative platelet dysfunction before heparin administration for cardiopulmonary bypass, as measured by using adenosine diphosphate aggregometry (response <40%), predicted all but 1 case of severe coagulopathy requiring multiple transfusions (16.6 ± 2.8 U of platelets and 5.8 ± 1.0 U of packed red blood cells).

Conclusions: A strict transfusion algorithm can reduce the transfusion requirement for all blood components. Preheparin testing of platelet function with adenosine diphosphate aggregometry can identify patients at highest risk for perioperative bleeding and transfusions and might further reduce the perioperative transfusion requirement.

Clopidogrel is frequently administered to patients undergoing coronary angiography in anticipation of percutaneous coronary intervention. If angiography indicates coronary artery bypass grafting (CABG) rather than percutaneous coronary intervention, the question arises of whether to delay operation in all but urgent cases. In addition, many patients are now receiving long-term clopidogrel with or without aspirin for secondary prevention of coronary or cerebrovascular
ischemic events, and some will require CABG or other operations urgently. The effect of clopidogrel on platelets is irreversible, and when discontinued, full recovery of platelet function takes 3 to 5 days. Some have recommended that clopidogrel be stopped 5 days before the elective operation, and others have recommended stopping the drug at 7 days. Optimal management of these patients remains uncertain.

In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, the relative risk of major bleeding increased by 50% for patients who received clopidogrel within 5 days of the operation. In 3 single-center observational studies, patients who received clopidogrel within 7 days of surgical intervention, with or without concomitant aspirin, required significantly more perioperative blood component transfusions. Hongo and colleagues studied 224 consecutive patients, finding that the 59 patients with preoperative clopidogrel exposure received significantly more units of packed red blood cells (PRBCs), platelets, and fresh frozen plasma (FFP) and had significantly more chest tube drainage than patients without preoperative clopidogrel exposure. Similar findings were reported by Yende and Wunderlink and by Ray and coworkers. In these studies administration of blood components was not based on any prespecified laboratory or clinical criteria.

A chart review in our institution revealed a high incidence and volume of PRBC, platelet, and FFP transfusion in patients receiving clopidogrel within 6 days of CABG surgery. In view of the increased morbidity and mortality associated with transfusion in patients undergoing CABG, we prospectively studied patients undergoing elective primary CABG with and without clopidogrel to identify means of reducing excess transfusions through use of a strict transfusion algorithm. This algorithm was guided by clinical criteria and by serial measurement of coagulation and tests of platelet function, which would potentially yield predictive information about the development of significant coagulopathy.

**Methods**

The study design and protocol were approved by the Institutional Review Board at St Luke’s Episcopal Hospital. After informed consent was obtained and in accord with institutional guidelines, we prospectively enrolled 90 patients undergoing primary elective CABG surgery with cardiopulmonary bypass (CPB). This population included 45 patients who received clopidogrel by mouth within 6 days of surgical intervention (clopidogrel group) and 45 patients who had never received clopidogrel (control group). After enrollment of each clopidogrel-exposed patient, we enrolled the next available consenting patient on the surgical schedule who had never received clopidogrel. Patients who had recently received any platelet inhibitor other than aspirin or any other anticoagulant were excluded, as were patients with any preexisting bleeding disorders, end-stage renal disease, or end-stage heart failure.

CPB was performed by using a standard circuit and crystalloid prime. Anticoagulation was achieved with heparin (300 U/kg). Aprotinin was not used in any patient; aminocaproic acid was used according to the preference of the anesthesiologist in 42% of patients receiving clopidogrel and 31% of control subjects. The degree of hypothermia induced during CPB was monitored by using a nasopharyngeal temperature probe and ranged from 28°C to 32°C. Patients were rewarmed to a target temperature of 36.5°C before CPB was discontinued. After weaning from CPB, heparin was neutralized with protamine sulfate (1.0-1.5 mg/100 U heparin). When patients achieved hemodynamic stability, weaning from mechanical ventilation was accomplished according to an institutional protocol, with incremental decreases in intermittent mandatory ventilation rates from 10 to 4 beats/min and then to zero (with 5 cm H2O of continuous positive airway pressure). Patients were then traheally extubated if the appropriate criteria (ie, negative inspiratory force of >–25 cm H2O and vital capacity of at least 12-15 mL/kg) were met.

Blood samples were collected from patients after anesthesia induction but before heparinization for CPB, 15 minutes after protamine administration, and then every 2 hours up to 8 hours. Additional coagulation testing was done within 30 minutes after completion of any platelet transfusion to assess the transfusion effect. All samples were analyzed for hemoglobin level and coagulation profile in an onsite rapid-response laboratory immediately after collection. The coagulation profile included prothrombin time, activated partial thromboplastin time, platelet count, and platelet function, as determined by using 3 methods. These methods were adenosine diphosphate (ADP) aggregometry (Biodata, Philadelphia, Pa), which requires 30 to 45 minutes, and 2 rapid-response tests, Platelet Function Analyzer 100 (PFA-100; Dade Behring, Miami, Fla) and Platelet Works (Helena Laboratories, Beaumont, Tex), which require approximately 10 minutes each. For ADP aggregometry, we measured the platelet aggregation response of platelet-rich plasma (prepared by standard methods) to a 2 μmol/L concentration of ADP. Platelet function in this assay is expressed as the percentage of light transmittance through a standardized glass tube containing the patient’s platelet-rich plasma. A value of 70% to 100% indicated normal function, 50% to 69% indicated mild dysfunction, 40% to 49% indicated moderate dysfunction, and 0% to 39% indicated severe dysfunction. A value of less than 50% was selected a priori as the laboratory criterion for platelet transfusion in our algorithm. For PFA-100 analysis, platelet function is expressed as the time to thrombotic occlusion (closure) of an aperture in a membrane coated with collagen and ADP. A closure time of 128 seconds or less indicated normal platelet function. In the algorithm, a closure time of greater than 128 seconds was selected a priori as the laboratory criterion for platelet transfusion. All normal ranges were determined in our laboratory through study of healthy control subjects. The Platelet Works, a newer rapid-response test, assesses platelet reactivity by measuring the ratio of activated platelet count to nonactivated platelet count in tubes containing ADP. Normal ranges had not been determined in our laboratory for this test, and therefore Platelet Works data were not used in any clinical decision making and are not included.

No platelet or FFP units were administered after protamine administration or in the postoperative period unless a patient met
When Microvascular Bleeding is Excessive

![Algorithm Diagram]

Figure 1. Bleeding management algorithm used for treatment of excessive microvascular bleeding. PF, Platelet function; ADP, adenosine diphosphate; CT, closure time; PT, prothrombin time; PTT, partial thromboplastin time; FFP, fresh frozen plasma.

both laboratory and clinical criteria of the algorithm (Figure 1). In such cases, the laboratory results for the preheparin blood sample were not considered. For the postprotamine blood sample, only the PFA-100 analysis was available in the onsite rapid-response laboratory; therefore, this value guided algorithm use. After admission to the intensive care unit (ICU), the primary assay for decision making was ADP aggregometry. The clinical criterion for platelet and FFP transfusion in the operating room was excessive microvascular bleeding, as determined by the surgeon. In the ICU, the clinical criterion was chest tube drainage of greater than 250 mL/h after the first hour. If both laboratory and clinical criteria were met, transfusion of platelets, FFP, or both proceeded with strict adherence to the algorithm (Figure 1). After transfusion, blood tests were repeated, and the algorithm was used until bleeding ceased.

During CPB, 1 U of PRBCs was administered only when the hemoglobin level decreased to less than 6.0 g/dL. At all other times, 1 U of PRBCs was transfused only if the hemoglobin level decreased to less than 8.0 g/dL, except in patients with major ongoing hemorrhage.

To estimate the algorithm’s efficacy, current data were compared with historical data obtained in the chart review performed during the 4-month period from September 1, 1999, through December 31, 1999, just before development and implementation of the algorithm. Of all patients undergoing primary elective CABG during that historical period, 53 received clopidogrel within 6 days of surgical intervention, and 428 received none. Mean units of PRBCs, platelets, and FFP administered in these 2 groups were compared.

Statistical analysis was performed with SAS software (SAS Institute, Inc, Cary, NC). A 2-tailed unpaired Student t test was used to compare the mean values of the 2 independent groups, and a χ² or Fisher exact test was used to compare categorical data. Values were reported as the mean ± SE.

| TABLE 1. Demographic and clinical characteristics of the study population |
|-----------------------------------|--------------------|--------------------|--------|
| Characteristic                    | Clopidogrel group  | Control group      | P value |
| Age, y                            | 58 ± 1.3           | 58 ± 1.5           | .86    |
| Body weight, kg                   | 85 ± 2.5           | 90 ± 2.5           | .18    |
| Male/female sex, n                | 31/14              | 35/10              | .34    |
| Preheparin aspirin exposure, %    | 29 (64)            | 22 (49)            | .14    |
| Preheparin platelet count, 10⁹/L  | 216 ± 10           | 231 ± 9            | .24    |
| Preheparin platelet function by ADP aggregometry, % | 51 ± 4 | 78 ± 2 | <.0001 |
| Postprotamine platelet function by ADP aggregometry, % | 42 ± 3 | 67 ± 3 | <.0001 |
| Preheparin platelet function by Preoperative Pt, s | 112 ± 12 | 96 ± 6 | .26 |
| PFA-100 analysis, s               | 127 ± 15           | 104 ± 8            | .13    |
| Postprotamine platelet function by Preoperative Pt, s | 134 ± 0.9 | 122 ± 0.1 | .20 |
| Preheparin aPTT                   | 30.6 ± 2.9         | 28.2 ± 1.1         | .66    |
| Preoperative Hgb, g/dL            | 12.4 ± 0.24        | 12.4 ± 0.19        | .93    |
| Aminocaproic acid administration, % | 19 (42) | 14 (31) | .27   |
| Duration of CPB, min              | 73 ± 6.2           | 63 ± 3.6           | .17    |
| Mean no. of vessels bypassed      | 3.0 ± 0.2          | 3.3 ± 0.1          | .20    |

ALD, Adenosine diphosphate; PFA, platelet function analyzer; PT, prothrombin time; aPTT, activated partial thromboplastin time; Hgb, hemoglobin; CPB, cardiopulmonary bypass.

Results

The clopidogrel and control groups were demographically similar, including exposure to aspirin (Table 1). Platelet
dysfunction was readily detected in the clopidogrel group by means of ADP aggregometry but not by means of PFA-100 analysis in both the preheparin and postprotamine blood samples (Table 1). As expected, transfusions of both platelets and PRBCs, but not FFP, were significantly greater in the clopidogrel group (Table 2). Fifty-three percent of patients exposed to clopidogrel received platelet transfusions compared with 13% of control subjects ($P < .0001$). FFP was transfused with similar frequency (22% and 13%; $P = .27$).

In the prospective control group, as compared with the historical control group (Table 2), use of the algorithm significantly reduced transfusions of platelets and PRBC, but not of FFP. The algorithm significantly reduced the use of PRBCs in the prospective clopidogrel group compared with that in the historical clopidogrel group.

Patients were stratified within the clopidogrel group by degree of platelet dysfunction, as determined by means of preheparin ADP aggregometry, to determine the sensitivity of ADP aggregometry as a predictor of postoperative bleeding (Table 3). Within the clopidogrel group, 2 of 4 patients who underwent mediastinal reexploration for persistent postoperative bleeding had identifiable surgical bleeding points, which were ligated. The aggregometry data of these 2 patients were excluded from this analysis. Of the remaining 43 clopidogrel-exposed patients, 12 had severe preoperative platelet dysfunction (<40% light transmittance; mean, 23.8% ± 2.8%), and 11 (92%) of these 12 received platelet transfusions (mean, 16.6 ± 2.8 U), as well as multiple transfusions of PRBCs (mean, 5.8 ± 1.0 U; Table 3). All 11 patients received intraoperative platelet transfusions after protamine, and 6 of these required additional platelet transfusions in the 4 hours after ICU admission. The postprotamine platelet function of the 12th patient was normal, raising the question of laboratory error in the preheparin sample. Patients in the clopidogrel group with intermediate preoperative platelet dysfunction (40%–60% light transmittance; mean, 50.8% ± 1.2%) had a significantly lower incidence of platelet and PRBC transfusions ($P < .001$) and received significantly fewer platelet and PRBC units ($P < .05$; Table 3). Patients with near-normal or normal preoperative platelet function (>60% light transmittance; mean, 77.9% ± 2.4%) also received significantly fewer units of platelets and PRBCs than did those with severe dysfunction ($P < .05$). Similar results were obtained by using the postprotamine results of ADP aggregometry testing (Table 3). By contrast, PFA-100 analysis in both the preheparin and postprotamine periods was not as predictive of who would bleed and require platelet or PRBC transfusions (Table 4). The Platelet Works data were similar to the PFA-100 data in this regard and were not included.

The number of days elapsed since the last dose of clopidogrel was not useful in estimating the degree of platelet dysfunction (Tables 3 and 4). There were no differences between groups stratified by degree of platelet dysfunction in either mean or range of days elapsed since last exposure to clopidogrel, up to and including 6 days. In the control group, after exclusion of 1 patient who had an identifiable surgical bleeding point on mediastinal reexploration, only 1 patient had severe preoperative platelet dysfunction, as measured by means of ADP aggregometry (<40% light transmittance). However, this patient received no transfusions because there was no evidence of clinical microvascular bleeding. Only 3 (6.8%) of 44 control subjects required platelet transfusions, all given in the operating room, when they met the appropriate clinical and laboratory criteria of the algorithm. Only one of these patients had received preoperative aspirin.

Total chest tube drainage was significantly greater in the clopidogrel group (Table 5). Also, the duration of controlled ventilation was significantly longer and there was a nonsignificant trend toward longer postoperative hospitalization in the clopidogrel group (Table 2). One patient, a clopidogrel recipient who experienced a postoperative myocardial infarction and then adult respiratory distress syndrome, died on postoperative day 5.

**Discussion**

The major objective of this study was to improve transfusion management of patients undergoing CAGB with a recent history of clopidogrel treatment. Our data and those of others clearly document the excess transfusion requirements of these patients. Two findings offer promise of improved care: the use of a strict transfusion algorithm and the availability of a better predictor of patients who will have severe bleeding. Use of the algorithm reduced the mean units of all blood components transfused per patient by about one third in both the prospective control and clopidogrel groups compared with values in historical subjects (Table 2). We attribute this to the strict limitation on platelet transfusion, as well as to the nonspecific effect of

**TABLE 2. Component transfusion in prospective and retrospective patients undergoing CAGB**

<table>
<thead>
<tr>
<th>Component</th>
<th>Prospective</th>
<th>Retrospective (historical)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>Control group</td>
</tr>
<tr>
<td></td>
<td>group</td>
<td>(n = 45)</td>
</tr>
<tr>
<td>PLT, U</td>
<td>9.0 ± 1.7*</td>
<td>1.2 ± 0.5</td>
</tr>
<tr>
<td>PRBC, U</td>
<td>4.3 ± 0.6*</td>
<td>2.3 ± 0.5</td>
</tr>
<tr>
<td>FFP, U</td>
<td>1.0 ± 0.6</td>
<td>0.5 ± 0.3</td>
</tr>
</tbody>
</table>

PLT, Platelets; PRBC, packed red blood cells; FFP, fresh frozen plasma.

* $P < .05$ compared with control subjects enrolled in the same time period.

† $P < .05$ compared with prospective clopidogrel-exposed subjects.

‡ $P < .05$ compared with prospective control subjects.
algorithm use. \cite{27} Despite the algorithm use, clopidogrel-exposed patients received 3.5 times more blood components than did control subjects. A more effective treatment regimen is required for clopidogrel-exposed patients.

We anticipated that degree of bleeding would correlate inversely with the number of days since the last clopidogrel exposure. This was not the case. Instead, we found that markedly abnormal ADP aggregometry (<40% light transmittance) in the pre-CPB period accurately identified 11 of the 12 patients who received multiple transfusions (on average 17 U of platelets and 6 U of PRBCs). A regimen providing earlier and more vigorous treatment of this group of patients might have a significant effect on this difficult clinical problem.

The obvious solution to the problem is to withhold clopidogrel preoperatively until normal coagulation is restored. The risks of acutely withdrawing this antiaggregatory agent in patients undergoing elective CABG surgery are probably minimal. However, patients requiring urgent or emergency CABG present a dilemma. Should operation be delayed while clopidogrel is withdrawn at the unknown risk of a thrombotic episode? Or should operation proceed with the knowledge that excessive bleeding and increased transfusions are likely?

Surgeons are justifiably wary of putting patients at risk of preventable perioperative bleeding, mediastinal tamponade,
blood product use (with its attendant risks), and possible surgical reexploration for bleeding. Blood transfusions during cardiac surgery are associated with increased in-hospital morbidity (infectious complications, sepsis, and renal dysfunction) and mortality.

Since publication of the CAPRIE trial and the CLASSICs study, chronic clopidogrel administration in patients with atherosclerotic disease, prior coronary stenting, or both has become common. Furthermore, the results of the CURE trial argue strongly for adding clopidogrel to aspirin as soon as possible after hospital admission for management of unstable angina and myocardial infarction without ST-segment elevation, despite the increased risk of major nonsurgical bleeding that was described as “life-threatening in nearly half of the cases.” In the trial, clopidogrel was discontinued in most patients scheduled for CABG surgery (the median time was 5 days before surgical intervention), which might be an impractical goal in most US centers. For those patients who did undergo CABG surgery less than 5 days after clopidogrel was discontinued, the relative risk of major or life-threatening bleeding increased by 50%.

An alternative suggested by others would be to withhold clopidogrel before diagnostic angiography in patients at increased risk of requiring CABG surgery until the timing of the operation is determined. In its guidelines for managing patients with unstable angina and myocardial infarction without ST-segment elevation, the American College of Cardiology/American Heart Association Task Force on Practice Guidelines notes that clopidogrel is withheld in many centers in which patients with acute coronary syndromes undergo diagnostic catheterization within 24 to 36 hours of admission until it is clear that CABG surgery will not be scheduled within the next several days. These guidelines suggest 2 options: first, if immediate percutaneous transluminal coronary angioplasty is indicated, then a loading dose of clopidogrel can be given in the cardiac catheterization laboratory; second, if immediate percutaneous transluminal coronary angioplasty is not indicated and so delayed, then clopidogrel can be started after catheterization. If clopidogrel has been administered and the decision to delay surgery is made, preoperative ADP aggregometry would be helpful in reevaluating the risk of bleeding and transfusion requirements before any operation is undertaken. When surgical intervention cannot be safely delayed, patients may receive platelets to achieve a target ADP aggregation response of greater than 40% if bleeding develops after protamine administration. In our study a total of approximately 17 U of platelets was required to correct microvascular bleeding in similar patients.

Our study had several limitations. First, although the clopidogrel and control groups were demographically similar, they were not randomized to clopidogrel exposure. Therefore, confounding factors, such as preoperative aspirin exposure, may have influenced outcome.

Second, neither of the rapid-response platelet aggregation tests was useful in predicting who would bleed. ADP aggregometry requires that blood be separated to obtain platelet-rich plasma, a technique not available in a rapid-response laboratory. In our study, ADP aggregometry required at least 30 minutes to complete and did not allow prompt treatment of bleeding.

Third, surgeons caring for the patients in our study were not blinded to preoperative exposures to antiplatelet medications. This knowledge may have biased their decision on microvascular bleeding. This limitation was mitigated in part by strict adherence to the bleeding management algorithm.

Finally, bleeding may have been somewhat dependent on individual surgical technique and skill, a potential confounder that this study was not powered to detect.

Despite these limitations, this prospective study demonstrates the predictability of perioperative bleeding and its consequences in patients undergoing elective CABG surgery after recent clopidogrel exposure. Serious consideration should be given to discontinuing clopidogrel earlier than 5 days before an elective operation. Preoperative or pre-CPB testing of platelet function by means of ADP aggregometry can identify patients at highest risk for bleeding and facilitate the decision to delay or proceed with the operation. When surgical intervention cannot be safely delayed, transfusion of platelets to achieve a target ADP aggregation response of at least 40% and possibly higher would seem reasonable, although its effectiveness requires demonstration. A more rapid method for assessing platelet ADP receptor function in a rapid-response laboratory would allow earlier transfusion decisions for clopidogrel-exposed patients. Additional study will be necessary to determine how early clopidogrel may be stopped before surgical intervention to allow recovery of platelet function, to determine the risks of acute clopidogrel withdrawal, and to determine whether some other algorithm for preoperative or intraoperative platelet transfusions will decrease overall transfusion.

References

6. Gerschutz GP, Bhatt DL. The clopidogrel in unstable angina to prevent...