Cessation of Clopidogrel Before Major Abdominal Procedures

Artur Chernoguz, MD; Dana A. Telem, MD; Edward Chu, BA; Junko Ozao-Choy, MD; Yolanda Tammaro, MD; Celia M. Divino, MD

Objective: To determine whether timing of clopidogrel bisulfate cessation influences outcome after abdominal operations.

Methods: A review was performed of 104 patients receiving clopidogrel who underwent abdominal operations between March 2003 and March 2009. Patients were grouped by last clopidogrel use: group A (< 7 days) and group B (≥ 7 days).

Results: Of 104 patients, 43 were in group A and 61 were in group B. Overall, 6 deaths occurred (group A, 5 patients [12%] vs group B, 1 [2%]; P = .03) and 27 patients required intensive care unit admission (group A, 16 patients [37%] vs group B, 11 [18%]; P = .03). Twenty-one patients developed a postoperative bleeding complication; 19 complications were managed by blood transfusion and 2 required reoperation. Group A vs group B had significantly increased rates of postoperative bleeding requiring blood transfusion (13 patients [30%] vs 8 [13%]; P = .03). No significant difference in postoperative bleeding resulting in reoperation or mortality was demonstrated. Timing of clopidogrel cessation within 7 days did not affect postoperative bleeding risk. Eighty-nine patients (86%) underwent elective operations (group A, 30 patients [70%] vs group B, 59 [97%]; P < .001). While elective patients in group A vs those in group B demonstrated a trend toward increased risk of postoperative bleeding requiring transfusion (7 patients [23%] vs 8 [14%]; P = .25), no significant difference in intensive care unit admission (group A, 6 patients [20%] vs group B, 9 [15%]; P = .31) or mortality (1 [3%] vs 1 [2%]; P = .62) was demonstrated.

Conclusions: While clopidogrel use within 7 days of an operation significantly increased the risk of postoperative bleeding, most bleeding episodes were successfully managed by transfusion without an increase in bleeding-related mortality or necessity for reoperation. After controlling for operative urgency, no significant difference in mortality or intensive care unit admission was demonstrated in patients undergoing elective procedures. High-risk patients undergoing elective operations may not require preoperative clopidogrel cessation. When clopidogrel cessation is warranted, 7 days before the procedure is recommended. Perioperative risk does not vary by timing of cessation within 7 days of an operation.


According to recent data, clopidogrel is one of the most commonly sold pharmaceuticals in the United States, at a cost of nearly $5 billion annually. Clinical trials have demonstrated that use of clopidogrel in select patients decreases the risk of cardiovascular death; however, its role as an irreversible antiplatelet agent predisposes patients to increased bleeding risk. Typical duration of clopidogrel therapy ranges from months to years in many patients. This exposes those who require operative procedures during that time to potential perioperative bleeding-related risks, such as hematoma formation, reoperation, and death. To date, cardiac studies have demonstrated increased postoperative bleeding complications in patients exposed to clopidogrel within 7 days of coronary artery bypass graft. Although bleeding complications may not directly translate into life-threatening postoperative morbidity or mortality, such findings led the Society of Thoracic Surgeons to recommend discontinuation of clopidogrel 5 to 7 days before coronary artery bypass graft.

Abdominal and cardiac operations differ vastly in anticipated incidence of bleeding, as well as cerebral and cardiovascular postoperative complications. No clear

See Invited Critique at end of article

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consensus on optimal management of clopidogrel before abdominal operations exists, and recommendations are often based on individualized assessment of a patient's operative risk vs thrombotic or ischemic risk. Without definitive evidence-based guidelines, a general surgeon is required to balance the presumed bleeding risk with the risk of a thrombotic complication. To date, only 1 study in the surgical literature directly addressed preoperative clopidogrel management in the general surgical patient. Similar to trials reported in the cardiac literature, this study demonstrated an increased rate of postoperative bleeding complications in patients who received their last dose of clopidogrel within 7 days before an operative procedure. However, no significant difference in life-threatening complications or mortality was shown. While this study suggested that major operative procedures should not be delayed because of recent clopidogrel use, limited study power precluded significance and prevented definitive conclusions. For the present study, we hypothesized that given appropriate study power, no significant effect on life-threatening morbidity or mortality would be demonstrated by timing of clopidogrel cessation despite an increase in postoperative bleeding complications. The purpose of this study was to evaluate the largest cohort of patients receiving clopidogrel who were undergoing abdominal operative procedures and determine the association between timing of clopidogrel cessation and postoperative outcome.

METHODS

With approval from the Mount Sinai School of Medicine Institutional Review Board, a medical record review was performed of 104 consecutive patients undergoing general surgical procedures while receiving antiplatelet therapy. All procedures were performed at The Mount Sinai Medical Center by 32 surgeons between March 2003 and March 2009. Patients were identified from an administrative database by cross-referencing clopidogrel with abdominal operative procedures. The records of only patients who were actively receiving antiplatelet therapy, with the last clopidogrel dose within 45 days of their operation, were considered in the study. The medical records of all patients undergoing a major general surgical procedure were evaluated. Major operative procedures were defined as any intervention in which extensive resection was performed, a body cavity was entered, organs were removed, or normal anatomy was significantly altered. Exclusion criteria were age less than 18 years, minor operative procedure, preoperatively identified bleeding disorders, Jehovah's Witnesses or otherwise documented transfusion refusal, and inability to determine length of time between the last dose of clopidogrel and the operative procedure. All patients had received a standard daily clopidogrel dose of 75 mg. Timing of clopidogrel cessation and operative intervention were at the discretion of each surgeon.

Patients were divided in 2 groups based on timing of the last preoperative clopidogrel dose: those who took clopidogrel less than 7 days before the procedure (group A) and those who stopped clopidogrel therapy 7 or more days before the operative intervention (group B). Seven days was chosen as the cut-off, since clopidogrel is an irreversible antiplatelet agent and this time period represents complete turnover of the platelet pool. Data were collected from the hospital's inpatient and electronic medical records. Preoperative patient demographics, comorbidity, indication for clopidogrel use, and length of clopidogrel therapy were reviewed. Operative and anesthesia records were assessed for preoperative American Society of Anesthesiologists score, acuity of the procedure, technical method used, intraoperative complication, operative time, intraoperative blood loss, and transfusion requirement. Hospital course, including transfusion requirement, hospital length of stay, and intensive care unit (ICU) requirement and length of stay, as well as postoperative morbidity, mortality, and 30-day readmission, were reviewed. Intensive care unit requirement was determined according to specific admission guidelines. Admission was necessary for patients with or without systemic medical problems who were undergoing extensive surgical procedures and for those requiring intensive monitoring and postoperative nursing care. Patients who experienced significant blood loss or perioperative respiratory failure were also admitted to the ICU.

Univariate analysis was performed by unpaired t test for quantitative variables and χ² test for categorical variables. Multivariate analysis to determine the odds ratio with 95% confidence interval was also performed. P values < .05 for associations conferred significance. Prism 4.0 statistical software (GraphPad Software, La Jolla, California) was used for all analyses.

RESULTS

Of the 104 patients who underwent major operative procedures, 71 were men and 33 were women. Mean patient age was 70.4 years. Of the 104 patients, 82 were receiving aspirin: 33 in group A (77%) and 49 in group B (80%) (P = .81). Forty-three patients received clopidogrel within 7 days of an operation and were placed in group A. Sixty-one patients composed group B because they stopped treatment with clopidogrel for 7 or more days before the procedure (range, 7-42 days). Table 1 demonstrates patient demographics, medical history, indication for clopidogrel, and mean preoperative American Society of Anesthesiologists score. Overall, mean operative blood loss was 326.7 mL and 24 patients (23%) required intraoperative blood transfusion. Perioperative platelet transfusions were administered to 8 patients (19%) in group A; no patients in group B required platelet transfusion. Each patient received 0.5 to 3 U of pooled platelets. Three of these patients (38%) developed postoperative bleeding requiring transfusion or reoperation. Fresh frozen plasma transfusions were given to 7 patients (7%). Three (7%) of the fresh frozen plasma recipients were in group A and 4 (7%) were in group B. Postoperatively, 6 deaths (6%) occurred. Twenty-one patients (20%) had postoperative bleeding requiring intervention; 19 were managed by transfusion (1-3 U of packed red blood cells) and 2 necessitated reoperation. Twenty-seven patients (26%) required ICU admission. Mean hospital length of stay was 9.6 days.

INTRAOPERATIVE COURSE BY TIMING OF CLOPIDOGREL CESSATION

The Figure demonstrates the major operative procedures performed by timing of the last clopidogrel dose. No significant difference in the type of procedure performed was demonstrated, and no significant difference
in postoperative bleeding was reported by the surgeons. Intraoperative factors of each procedure were compared. Group A patients underwent significantly more nonelective procedures (13 patients [30%] vs 2 [3%]; \(P = .001\)). Analysis of intraoperative factors revealed a trend toward increased intraoperative blood transfusion requirement and blood loss in group A patients; however, this was not statistically significant (Table 2).

### Table 1. Patient Demographics, Comorbidity, and Preoperative ASA Score by Last Dose of Clopidogrel

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 104)</th>
<th>Group A (n = 43)</th>
<th>Group B (n = 61)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, y</td>
<td>70.4</td>
<td>69.9</td>
<td>70.8</td>
<td>.74</td>
</tr>
<tr>
<td>Sex, No. (%); Male</td>
<td>71 (68)</td>
<td>30 (70)</td>
<td>41 (67)</td>
<td>.80</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>33 (32)</td>
<td>13 (30)</td>
<td>.78</td>
</tr>
<tr>
<td>Comorbidity, No. (%);</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>74 (71)</td>
<td>29 (67)</td>
<td>45 (74)</td>
<td>.48</td>
</tr>
<tr>
<td>CAD</td>
<td>88 (85)</td>
<td>37 (86)</td>
<td>51 (84)</td>
<td>.73</td>
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<td>DM</td>
<td>38 (37)</td>
<td>14 (33)</td>
<td>24 (39)</td>
<td>.48</td>
</tr>
<tr>
<td>ESRD</td>
<td>13 (12)</td>
<td>5 (12)</td>
<td>8 (13)</td>
<td>.82</td>
</tr>
<tr>
<td>Indication (n = 93), No. (%);</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVA</td>
<td>10 (10)</td>
<td>6 (14)</td>
<td>4 (7)</td>
<td>.21</td>
</tr>
<tr>
<td>Coronary stent</td>
<td>70 (67)</td>
<td>24 (56)</td>
<td>46 (75)</td>
<td>.04</td>
</tr>
<tr>
<td>CAD</td>
<td>24 (23)</td>
<td>11 (26)</td>
<td>13 (21)</td>
<td>.14</td>
</tr>
<tr>
<td>ASA score (n = 98), No. (%);</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>7 (7)</td>
<td>0</td>
<td>7 (11)</td>
<td>.02</td>
</tr>
<tr>
<td>3</td>
<td>71 (68)</td>
<td>27 (63)</td>
<td>44 (72)</td>
<td>.31</td>
</tr>
<tr>
<td>(\geq 4)</td>
<td>20 (19)</td>
<td>12 (28)</td>
<td>8 (13)</td>
<td>.06</td>
</tr>
</tbody>
</table>

Abbreviations: ASA, American Society of Anesthesiologists; CAD, coronary artery disease; CVA, cerebrovascular accident; DM, diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension.

Further stratification of outcome by operative procedure demonstrated that most of the postoperative morbidity and mortality occurred in patients who underwent colorectal resection. Fifteen (71%) of the 21 postoperative bleeding complications occurred in the colorectal resection group compared with 6 (29%) from other operative procedures (\(P = .006\)). Colorectal resection independently correlated with increased risk of postoperative bleeding complication with an associated odds ratio of 6.3 (95% confidence interval, 1.6-23.9). Assessment by timing of clopidogrel cessation demonstrated a trend toward increased bleeding complications in patients with last use of clopidogrel less than 7 days preoperatively (Table 3). No significant difference in bleeding requiring intervention was noted by timing of the last dose within 7 days (Table 4).

### OUTCOME BY OPERATIVE PROCEDURE

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OUTCOME BY ELECTIVE PROCEDURE

Outcome assessment by emergency vs nonemergency procedures demonstrated that 30 patients (70%) from group A and 59 patients (97%) from group B underwent nonemergency operations ($P < .001$). Analysis of outcome demonstrated a trend toward increased risk of postoperative bleeding requiring transfusion in group A patients (7 patients [23%] vs 8 [14%]; $P = .25$). Assessment of postoperative ICU requirement (group A, 6 patients [20%] vs group B, 9 [15%]; $P = .31$) and mortality (1 [3%] vs 1 [2%]; $P = .62$) demonstrated no significant difference between groups based on timing of the last clopidogrel dose.

COMMENT

Optimal preoperative management of clopidogrel therapy before abdominal surgical procedures remains controversial. While current guidelines suggest discontinuation of clopidogrel 5 to 7 days before an operative procedure, this recommendation is based on studies reported in the cardiac literature. Although our study demonstrates a significantly increased risk of postoperative bleeding requiring transfusion in group A patients, no significant difference in bleeding-associated reoperation, life-threatening morbidity, or mortality was demonstrated by timing of clopidogrel cessation. This result remained consistent after controlling for urgency of the operative intervention and procedure. We conclude that while clopidogrel use within 7 days of operation is an independent risk factor for increased postoperative bleeding, these complications are predominantly not life-threatening and are amenable to supportive care with transfusion. Clopidogrel use within 7 days of an operative procedure does not appear to increase patient morbidity or mortality secondary to postoperative hemorrhage.

Increased ICU requirements and mortality rates in group A patients identified in this study are likely attributable to population bias, since patients in group A were more likely to undergo emergency operative intervention and had higher preoperative American Society of Anesthesiologists scores. After controlling for urgency of an operation, our data demonstrated comparable mortality rates and ICU requirements for patients undergoing elective procedures, regardless of the timing of clopidogrel cessation. Adverse outcomes identified in this study are likely secondary in part to the acuity and severity of the underlying condition that called for operative intervention rather than timing of clopidogrel discontinuation. As such, delaying semi-emergency or emergency operations based on recent clopidogrel exposure may increase patient morbidity and mortality due to the underlying disease process. As most postoperative bleeding complications are amenable to supportive care, risk of surgical delay likely outweighs risk associated with those complications.

Outcome assessment by operative procedure suggested patients undergoing colorectal resection to be a particularly vulnerable population. Seventy-one percent of postoperative bleeding complications, 70% of ICU requirements, and 83% of mortalities occurred in this subset of patients. Colorectal resection was also an independent risk factor for postoperative bleeding complications, with an odds ratio of 6.3, regardless of timing of
Clopidogrel cessation. Unfortunately, the power of this study was not sufficient to ascertain whether this difference was secondary to timing of clopidogrel cessation or other factors, including population characteristics and urgency of operation. Studies specifically addressing colorectal resection are necessary.

While current guidelines recommend cessation of clopidogrel 5 to 7 days before an operative procedure, our data demonstrate that timing of clopidogrel cessation within 7 days of an operative procedure does not affect the prevalence of postoperative bleeding requiring transfusion or mortality. A trend toward decreased risk of postoperative bleeding complications, however, is evident in patients discontinuing clopidogrel 7 or more days before an operation. Thus, for physicians recommending cessation of clopidogrel before elective abdominal operations, we suggest 7 days as a guideline.

The major strength of this study is that, to our knowledge, it represents the largest single-institution experience of patients taking clopidogrel who underwent abdominal operations. All patients had access to comparable operative and postoperative care. Study limitations include the retrospective design, inability to verify precise criteria used for intraoperative or postoperative transfusion, and inability to assess the incidence of thrombotic and ischemic events subsequent to the immediate postoperative period. Overall, 6 patients experienced a postoperative ischemic event, 4 in group A (9%) and 2 in group B (3%). Studies addressing the incidence of postoperative ischemic and thrombotic complications are necessary. In addition, preoperative or intraoperative use of platelet function analysis was not routinely used at our institution during the study period. Moreover, it is still unclear whether the results of such tests reliably identify patients at increased risk of bleeding.10 Nevertheless, as platelet function testing becomes more accurate and accessible, the value of such measurements in our patient population would grow because they would minimize the risk of bleeding and thrombotic complications for patients at high risk. Studies including this factor are necessary.

CONCLUSIONS

Clopidogrel cessation less than 7 days before an abdominal operation significantly increases the risk of postoperative bleeding requiring transfusion; however, it does not appear to increase the risk of life-threatening morbidity or mortality after controlling for the urgency of operative intervention. We conclude that semi-emergency and emergency operative interventions should not be delayed based on recent clopidogrel use. In addition, cessation of clopidogrel before elective operative procedures in high-risk patients may not be necessary. Colorectal resection, however, may be an exception, and cessation before elective procedures is advisable. For physicians advising cessation of clopidogrel before elective abdominal surgical procedures, we recommend 7 days as a guideline.

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REFERENCES


Is Timing Really Everything in Patients Receiving Antiplatelet Therapy?

A 65-year-old man with a nearly obstructing sigmoid colon cancer underwent cardiac catheterization 4 months ago and was receiving clopidogrel for his coronary stent (last dose on the day prior to my evaluation). Therefore, his circulating platelets had undergone irreversible inhibition, causing altered function. An emergent/urgent operation may be associated with increased bleeding that could be managed with either platelet or red blood cell transfusion; cessation of clopidogrel for 7 days before the procedure would be anticipated to allow replacement of the circulating platelet volume with functional platelets but perhaps put his coronary stent at risk for thrombosis. While this latter event may be catastrophic, the per-day risk is quite minimal; in the placebo arm of the PCI-CURE (Percutaneous Coronary Intervention—Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial of clopidogrel therapy in patients undergoing percutaneous coronary intervention with stent placement, 7.2% of the patients experienced myocardial infarction, urgent revascularization, or cardiovascular death during a year of follow-up. The question remains whether the bleeding that occurs in patients undergoing abdominal surgery during active antiplatelet therapy is manageable or whether it is associated with life-threatening complications. Cherignoz et al retrospectively reviewed the medical records of 104 patients who underwent a variety of abdominal operations and evaluated the outcomes stratified by the timing of clopidogrel cessation. The finding of an increased rate of postoperative bleeding requiring red blood cell transfusion in patients whose clopidogrel was withdrawn less than 7 days prior to surgery compared with those in whom it was stopped 7 or more days prior to surgery is not surprising and is consistent with many other studies. However, when controlling for other factors associated with operative morbidity or mortality (eg, American Society of Anesthesiologists classification, urgency of procedure), there was not a significant increase in major morbidity or overall mortality.

For ethical reasons, there will never be a randomized trial to determine the optimal timing of clopidogrel cessation in elective abdominal surgery, so retrospective series are the only source of data to guide surgeons in choices of operative management. The data as presented by Cherignoz et al demonstrate that the timing of clopidogrel cessation has little effect in most elective abdominal operations if perioperative transfusion is an acceptable tradeoff for a 7-day delay. The devil lies in the details—the consequences of blood product transfusion (which are not insignificant) must be acceptable to both the surgeon and the patient in the decision-making process of the timing of operative intervention.

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