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The evaluation of clopidogrel use in perioperative general surgery patients: a prospective randomized controlled trial

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Abstract

BACKGROUND: The perioperative safety profile of clopidogrel, a potent antiplatelet agent used in the management of cardiovascular disease, is unknown, and there are no evidence-based guidelines recommending for either its interruption or continuation at this time. The aim of this study was to determine whether patients who are maintained on clopidogrel before general surgical procedures are at increased risk of perioperative bleeding complications.

METHODS: Patients receiving clopidogrel at the time of elective general surgery were randomized to either discontinue clopidogrel 1 week before surgery (group A) or continue clopidogrel into surgery (group B). All other antiplatelet and anticoagulant agents were discontinued before surgery. The primary end points were perioperative bleeding requiring intraoperative or postoperative transfusion of blood or blood components and bleeding-related readmission, reoperation, or mortality within 90 days of surgery. The secondary end points were perioperative myocardial infarction or cerebrovascular accidents within 90 days of surgery.

RESULTS: Thirty-nine patients were enrolled and underwent 43 general surgical operations. Twenty-one procedures were randomized to group A and 22 to group B. The most commonly performed individual procedures were open inguinal hernia repair (23%), laparoscopic cholecystectomy (21%), open ventral hernia repair (15%), laparoscopic ventral hernia repair (11%), and laparoscopic inguinal hernia repair (9%). No perioperative mortalities, bleeding events requiring blood transfusion, or reoperations occurred. One readmission for intra-abdominal hematoma requiring percutaneous drainage occurred in each group (group A: 4.8% vs group B: 4.5%; $P = 1.0$). No myocardial infarctions or cerebrovascular accidents were observed or reported.

CONCLUSIONS: The outcomes from this prospective study suggest that, patients undergoing commonly performed elective general surgical procedures can be safely maintained on clopidogrel without increased perioperative bleeding risk.

Within a year of undergoing percutaneous coronary intervention with stent placement, 5% of patients will require noncardiac surgery.[1–6] Most of these patients will have been prescribed aspirin and/or clopidogrel to reduce the risk of coronary stent occlusion. In this setting, perioperative management can be challenging as interruption of

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antiplatelet agents may lead to major adverse cardiac events whereas continuation may predispose to increased surgical bleeding.

The high-level evidence regarding perioperative aspirin and clopidogrel use in general surgical procedures is limited. The few prospective studies evaluating bleeding and thrombotic risks of perioperative aspirin use have yielded contradictory outcomes,[7–10] and there exist no prospective trials on perioperative clopidogrel use. As a result, current guidelines, largely derived from other fields, tend to be variable and, in some cases, even paradoxical. For example, aspirin and clopidogrel are routinely held before low-risk endoscopic procedures,[11,12] whereas in many high-risk vascular procedures, maintenance of these agents is recommended.[13] In general surgical procedures, which tend to carry a more intermediate risk of bleeding, no clear evidence-based guidelines on the management of antiplatelet agents currently exist.

Although perioperative continuation of dual antiplatelet therapy carries an unacceptably high bleeding risk, continuation of a single antiplatelet agent may be a reasonable approach toward balancing antithrombosis and hemostasis. This notion was recently supported by a meta-analysis of 18 randomized trials (>1,000 patients) specifically describing the significant increase in bleeding risk observed in dual antiplatelet regimens.[14] In this regard, there have been no randomized controlled trials evaluating the perioperative use of single antiplatelet clopidogrel therapy in noncardiac surgery. Several observational studies have identified clopidogrel cessation as a leading cause of major adverse cardiac events in the setting of noncardiac surgery,[15–17] and multiple retrospective studies have demonstrated that continuation of clopidogrel into general surgery was not associated with increased bleeding events.[18–20] Given the increasing prevalence of clopidogrel use, the lack of prospective data regarding its perioperative safety profile and its potential to significantly impact bleeding and thrombotic risk and the management of clopidogrel during general surgical procedures should be specifically addressed. In our randomized controlled trial, we hypothesized that maintenance of clopidogrel during the perioperative period would not increase the rate of clinically significant complications related to bleeding in elective general surgical procedures.

Methods

After the approval of the Mount Sinai School of Medicine Institutional Review Board, we performed a prospective, single-center, randomized controlled trial evaluating perioperative bleeding-related and thrombotic complications in patients who received clopidogrel therapy before general surgical procedures. This trial was registered on ClinicalTrials.gov with the identification number NCT01960296.

Overview and patient enrollment

Preliminary power calculations using an alpha .05 and power of .8 revealed that 3,142 patients (total) would have to be recruited to demonstrate an intergroup difference of 10%. Patient participants from 6 institution-affiliated ambulatory general surgery clinics were assessed for trial eligibility between January 2011 and May 2013. Eligibility requirements included age older than 18 years, receiving clopidogrel 75 mg daily at the time of evaluation, and a nonemergent procedure indication. All patients who fulfilled inclusion criteria were randomly assigned by 1:1 ratio to maintain perioperative clopidogrel or discontinue clopidogrel at least 7 days before surgery. Randomization was performed using statistical software program R (R Development Core Team, Vienna, Austria). Patients concomitantly receiving aspirin or warfarin were instructed to discontinue these medications at least 1 week before surgery. No patients received heparin products or any other form of anticoagulation perioperatively. Exclusion criteria included the use of any nonaspirin, nonclopidogrel antiplatelet agents (ie, prasugrel, ticagrelor, cilostazol, and so forth), emergent nature of surgery, pregnancy, history of bleeding disorders unrelated to medication, and inability to obtain medical clearance from the anesthesiologist, cardiologist, or surgeon. Demographic and medical data were collected on each enrolled patient and included intraoperative estimated blood loss, procedure time, perioperative hospital course, and postoperative length of hospital stay. A flow diagram of the enrollment process is shown in Fig. 1.

Laboratory studies

Preoperative hemoglobin and hematocrit levels were obtained within 30 days of surgery. Preoperative platelet activity was measured using the Platelet Function Assay-100 (Siemens Healthcare, Erlangen, Germany) within 24 hours of surgery. Additional laboratory studies were performed in patients admitted to the hospital based on clinical need.

Perioperative care and follow-up

The result of the randomization was known to the patient and the surgeon in all cases. All enrolled patients were interviewed before the operation to verify adherence to the study protocol. Standard intraoperative hemostatic techniques and materials were used throughout the study period. Decision to transfuse intraoperative blood products was made by the attending surgeon and anesthesiologist involved in the operation and was based on need and the individual risks of each patient. Transfusions in the postoperative period were left up to the discretion of the attending surgeon on record, or the intensive care team, when clinically indicated. Percutaneous interventions were performed by the institution-based interventional radiology