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Perioperative Management of Patients on Clopidogrel (Plavix) Undergoing Major Lung Resection

DuyKhanh P. Ceppa¹, Ian J. Welsby², Tracy Y. Wang³, Mark W. Onaitis¹, Betty C. Tong¹, David H. Harpole¹, Thomas A. D'Amico¹, and Mark F. Berry¹

¹Department of Surgery, Division of Thoracic Surgery, Duke University Medical Center, Durham, North Carolina

²Department of Anesthesiology, Division of Cardiology, Duke University Medical Center, Durham, North Carolina

³Department of Medicine, Division of Cardiology, Duke University Medical Center, Durham, North Carolina

Abstract

BACKGROUND—Management of patients requiring antiplatelet therapy with clopidogrel (Plavix) and major lung resection must balance the risks of bleeding and cardiovascular events. We reviewed our experience with patients treated with clopidogrel perioperatively to examine outcomes, including results of a new strategy for high-risk patients.

METHODS—Patients who underwent major lung resection and received perioperative clopidogrel between January 2005 and September 2010 were reviewed. Initially, clopidogrel management consisted of discontinuation approximately 5 days before surgery and resumption immediately after surgery. Following July 2010, high-risk patients (drug-eluting coronary stent placement within prior year or previous coronary event after clopidogrel discontinuation) were admitted 2–3 days preoperatively and bridged with the intravenous GP IIb/IIIa receptor inhibitor eptifibatide (Integrilin) according to a multidisciplinary cardiology/anesthesiology/thoracic surgery protocol. Outcomes were compared to control patients (matched for preoperative risk factors and extent of pulmonary resection) who did not receive perioperative clopidogrel.

RESULTS—Fifty-four patients who had major lung resection between January 2005 and September 2010 and received clopidogrel perioperatively were matched with 108 controls. Both groups had similar mortality, postoperative length of stay, and no differences in the rates of perioperative transfusions, reoperations for bleeding, myocardial infarctions, and strokes. Seven of the 54 clopidogrel patients were admitted preoperatively for an eptifibatide bridge. Two of these patients received perioperative transfusions, but there were no mortalities, reoperations, myocardial infarctions, or stroke.

CONCLUSIONS—Patients taking clopidogrel can safely undergo major lung resection. Treatment with an eptifibatide bridge may minimize the risk of cardiovascular events in higher risk patients.

Keywords

Lung Cancer Surgery; Outcomes

Introduction

Patients who undergo major lung resection may have complex comorbidities, including coronary artery disease (CAD). Both single-institution [1, 2] and multi-institution studies [3, 4] have reported the incidences of CAD in this patient population of 16 to 27.5%. Furthermore, in the veteran population Harpole, *et al* reported that 10% of 3516 patients undergoing pulmonary resection previously had coronary artery bypass grafting or percutaneous coronary intervention [5].

Currently, the management of CAD may include either bare-metal or drug-eluting stents followed by an appropriate antiplatelet regimen, which generally includes aspirin and clopidogrel (Plavix) for a defined period of time. Premature cessation of antiplatelet therapy is an important cause of in-stent thrombosis [6–8]. Patients who need surgery within the time period during which clopidogrel is required are a unique population. The risks of cardiovascular events from stent thrombosis due to antiplatelet therapy cessation and the procoagulant response to surgical trauma must be balanced with the risks of major bleeding if antiplatelet agents are not held [9, 10]. This clinical situation is relatively common, as 560 000 of 850 000 patients in the United States who underwent treatment of CAD in 2007 had coronary stents placed [11]. Up to five percent of percutaneous coronary intervention (PCI) patients undergo surgery within the first year after coronary stenting [12]. Moreover, the perioperative morbidity and mortality in patients undergoing surgical procedures following PCI with stenting is as high as 40% and 20%, respectively [7, 13].

Data to guide the appropriate management of patients who require both non-cardiac surgical intervention and the use of clopidogrel is limited. In particular, most studies addressing the issue of surgery following coronary stenting have not considered patients undergoing lung resection. We reviewed our experience with patients treated with clopidogrel perioperatively. The purpose of this study was to examine perioperative outcomes in a single center, including a new strategy for high-risk patients. We hypothesized that patients requiring perioperative clopidogrel and major lung resection could be managed such that the risks of both bleeding and cardiovascular events are not different to patients who do not require perioperative clopidogrel.

Patients and Methods

After local Institutional Review Board approval was granted, including waiver of the need for patient consent, the Duke University Medical Center prospectively maintained General Thoracic Database was queried for patients who had undergone pulmonary resection and had received clopidogrel during the same hospitalization between January 2005 and

September 2010. Initially, perioperative clopidogrel management for all patients consisted of discontinuation approximately 5 days before surgery and reinitiation 12 to 72 hours after surgery at the daily maintenance dose of 75mg without a loading dose. Following July 2010, high-risk patients (drug eluting coronary stent placement within prior year, off-label use of coronary stent, critical location, or previous coronary event after clopidogrel discontinuation) stopped clopidogrel 5 days preoperatively, were admitted 2–3 days preoperatively and bridged with the intravenous GP IIb/IIIa receptor inhibitor eptifibatide (Integrilin) according to a multidisciplinary cardiology/anesthesiology/thoracic surgery protocol. Clopidogrel was reinitiated 12 to 48 hours after surgery at the daily maintenance dose of 75mg; the eptifibatide was infused at 2 mcg/kg/min or 1mcg/kg/min if the creatinine clearance was <60 ml/minute and discontinued eight hours prior to surgery. Clopidogrel reinitiation was the same regardless of surgical approach or extent of resection.

Patients who underwent a lobectomy or lung volume reduction surgery had an epidural for post-operative analgesia. Epidurals were removed at least six hour prior to resumption of clopidogrel. In general, patients who received eptifibatide did not undergo epidural placement. All patients remained on their preoperative dose of aspirin throughout the perioperative period. Evaluation of platelet function with laboratory testing was not routine.

Thoracoscopic procedures, including lobectomy, were performed without any rib spreading with the thoracoscope placed in the 8th intercostal space in the midaxillary line and a 4–5cm anterior utility incision in the 5th intercostal space. Thoracotomy in most patients was via standard posterolateral approach with sparing of the serratus muscle; one surgeon during the study time period utilized an approach where both the latissimus and serratus muscles were spared and notching of the sixth rib was performed. Hemostatic agents and/or sealants are available in our institution but infrequently used in lung resection procedures and were not used as a routine basis in the patients in this study. Chest tubes were routinely placed on water seal immediately postoperatively and removed when no air leak was present and drainage over 24 hours was less than 200ml over a 24hr period. Chest tube management for patients receiving clopidogrel did not differ from the management used in general for lung resection patients, and the timing of clopidogrel reinitiation did not depend on the presence of a chest tube.

Patients who had received perioperative clopidogrel were matched 1:2 with control patients who did not receive clopidogrel from an institutional, prospective database of 2246 patients who underwent lung resection between 1999 and 2010 using a greedy matching algorithm. Control patients were consecutively identified using a computer program that compared each study patient to all remaining patients in the database who had not been given clopidogrel. The matching algorithm calculated a value of the distance between the study patient and potential control patient from the database using a weighted formula that considered age, stage, resection extent, surgical approach, history of coronary artery disease, history of radiation, history of chemotherapy, FEV1, and DLCO. The patient from the database with the minimum distance was selected as the control for that study patient and removed from future consideration for other study patients. This comparison was repeated for each study patient, and then the entire process was repeated for all study patients to form the 1:2 control group.

Retrospective review of the clopidogrel and control patients was performed with comparison of demographics, preoperative characteristics and comorbidities, histology and stage of disease, intraoperative details, and postoperative course. Any postoperative event prolonging or otherwise altering the postoperative course was recorded along with all operative deaths, which were defined as deaths that occurred within 30 days after operation or those that occurred later but during the same hospitalization. Deaths were captured both by chart review and use of the Social Security Death Index Database. The definitions of postoperative events were based on the Society of Thoracic Surgeons General Thoracic Surgery Database [14]. Overall morbidity was defined as the occurrence of at least one postoperative event. Unpaired student's *t* tests were used to compare continuous data, Fisher's exact tests for dichotomous data, and χ^2 for categorical variables. A two-tailed *p* value of less than 0.05 was considered significant. Data are presented as mean $\pm$ standard error of the mean unless otherwise noted. The SAS 9.2 statistical package (SAS Institute, Cary, North Carolina) was used for statistical analyses.

Results

Between January 2005 and September 2010, 54 patients who had major lung resection and received clopidogrel perioperatively. The indications for antiplatelet therapy in the clopidogrel patients were history of coronary stent (n=40, 74%), medically treated coronary artery disease (n=7, 13%), postoperative myocardial infarction with PCI (n=3, 5.6%), cerebrovascular or peripheral vascular disease (n=3, 5.6%), and unknown (n=1, 1.8%). Of the 40 patients with coronary stents, 20 (37%) patients met criteria for high risk of stent thrombosis.

This group was matched with 108 patients not receiving clopidogrel who underwent major lung resection during the same time period (controls). Demographic, baseline characteristics, and comorbid conditions are shown in Table 1. Indications for resection and operative details are listed in Table 2. Clopidogrel and control patients were well matched in terms of characteristics that could be risk factors for coronary events, including age, history of coronary disease, hypertension, diabetes, cerebrovascular disease, peripheral vascular disease, congestive heart failure, tobacco abuse, and renal insufficiency. Clopidogrel and control patients were also well matched in terms of characteristics that could be risk factors for increased blood loss, including indication for operation, operative approach, extent of resection, previous thoracic surgery, preoperative chemotherapy, and preoperative radiation therapy. Clopidogrel and control patients were also similar in terms of characteristics that could be risk factors for morbidity in general, including COPD, FEV1, and steroids. The only variable in which the two groups of patients differed statistically was DLCO, though the actual difference is small and likely not clinically significant (62 vs. 69% predicted). Seventy-eight percent of patients in the clopidogrel group (42 of 54) and 76% of patients in the control group (82 of 108) were approached thoracoscopically.

Twenty-nine (53.7%) patients underwent the placement of thoracic epidurals for postoperative analgesia, including one of the patients who received eptifibatide. Thoracic epidurals remained in place for a median of 2 days (range 1 to 3 days).

Postoperative events are listed in Table 3. Both groups had no difference in mortality, postoperative length of stay, and no differences in the rates of perioperative transfusions, reoperations for bleeding, myocardial infarctions, and strokes. The occurrences of other postoperative events were also not different between the two groups.

Seven of the 54 clopidogrel patients were admitted preoperatively for an eptifibatide bridge according to our protocol for high risk of stent thrombosis (Figure 1). All of these patients had recent coronary stents or a history of previous cardiovascular events after clopidogrel discontinuation. The procedures performed in these seven patients were thoracoscopic lobectomy (n=3), lobectomy via thoracotomy (n=1), thoracoscopic wedge resection (n=2), and bilateral thoracoscopic lung volume reduction surgery (n=1). There were no preoperative events related to eptifibatide infusion. Two of these patients (28.6%) received perioperative transfusions, but there were no mortalities, reoperations, myocardial infarctions, or stroke.

Comment

Data to guide the most appropriate management of patients who require noncardiac surgical intervention and who have recently undergone coronary stenting is very limited [15]. It is clear, however, that premature cessation of antiplatelet therapy is a significant contributor to in-stent thrombosis [6]. Patients who undergo surgery, and thus stop antiplatelet therapy, less than 35 days following coronary stenting are at the highest of stent thrombosis [12]. ACC/AHA 2007 guidelines recommend continuing dual anti-platelet therapy and delaying surgery for 6 weeks in patients with bare metal stents and for 12 months in patients with drug-eluting stents [16, 17].

Unfortunately, the majority of patients undergoing noncardiac thoracic surgery cannot afford to delay surgery for 12 months due to oncologic reasons. Additionally, there is a significant growing population of patients in whom coronary stents were placed under “off-label” uses (i.e., high risk locations, bifurcations, distal small vessels) who may have a heightened risk of stent thrombosis if not protected by dual antiplatelet agents regardless of when the stent was placed [18]. Although stereotactic radiosurgery can be considered for particular patients with malignant lesions in appropriate locations, other non-operative percutaneous techniques (such as radiofrequency ablation, where the ability to control peri-procedural bleeding is limited) also face similar clopidogrel management decisions. Therefore, the perioperative management options for those patients for whom surgery is the optimal or only therapy are (1) clopidogrel cessation for surgery and reinitiation as soon as possible postoperatively, which may involve a higher risk of cardiovascular events (2) continuation of dual-antiplatelet therapy through the perioperative period for patients, which likely involves an increased risk of perioperative bleeding, and (3) implementation of a “bridging” therapy to balance the risks of bleeding and cardiovascular events [19–21]. The use of a heparin infusion as a bridge to surgery has not been shown to be beneficial, perhaps because heparin does not have antiplatelet properties and is not protective against stent thrombosis [12, 22]. GP IIb/IIIa inhibitors are favored since the platelet receptor it binds to is the pivotal mediator for platelet aggregation and thrombus formation [23]. To date, however, there are

not sufficient data to either support or discount the use of GP IIb/IIIa inhibitors as a bridge to surgery upon cessation of clopidogrel.

We present in this report our series of 54 patients taking clopidogrel perioperatively who underwent major pulmonary resection. Our initial protocol involved reinitiation of clopidogrel as soon as possible following surgery, preferably within 12 to 72 hours postoperatively. Although outcomes overall were not different to matched controls, two of the patients under the initial protocol had a myocardial infarction. One patient was not identified as having CAD preoperatively but suffered a myocardial infarction. The patient underwent cardiac catheterization and was initiated on clopidogrel as his anatomy was unfavorable for either percutaneous or surgical revascularization. The second patient thrombosed a drug-eluting stent on the evening of post-operative day zero. The stent had been placed in the left anterior descending artery less than one year prior to surgery. This patient underwent immediate cardiac catheterization and patency of the stent was achieved. However, the patient succumbed to subsequent complications twenty-seven days postoperatively. This patient's perioperative course was the initiating factor in the multi-disciplinary development of a new management strategy using the eptifibatide bridge for patients considered to be at high risk for complications due to clopidogrel cessation.

In order to better manage patients considered to have higher risks of cardiovascular events if clopidogrel were discontinued, we developed a protocol incorporating anesthesia and cardiology input using the GP IIb/IIIa receptor inhibitor eptifibatide as a bridge to surgery. While the study was not sufficiently powered to detect a difference in cardiovascular events given the limited sample size, none of the seven patients on an eptifibatide bridge suffered a major adverse cardiovascular event.

Two of the seven patients (28.6%) who were placed on an eptifibatide bridge required transfusion of blood products. The first patient had bronchiectasis with a history of multiple recurrent pulmonary infections. Not surprisingly, this patient's operation involved an extensive period of lysis of adhesions prior to completion of the lobectomy. The patient received postoperative transfusion of blood on account of high chest tube output with a concurrent decrease in the patient's hemoglobin level. This fact is concurrent with a prior study in which patients undergoing redo thoracotomy while taking clopidogrel required blood transfusions [21]. The second patient had platelet dysfunction, as evidenced by abnormal platelet aggregation studies, despite cessation of clopidogrel five days preoperatively and discontinuation of eptifibatide eight hours preoperatively. A previous study on patients with preoperative eptifibatide infusions undergoing urgent coronary artery bypass grafting suggests, however, that being treated with eptifibatide preoperatively does not increase the risk of perioperative bleeding [24]. Routine use of platelet function testing was not performed during this study. However, we are increasing our use of platelet aggregation studies in the setting of patients on clopidogrel and eptifibatide pre-operatively. Perhaps these platelet function studies will play a role in our management of these patients in the future in order to decrease bleeding complications.

While this study suffers from the inherent limitations of a retrospective case series, it represents the largest case series of perioperative management of clopidogrel in patients

undergoing pulmonary resection on clopidogrel. We demonstrate that patients taking clopidogrel can safely undergo major lung resection with a morbidity and mortality rate similar to those of matched controls. Additionally, we describe the use of a GP IIb/IIIa receptor inhibitor as an antiplatelet agent bridge designed to minimize the risk of cardiovascular events in patients classified by our multidisciplinary protocol to be at high risk of stent thrombosis. Although ongoing studies with either randomized controlled trials or prospective, multi-institutional registries are clearly needed to better refine the optimal management strategy in this complex set of patients, we believe that our approach is a rational method of balancing the risks of cardiovascular events and bleeding in patients who require a major lung resection and the antiplatelet agent clopidogrel.

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Figure 1.

Algorithm for perioperative clopidogrel management.

Patients who are at lower risk of in-stent thrombosis (coronary stenting >3 years prior to surgery, bare-metal stent >1 year with no history of acute MI) proceed to surgery on aspirin following a 5 day period of clopidogrel cessation. Patients who are at higher risk of in-stent thrombosis (drug-eluting stent <12 months, drug-eluting stent >12 months who have a high risk clinical factors--renal insufficiency, critical location, off-label placement of coronary stent) are bridged to surgery with an eptifibatide infusion after 3 days of clopidogrel cessation.

Table 1

Demographics, Baseline Characteristics, and Comorbid Conditions.

Characteristic	Clopidogrel (n=54)	Controls (n=108)	p-value
Age (years)	68±9	68±9	0.8
History of Coronary Artery Disease	47 (87%)	94 (87%)	1
Preoperative Chemotherapy	4 (7%)	8 (7%)	1
Preoperative Radiation Therapy	3 (6%)	4 (4%)	0.6
Prior Thoracic Surgery	13 (24%)	32 (30%)	0.5
Forced Expiratory Volume in one second (% predicted)	68±20	65±21	0.47
Diffusing Capacity of the Lung for Carbon Monoxide (% predicted)	62±18	69±20	0.03
Tobacco Abuse	46 (85%)	79 (73%)	0.11
Pack Years	47±27	56±31	0.1
Hypertension	45 (83%)	80 (74%)	0.23
Chronic Obstructive Pulmonary Disease	21 (39%)	42 (39%)	1
Diabetes	14 (26%)	24 (22%)	0.7
Cerebrovascular Disease	7 (13%)	9 (8%)	0.4
Peripheral Vascular Disease	7 (13%)	9 (8%)	0.4
Congestive Heart Failure	4 (7%)	12 (11%)	0.6
Renal Insufficiency	4 (7%)	7 (6%)	1
Steroid Use	3 (6%)	6 (3%)	1

Table 2

Indications for resection and operative details.

	Clopidogrel (n=54)	Controls (n=108)	p-value
Operative Approach			
Thoracoscopy	42 (78%)	82 (76%)	0.8
Thoracotomy	12 (22%)	26 (24%)	
Extent of Resection			
Wedge Resection or Segmentectomy	19 (37%)	36 (33%)	1
Bilateral Lung Volume Reduction	1 (2%)	2 (2%)	
Lobectomy or Bilobectomy	31 (57%)	64 (59%)	
Pneumonectomy	3 (6%)	6 (6%)	
Indication for Operation			
Benign Disease	9 (17%)	19 (18%)	0.9
Primary Lung Cancer	40 (74%)	81 (75%)	
Metastatic Disease	5 (9%)	8 (7%)	

Table 3

Postoperative Events.

Event	Clopidogrel (n=54)	Controls (n=108)	p-value
Thirty-day Mortality	2 (3.7%)	4 (3.7%)	1
Thirty-day Morbidity	21 (39%)	54 (50%)	0.2
Median Length of Postoperative Stay (days)	4 (range 1–65)	5 (range 1–48)	0.9
Chest Tube Duration (days, median)	3 (range 1–20)	3 (range 1–53)	0.6
Perioperative Transfusion	11 (20%)	17 (16%)	0.5
Reoperation for Bleeding	0	1 (1%)	1
Myocardial Infarction	2 (4%)	0	0.11
Stroke	2 (4%)	1 (1%)	0.3
Atrial arrhythmia	12 (22%)	27 (25%)	0.8
Need for chest tube > 5 days	9 (17%)	18 (17%)	1
Post-operative bronchoscopy	8 (15%)	10 (9%)	0.3
Pneumonia	6 (11%)	7 (6%)	0.4
Delirium/Mental Status Changes	2 (4%)	7 (6%)	0.7
Unplanned reintubation	3 (6%)	4 (4%)	0.7
Need for enteral nutrition tube	0	4 (4%)	0.3
Wound Infection/Empyema	2 (4%)	2 (2%)	0.6
Need for tracheostomy	2 (4%)	2 (2%)	0.6
Deep Venous Thrombosis	2 (4%)	1 (1%)	0.3
New Renal Insufficiency	0	2 (2%)	0.6
Re-operation for decortication	1 (2%)	0	0.3
Vocal cord paralysis	0	1 (1%)	1