Interactive CardioVascular and Thoracic Surgery 14 (2012) 162–166
doi:10.1093/icvts/ivr005 Advance Access publication 30 November 2011

INSTITUTIONAL REPORT

Risk is not our business: safety of thoracic surgery in patients using antiplatelet therapy†

Luca Bertolaccini[a,*], Alberto Terzi[a], Giovanna Rizzardi[a], Alberto Gorla[a], Andrea Viti[a], Sarah Palmisano[b], and Giuseppe Coletta[b]

[a] Thoracic Surgery Unit, S. Croce e Carle City Hospital, Cueno, Italy
[b] Anesthesiology Unit, S. Croce e Carle City Hospital, Cuneo, Italy

* Corresponding author. Thoracic Surgery Unit, S. Croce e Carle City Hospital, Via Michele Coppino 26, 12100 Cuneo, Italy. Tel: +39-0171-642286; fax: +39-0171-642491; e-mail: luca.bertolaccini@unito.it (L. Bertolaccini).

Received 15 June 2011; received in revised form 14 August 2011; accepted 17 August 2011

Abstract

American Heart Association recommendations have changed preoperative management of patients with antiplatelet therapy (APT). We assessed safety and outcomes of surgery in patients who were receiving APT. A prospective study of patients operated on while receiving APT was matched with those with no APT (ratio 1:4), using the propensity score method. Logistic regression analysis was used to identify covariates among imbalanced baseline patient variables. Both χ^2 test and Fisher's test were used to calculate the probability value for the comparison of dichotomous variables. Between January 2008 and December 2010, 38 patients who received APT at the time of surgery were matched with 141 patients who had not received APT. APT indications were a history of myocardial infarction, coronary artery by-pass graft and/or valve replacement (19), coronary artery stent (11) and severe peripheral vascular disease (8). None of the patients required re-operation for bleeding. Two patients received blood transfusions. The amount of chest tube drainage was not statistically significantly different. There were no statistically significant differences between the outcomes for the operative time, length of hospital stay, estimated blood loss or morbidity. The results show that thoracic surgical procedures can safely be performed in patients receiving APT at the time of surgery, with no increased risk of bleeding or morbidity and no differences in the operative time and the length of hospital stay.

Keywords: Antiplatelet therapy • General thoracic surgery • Surgical outcome • Propensity score-matching methods

INTRODUCTION

Advances in anticoagulant and antiplatelet regimens are associated with a significant risk reduction in the occurrence of thrombotic events. However, this risk reduction carries an increased risk of bleeding during and after surgery. Aspirin is the main antiplatelet medication used in patients with coronary artery disease, but there is growing evidence that the use of the more potent antiplatelet Clopidogrel, on its own or in combination with aspirin, has superior outcomes in both chronic and acute settings. Clopidogrel and Ticlopidine are thienopyridines. They are prodrugs that are metabolized in the liver into active metabolites that are non-competitive antagonists of the platelet adenosine diphosphate receptor, P2Y12. Clopidogrel is an acetate derivative of Ticlopidine, which has several advantages, including more rapid onset of action, more potent antiplatelet effect and lower incidence of severe neutropenia and thrombotic thrombocytopenic purpura. The antiplatelet effect of Clopidogrel is time and dose dependent. A maximal inhibition of platelet aggregation of 50–60% can be achieved with a dose of 75 mg daily (without a loading dose) within 4–7 days, or more rapidly with a loading dose of 300–600 mg within 4–24 h. This level of platelet inhibition caused an increase in the bleeding time of healthy human volunteers. Platelet function recovered completely 7 days after Clopidogrel stoppage in healthy volunteers [1]. The recent recommendation from the American Heart Association's Science Advisory Committee is that patients who have undergone placement of a drug-eluting coronary artery stent should continue to receive dual antiplatelet therapy (APT) for at least 12 months [2]. Dual APT has become the mainstay treatment strategy for the prevention of stent thrombosis. Premature discontinuation of APT markedly increases the risk of stent thrombosis, a catastrophic event that frequently leads to myocardial infarction and/or death. Factors contributing to premature cessation of APT may include drug cost, physician/dentist instructions to patients to discontinue therapy before procedures and inadequate patient education and understanding about the importance of continuing therapy. To eliminate the premature discontinuation of APT, the American Heart Association's Science Advisory Committee has given the innovative recommendations, which have changed the setting of the preoperative management of these patients all over the world [3]. The discontinuation

† Presented at the 19th European Conference on General Thoracic Surgery, Marseille, France, June 5–8, 2011.

Table 1: Characteristics of patients

Patient characteristics	Patients receiving anti-aggregation ($n = 38$)	Propensity score-matched patients not receiving antiplatelet therapy ($n = 141$)	*P*
Age, years (mean) ± SD (range)	68 ± 5 (47–81)	67 ± 8 (49–71)	1.00
Male, *n* (%)	21 (55)	103 (73)	
Female, *n* (%)	17 (45)	40 (28)	
History of myocardial infarction, CABG and/or valve placement, *n* (%)	19 (50)	78 (55)	0.6963
Presence of a coronary stent, *n* (%)	11 (29)	42 (30)	1.00
History of severe peripheral vascular disease, *n* (%)	8 (21)	17 (12)	0.1673
Patient on dual APT	9 (24%)	0	
Patient taking aspirin	17 (45%)	0	
Patient taking Clopidrogel	12 (31%)	0	

Table 2: Types of surgical operation

	Patients receiving anti-aggregation ($n = 38$)	Propensity score-matched patients not receiving antiplatelet therapy ($n = 141$)
Lobectomy	18	68
Mediastinoscopy	8	28
VATS ± wedge resection	7	25
Wedge resection	2	9
Decortication	2	8
Thymectomy	1	3

of different types of APT can delay thoracic surgery for at least 6 weeks; in addition, it exposes patients to a higher risk of a perioperative myocardial infarction. Because of these new perspectives in APT, we assess the safety of surgical operation on patients who were receiving APT.

MATERIALS AND METHODS

We report a consecutive series of patients who received APT up to and including the day of thoracic surgery, as well as each day postoperatively, between January 2008 and December 2010. According to the guidelines, individual consent to go on with APT was obtained after open discussion about the risk of therapy discontinuation. These patients were matched 1:4 with patients who were not receiving APT at the time of surgery according to a propensity score as the greedy matching technique (Appendix A).

Statistical analysis

Logistic regression analysis was used to identify covariates among the baseline patient variables that were imbalanced between the two groups from which the model was derived. Resulting matched patients were analysed for differences in selected intraoperative and postoperative outcomes such as operating time, estimated blood loss, length of hospital stay and 30-day operative morbidity and mortality. Pearson's χ^2 test was used to calculate the probability value for the comparison of dichotomous variables. Fisher's exact test was used when the number in any cell was less than five. Statistical and mathematical models were created and analysed using Wolfram Mathematica 8.0 (Wolfram Mathematica is a computational software program used in scientific, engineering and mathematical fields and other areas of technical computing. See http://www.wolfram.com/).

RESULTS

From January 2008 to December 2010, 38 patients were receiving APT at the time of thoracic surgery. Logistic regression analysis identified history of myocardial infarction and/or coronary artery by-pass graft (CABG) and/or valve placement, coronary stent and history of peripheral vascular disease as predictors for being on a regimen of APT at the time of surgery. This process matched 141 control patients from our prospective database. Table 1 lists selected preoperative patient characteristics between the two groups. There were no significant differences in age, history of coronary artery disease, presence of a coronary stent and peripheral vascular disease between the two groups. The indications for APT at the time of surgery were as follows: coronary artery stents in 11 (29%) patients, history of coronary artery diseases in 19 (50%) patients and severe peripheral vascular disease in 8 (21%) patients. Table 2 shows the types of thoracic operations performed. Table 3 shows the intraoperative and postoperative outcomes. Nine (24%) of the 38 patients receiving APT were receiving dual APT at the time of surgery. Two (5%) of the 38 patients receiving APT had atrial fibrillation, and blood transfusion was required in an other two (5%) patients. None of the patients who underwent primary thoracotomy required a re-operation for bleeding. The amount of chest tube drainages was not statistically significantly higher in patients receiving APT. Chest tube drainages were removed when the daily amount of drainage was <200 ml without the

Table 3: Intraoperative and postoperative outcomes

	Patients receiving anti-aggregation ($n = 38$)	Propensity score-matched patients not receiving antiplatelet therapy ($n = 141$)	*P*
Total amount of chest tubes, ml ± SD (range)	340 ± 70 (220–470)	370 ± 110 (150–680)	0.2764
Redo thoracotomy for bleeding, *n* (%)	0	2 (1%)	0.3473
Average length of hospital stay, days (range)	4.3 (0–6)	5.5 (0–28)	0.2665
Postoperative surgical morbidity, *n* (%)	0	5 (4)	0.4563
Postoperative medical morbidity (including blood transfusions), *n* (%)	4 (11)	23 (16)	0.4414
Operative mortality, *n* (%)	0	2 (1)	0.3562

presence of air leaks. There was no operative death in the antiaggregation group. There were two (1%) postoperative deaths in the control group. Both the patients underwent lobectomy and had a postoperative pneumonia with acute respiratory distress syndrome. There were no statistically significant differences between the outcomes for the 38 patients receiving APT compared with the controls for operative time, length of hospital stay, estimated blood loss or morbidity when stratified by the procedure.

DISCUSSION

Cardiovascular diseases are the most common disease in the general population and APT is increasingly used; thus, thoracic operation may be needed in patients with APT. On the other hand, bleeding after thoracic surgery operations is a well-known issue, mainly after major surgical operations. Clopidogrel and aspirin affect platelet inhibition through different mechanisms; Clopidogrel acts by inhibiting adenosine diphosphate-dependent platelet activation and aspirin acts by inhibiting thromboxane-dependent platelet activation [4]. In current daily practice, concerns on perioperative bleeding still lead to premature discontinuation of APT preoperatively. However, despite the increased risk of haemorrhage, the transfusion rate after surgery in patients with or without APT was not found to be significantly different in some studies [5]. In contrast, a significant increase in major bleeding and re-operation was seen in patients with acute coronary syndromes requiring CABG with cardiopulmonary bypass, if Clopidogrel was not stopped at least 5 days before the intervention [6]. On the other hand, no significant increase in bleeding was described despite continuation of APT in patients with acute coronary syndrome and off-pump bypass surgery [7]. Perioperative bleeding risk is related to the type of surgery. Minor surgical interventions, as well as angiographic diagnostic procedures or diagnostic endoscopies, can be performed under full APT if no additional bleeding risks exist while a haemorrhagic risk with dual APT is reported in trans-bronchial surgery [8]. In patients on dual APT undergoing any type of urgent surgery, stopping APT will not reduce platelet inhibition in a timely manner and multidisciplinary preparations for potential haemorrhagic complications should be undertaken. When aspirin is used for primary prevention, cardiovascular events had not been reported by discontinuation of aspirin 5–7 before any type of surgery [9]; when aspirin is needed for secondary prevention data from meta-analysis on discontinuation or non-adherence to aspirin therapy indicated an increased risk of cardiovascular events [10]. So, except for intracranial surgery and transurethral prostatectomy, aspirin should not be discontinued. Only when major bleeding complications are to be expected, discontinuation of APT 5–7 days before operation should be evaluated on a case-by-case basis [11]. Cardiac surgery is the field where Clopidogrel has extensively been studied [12]. There are few studies reporting on the use of Clopidogrel in addition to aspirin; a recent review of cardiac surgical procedures concluded Clopidogrel added to aspirin increased the risk of bleeding with no increase in mortality [13].

In the field of general thoracic surgery, only one paper by Cerfolio [14] reported the use of Clopidogrel, showing that many types of general thoracic surgical procedures can safely be performed in patients who are receiving Clopidogrel and aspirin without increased risk of bleeding after primary thoracotomy or minimally invasive thoracic surgery although in the preoperative evaluation he did not obtain a thromboelastogram to evaluate platelets function. Patients with thoracic diseases were sometimes not able to undergo surgical operation because of the widely documented risk of stopping these medicines prematurely [15], because of the assumption that surgery could not be safely performed on patients who were receiving Clopidogrel and aspirin. This treatment strategy, while the standard of care in many institutions, actually provides a non-optimal care for the patients.

Despite the paucity of literature to support the feasibility of this approach, we were conscious of cardiac surgeons who operated on patients taking APT either urgently or unknowingly with good results. In our limited and initial experience, we have shown that general thoracic surgery can be performed safely in patients who are receiving APT and who also underwent a major operation. There was no increased risk of bleeding in patients who were receiving both Clopidogrel and aspirin. There were not statistically significant differences in the amount of drainage and in the timing of chest tube removal between the two groups.

Our study has some limitations like those reported by Cerfolio [14]. Being a single centre study, the number of patients is relatively small. The propensity scores have confidence in the ability of matching from the population of potential controls. The small number of events is also a limitation of the current study.

Multivariate analysis could not be performed because of this small number.

Even if further studies are needed, thoracic surgical procedures can safely be performed in patients who are receiving APT at the time of surgery. There is no increased risk of bleeding or morbidity, and there are no differences in the operative time and length of hospital stay. In conclusion, until more evidence is available, APT during surgery should be continued unless there is an absolute contraindication. In our opinion, therefore, in patients who are receiving APT at the time of surgery having packed red blood cells and platelets ready is safer than having an acute vascular or cardiac event.

Conflict of interest: none declared.

REFERENCES

[1] Patrono C, Bachmann F, Baigent C, Bode C, De Caterina R, Charbonnier B *et al.*; European Society of Cardiology. Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European Society of Cardiology. Eur Heart J 2004;25: 166–81.

[2] Grines CL, Bonow RO, Casey DE Jr, Gardner TJ, Lockhart PB, Moliterno DJ *et al.*; American Heart Association; American College of Cardiology; Society for Cardiovascular Angiography and Interventions; American College of Surgeons; American Dental Association; American College of Physicians. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. Circulation 2007;115: 813–8.

[3] Kim DH, Daskalakis C, Silvestry SC, Sheth MP, Lee AN, Adams S *et al.* Aspirin and Clopidogrel use in the early postoperative period following on-pump and off-pump coronary artery bypass grafting. J Thorac CardioVasc Surg 2009;138:1377–84.

[4] Payne DA, Hayes PD. Combined therapy with Clopidogrel and aspirin significantly increases the bleeding time through a synergistic antiplatelet action. J Vasc Surg 2002;35:1204–9.

[5] Wilson SH, Fasseas P, Orford JL, Lennon RJ, Horlocker T, Charnoff NE *et al.* Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. J Am Coll Cardiol 2003;42: 234–40.

[6] Ebrahimi R, Dyke C, Mehran R, Manoukian SV, Feit F, Cox DA *et al.* Outcomes following pre-operative Clopidogrel administration in patients with acute coronary syndromes undergoing coronary artery bypass surgery: the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. J Am Coll Cardiol 2009;53:1965–72.

[7] Song SW, Youn YN, Yi G, Lee S, Yoo KJ. Effects of continuous administration of Clopidogrel before off-pump coronary artery bypass grafting in patients with acute coronary syndrome. Circ J 2008;72: 626–32.

[8] Ernst A, Eberhardt R, Wahidi M, Becker HD, Herth FJ. Effect of routine Clopidogrel use on bleeding complications after transbronchial biopsy in humans. Chest 2006;129:734–7.

[9] Cahill RA, McGreal GT, Crowe BH, Ryan DA, Manning BJ, Cahill MR *et al.* Duration of increased bleeding tendency after cessation of aspirin therapy. J Am Coll Surg 2005;200:564–73; quiz A59–61.

[10] Biondi-Zoccai GG, Lotrionte M, Agostoni P, Abbate A, Fusaro M, Burzotta F *et al.* A systematic review and metaanalysis on the hazards of discontinuing or not adhering to aspirin among 50 279 patients at risk for coronary artery disease. Eur Heart J 2006;27:2667–74.

[11] Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ *et al.*; American College of Cardiology/American Heart Association Task Force on Practice Guidelines Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery; American Society for Thoracic Surgery; Society of Thoracic Surgeons. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery. Summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to update the 1999 guidelines on coronary artery bypass graft surgery). J Am Coll Cardiol 2004;44: 1146–54.

[12] Korte W, Cattaneo M, Chassot PG, Eichinger S, von Heymann C, Hofmann N *et al.* Peri-operative management of antiplatelet therapy in patients with coronary artery disease. Joint position paper by members of the working group on Perioperative Haemostasis of the Society on Thrombosis and Haemostasis Research (GTH), the working group on Perioperative Coagulation of the Austrian Society for Anesthesiology, Resuscitation and Intensive Care (ÖGARI) and the Working Group Thrombosis of the European Society for Cardiology (ESC). Thromb Haemost 2011;105: doi: 10.1160/TH10-04-0217.

[13] Purkayastha S, Athanasiou T, Malinovski V, Tekkis P, Foale R, Casula R *et al.* Does Clopidogrel affect outcome after coronary artery bypass grafting? A meta-analysis. Heart 2006;92:531–2.

[14] Cerfolio RJ, Minnich DJ, Bryant AS. General thoracic surgery is safe in patients taking Clopidogrel (Plavix). J Thorac CardioVasc Surg 2010;140: 970–6.

[15] Sharma AK, Ajani AE, Jamwi SM, Maniar P, Lakhani SV, Waksman R *et al.* Major noncardiac surgery following coronary stenting: when is it safe to operate? Catheter CardioVasc Interv 2004;63:141–5.

APPENDIX A: THE GREEDY MATCHING ALGORITHM

The greedy algorithm is an algorithm that follows the problem solving heuristic of making the locally optimal choice at each stage with the hope of finding the global optimum. To reduce the influence of selection on the comparison of outcome, we used propensity scores to compare patients who were receiving APT at the time of pulmonary resection with those who were not receiving APT during pulmonary resection. The propensity-matched analysis is a balancing score method that attempts to correct bias in patient selection by creating equivalent risk groups for analysis. In the statistical analysis of observational data, propensity score matching is a methodology attempting to provide unbiased estimation of treatment effects. In randomized experiments, the randomization enables unbiased estimation of treatment effects; for each covariate, randomization implies that treatment groups will be balanced on average, by the law of large numbers. Unfortunately, for observational experiments, the assignment of treatments to experimental subjects is haphazard; lacking randomization, observational studies frequently provide a biased estimation of treatment effects and have imbalance on covariates. In observational studies, the 'treatment' groups (or 'exposure' groups) often exhibit imbalance on covariates. This covariate imbalance is confounded with treatments. It is difficult to attribute differences in responses to the 'treatment' or 'exposure' because the covariates are also believed to influence the response. The propensity score matching attempts to reduce the confounding effects of covariates allowing so to attribute differences of responses to differences of treatments (exposures).

APPENDIX B: CONFERENCE DISCUSSION

Dr H. Hansen (*Copenhagen, Denmark*): What is your limit for removal of the tube and is the limit the same in the two groups, or do you take into consideration whether the patient is on antiplatelet therapy? How many millimeters do you accept?

Dr L. Bertolaccini (*Cueno, Italy*): First of all, the next study must be multi-institutional. Therefore, an increase in the number of patients could decrease the limits of our study.

Dr Hansen: Yes, but you say you had no difference in the two groups. Are the indications for tube removal the same in the two groups or do you keep the tube in for longer in the patients who are on antiplatelet therapy?

Dr Bertolaccini: Yes.

Dr Hansen: You do?

Dr Bertolaccini: Yes.

Dr Hansen: So what are the limits for tube removal, is it 100 cc's, 300 cc's, and what are your limits?

Dr J. Kuzdzal (*Krakow, Poland*): When do you remove the chest drain?

Dr Bertolaccini: We remove the chest drain when the amount of the pleural effusion is less than 200 ml/day.

Dr Hansen: And it is the same in the two groups?

Dr Bertolaccini: Yes, it is the same in the two groups.

Dr Hansen: You mentioned the work of Cerfolio. He published papers on 450 cc's. Would you consider raising your limits to that level?

Dr Bertolaccini: Yes, I would probably try raising my limits.

Dr J. Kuzdzal: Could you tell us a little bit more about the type of antiplatelet medication your patients received?

Dr Bertolaccini: Nine (24%) patients received dual antiplatelet therapy with Clopidogrel and aspirin, but these patients had a coronary stent which needs Clopidogrel. A lot of the patients, 45%, received only aspirin and 31% received Clopidogrel alone.