Novel Antiplatelet Perioperative Bridging Protocol for Lung Lobectomy: A Case Report

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ABSTRACT

Introduction: Some patients with cardiac stents will need thoracic surgery during the dual antiplatelet therapy (DAPT) period. When surgery cannot be safely delayed to allow 1 year of uninterrupted DAPT, appropriate perioperative management of anticoagulation is critical.

Case Presentation: A patient treated with new drug-eluting stents and DAPT was concomitantly diagnosed with lung cancer and required a lobectomy. We describe the novel addition of ticagrelor (a short-acting oral antiplatelet agent) to eptifibatide (a short-acting intravenous antiplatelet agent) to bridge DAPT for surgery.

Discussion: This ticagrelor-eptifibatide perioperative bridge resulted in decreased preoperative hospitalization compared with eptifibatide alone. There were no associated perioperative cardiac or bleeding complications.

INTRODUCTION

In the Medicare population alone, more than 300,000 patients undergo stent placement via percutaneous coronary intervention (PCI) each year.[1] It is therefore not surprising that up to 10% of candidates for major lung resection will have had prior coronary artery intervention.[2,3] Patients with drug-eluting stents (DESs) placed via PCI are generally maintained on at least 1 year of dual antiplatelet therapy (DAPT), most commonly aspirin and clopidogrel. The most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines on this topic recommend an absolute minimum of 3 months of uninterrupted DAPT before cessation for elective surgery, and an ideal minimum of 6 months.[4] Stent thrombosis and perioperative myocardial infarction are the most feared complications of DAPT interruption and are associated with considerable mortality. The risk of these complications is highest in the first 4 to 6 weeks after PCI, but remains substantial for up to 6 months.[4]

Evidence-based guidance for the perioperative management of patients who need noncardiac surgery during this high-risk timeframe is extremely limited. Although all major guidelines and standards of practice recommend the continuation of aspirin in most cases, the appropriate management of the second component of DAPT, usually clopidogrel, is much less clear. The ACC/AHA did not find sufficient evidence to recommend a bridging regimen in their guidelines.[4] The Society of Thoracic Surgery guidelines for antiplatelet drug management suggest that shorter-acting, reversible, intravenous antiplatelet agents may be used to reduce the amount of time without DAPT when noncardiac surgery must be performed sooner than 6 months after DES placement, but similarly do not describe or recommend a bridging regimen.[5] Although the major guidelines do not provide information on specific bridging therapy, a handful of case reports and case series have described the successful use of eptifibatide, a glycoprotein IIb/IIIa-inhibitor with a half-life of 2.5 hours,[6] to bridge patients for surgery. Eptifibatide's inhibition of the glycoprotein IIb/IIIa receptor occurs downstream of clopidogrel's inhibition of the $P2Y_{12}$ receptor,[7] but still provides an adequate second target of antiplatelet therapy to aspirin's COX-2 inhibition. Epitifibatide intravenous infusion ("drip") is generally begun at 72 hours and stopped 4 to 12 hours before a planned procedure[2,8-10] because platelet function returns to normal 4 to 6 hours after cessation.[6] This timing requires preoperative admission of more than 72 hours in most reports, to begin the eptifibatide drip at the appropriate time after clopidogrel cessation, which usually occurs 5 days before surgery. Eptifibatide drip was not resumed postoperatively in any of the reports; rather, in most cases, clopidogrel was restarted 12 to 72 hours after surgery, often with a loading dose.

To reduce the nontrivial length of preoperative admission as well as the overall duration of DAPT interruption, we developed a new, multidisciplinary plan for management. Our bridging protocol includes an inpatient pre- and postoperative bridge with eptifibatide in addition to an outpatient bridge with ticagrelor, an oral antiplatelet agent with a short half-life of 7 hours.[5] Like clopidogrel, ticagrelor is a $P2Y_{12}$ inhibitor, but they differ in 2 key properties. First, ticagrelor is a direct-acting agent, giving it a faster onset of activity after initial dosing than clopidogrel, which must first be processed from its prodrug to active form. Second, its receptor-binding is reversible, so recovery after the last dose is comparatively rapid—whereas recovery after the last dose of clopidogrel, which acts irreversibly, takes days because new platelet synthesis is required.[11,12] Platelet activity after ticagrelor cessation becomes subtherapeutic by 24 hours, and function is only substantially reconstituted after 48 to 72 hours.[5,13] Ticagrelor is approved for use in DAPT and may actually provide superior prevention of acute coronary syndrome, with ACC/AHA guidelines recommending its use over clopidogrel in selected patients.[4]

CASE PRESENTATION

Presenting Concerns

A 72-year-old man with history of hypertension, diabetes, and benign prostatic hypertrophy presented with dyspnea

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on exertion. Coronary artery computed tomography (CT) revealed atherosclerotic disease, and an elective cardiac catheterization later that same month resulted in placement of 2 DESs. He was subsequently prescribed aspirin and clopidogrel according to the standard of care. A small pulmonary nodule had been detected incidentally during the coronary CT, and a dedicated chest CT further characterized it as a 1.8-cm, spiculated, right upper lobe nodule with imaging features highly suggestive of malignancy. Because of the risk of bleeding associated with an interventional radiology biopsy while on DAPT, the nodule was instead further evaluated with positron emission tomography-CT and was found to be strongly tracer-avid, also highly suggestive of malignancy.

Therapeutic Intervention and Treatment

The patient was evaluated in our thoracic surgery clinic only 3 weeks after placement of DESs. To avoid a substantial delay in curative surgery for this early-stage cancer, we developed a plan for perioperative management of his DAPT via collaborative decision making among members of a multidisciplinary care team. A detailed discussion of thrombotic risk assessment is beyond the scope of this report, but a number of factors were considered by the team, including the patient's comorbidities, stent size and length, number of stents, and size of the territory at risk. These were weighed against the risk of interval cancer metastasis, at which point the high chance of cure would be lost. Ultimately, the surgery was postponed for the 6-week period of highest risk after DES placement but not for the usual 3 months. It was believed that the new protocol's minimization of the patient's time on antiplatelet monotherapy allowed an acceptable risk-benefit balance to enable a sooner oncologic operation. The surgery was planned at a facility where interventional cardiology would be available in case of perioperative cardiovascular complications.

The timeline and details of his perioperative bridging protocol are shown in Table 1. Consistent with the ACC/AHA guidelines, aspirin therapy was never interrupted. The incision was made less than 8 hours after the eptifibatide drip was stopped. His video-assisted thoracoscopic surgery right upper lobectomy proceeded without complication. The estimated blood loss was 50 mL, and the case duration was 135 minutes. The eptifibatide drip was restarted by 6 hours after surgery. We had intended to restart clopidogrel on postoperative day 1, but this was postponed and the eptifibatide was continued for possible chest tube removal. On postoperative day 2, the decision was made to leave the chest tube in place because of the persistence of a small air leak. Clopidogrel was subsequently restarted, and the eptifibatide drip was discontinued 3 hours later. The loading dose of clopidogrel, which had been part of the planned protocol, was omitted on the basis of the surgeon's assessment of bleeding risk based on intraoperative findings.

Table 1. Timeline of the case of a 72-year-old man on DAPT (aspirin 81 mg daily + clopidogrel 75 mg daily) with suspicious primary nodule

Day[a]	Events/Treatment
−49 (−7 weeks)	Patient underwent cardiac catheterization with placement of 2 DESs.
−32	PET-CT results confirmed likelihood of lung cancer diagnosis. Thoracic surgery consult was ordered.
−28	In thoracic surgery consult, the very likely new lung adenocarcinoma with no evidence of metastatic disease was discussed with the patient, as well as treatment options. VATS lobectomy was recommended. Multidisciplinary discussions of timing and DAPT management began.
−26	Multidisciplinary consensus was reached (protocol as noted below).
−10	Last dose of clopidogrel 75 mg was taken in the morning (aspirin 81 mg was also taken on this and all mornings, which was unchanged).
−9	Patient took ticagrelor 85-mg loading dose in the morning and first dose of ticagrelor 90 mg in the evening, which continued twice daily.
−2	Patient took last dose of ticagrelor 90 mg in the morning.
−1	Patient was admitted to the hospital and was given eptifibatide 2 μg/kg/min.
0	Eptifibatide was stopped 6 h before surgery (8 h before incision time). Patient underwent VATS lobectomy. Eptifibatide 2 μg/kg/min was resumed 6 h after surgery.
+2	Clopidogrel was restarted with the first dose of 75 mg in the morning. Eptifibatide drip was stopped 3 h after the clopidogrel dose. Patient was discharged home in the afternoon.

Consult = consultation; DAPT = dual antiplatelet therapy; DESs = drug-eluting stents; PET-CT = positron emission tomography-computed tomography; VATS = video-assisted thoracoscopic surgery.
[a] day 0 = day of surgery.

Follow-up and Outcomes

The patient's postoperative course was uneventful, without bleeding or cardiovascular complications. There were no Emergency Department visits or hospital re-admissions after discharge. The patient recovered appropriately, and continued to be well at 24-month follow-up.

DISCUSSION

Our protocol resulted in only 17 hours of perioperative antiplatelet monotherapy (vs a usual 22-58 hours).[2,8-10] This regimen additionally allowed a decrease in the preoperative hospitalization (1 day vs a usual 3-4 days) and thus in total length of stay.[2,8-10] There were no complications in the 2-year follow-up period.

There are several unique features of this novel bridging protocol that may have contributed to its success, both in terms of acceptance by the consulting teams and in terms of its clinical outcomes. Ticagrelor has a rapid onset of action and allows a more rapid reconstitution of platelet function after its withdrawal than does clopidogrel; as such, the surgery team was comfortable with continuing oral antiplatelet therapy until closer to the time of surgery, minimizing the duration of preoperative admission for intravenous therapy. The novel continuation of eptifibatide postoperatively also permitted an earlier return to full DAPT; the rapid onset resulted in a near-immediate therapeutic effect after redosing, and the surgeons were willing to accept the risk because the eptifibatide could be rapidly withdrawn in case of a bleeding event. The combination of the preoperative oral

ticagrelor and intravenous eptifibatide bridge with a postoperative eptifibatide bridge reduced the interruption of DAPT and the associated cardiac risk to a level that was acceptable to the cardiology team. Both the ACC/AHA and the Society of Thoracic Sugeons guidelines promote multidisciplinary risk-assessment and decision making individualized for each patient and clinical situation.[4,5] This measure was crucial in our case, as it ultimately led to the development of this new bridging protocol.

Although this operation would be considered "elective noncardiac surgery" by most guidelines, delays on the order of months are considered clinically significant for the curative resection of lung cancer that is localized on presentation. This bridging protocol could potentially be applied to any patient with DESs and a similar indication for time-sensitive "elective" surgery during the DAPT period. We describe our first experience with this protocol in a single patient; additional studies will be needed to verify the efficacy and safety of this novel bridging protocol in a larger cohort. Future applications of the regimen should attempt to restart clopidogrel with a loading dose, as was originally intended in this case.

CONCLUSION

Necessary thoracic surgery (in this case, a lung cancer operation) during the recommended period of DAPT following DES placement is not an uncommon clinical scenario, and yet there are no well-defined bridging guidelines. A bridging protocol of oral ticagrelor followed by short-duration intravenous eptifibatide preoperatively and intravenous eptifibatide postoperatively may be used in these situations to permit a prompt oncologic resection while minimizing the balanced risks of cardiac and surgical complications. The reduction in length of stay by 2 to 3 days is an important advantage of this protocol over similar eptifibatide-based bridging regimens. Consideration should also be given to application of this protocol to other surgical subspecialty operations necessitated within the DAPT period. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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How to Cite this Article

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