Clinical Vignettes

Perioperative Management of a Patient with Recently Placed Drug-Eluting Stents Requiring Urgent Spinal Surgery

Eira Roth, MD[3], Chad Purnell, MD[1], Olga Shabalov, MD[2], Diego Moguillansky, MD[2], Caridad A. Hernandez, MD[1], and Michael Elnicki, MD[1]

[1]Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; [2]Department of Cardiology, University of Pittsburgh Medical Center Shadyside Hospital, Pittsburgh, PA, USA; [3]Department of Radiology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA.

Patients receiving drug-eluting coronary stents (DES) require antiplatelet therapy for at least 12 months to prevent stent thrombosis (ST), a potentially calamitous event. Since interruption of antiplatelet therapy is the greatest risk factor for ST, it is imperative that the decision to discontinue these agents be based on an accurate assessment of the patient's risk for bleeding complications. Individuals who are regarded as being at a high risk are those undergoing intracranial, spinal or intraocular surgeries. These patients require alternative agents during the perioperative period to minimize both their risk of perioperative thrombosis and intraoperative hemorrhage. We report the case of a woman who required spinal surgery 3 months after she underwent placement of two drug-eluting stents. The patient's clopidogrel was stopped 5 days prior to surgery and an infusion of eptifibatide was used to "bridge" antiplatelet therapy during the perioperative period. Postoperatively, anticoagulation therapy was reinstituted using aspirin with clopidogrel. This case serves as a successful example of bridging therapy using a short acting and gycoprotein (GP) IIb/IIIa inhibitor as a means of maintaining antiplatelet therapy during the perioperative period to minimize the risk of stent thrombosis and the risk of intraoperative bleeding.

KEY WORDS: antiplatelet management; stents; surgery.
J Gen Intern Med 27(8):1080–3
DOI: 10.1007/s11606-012-1995-7

INTRODUCTION

Perioperative management is challenging in patients who have recently had drug-eluting coronary stents (DES) implanted. The American Heart Association, American College of Cardiology, and the Society for Cardiovascular Angiography and Interventions recommend that patients receive dual antiplatelet therapy with clopidogrel and aspirin for at least 12 months, followed by lifelong aspirin[1,2]. There is mounting evidence that patients have a slight but continued increase in the risk of thrombotic events beyond the first 12 months following DES placement [1–7]. Because the cessation of clopidogrel is a major predictor of stent thrombosis, long-term or even life-long use of dual antiplatelet therapy is being discussed [1–3]. Thus, physicians will see a growing population of patients whose medical and surgical management are complicated by the need for continued dual antiplatelet therapy.

The difference in the risk of perioperative bleeding in patients receiving aspirin monotherapy versus dual antiplatelet therapy is difficult to quantify. The "CURE" (The Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial demonstrates that patients on both aspirin and clopidogrel have a higher risk of major bleeding events (life threatening and/or requiring more than two units of blood) and total bleeding complications compared with aspirin therapy alone, (relative risk (RR) 1.38, $p < 0.01$, and RR 1.69, $p < 0.01$, respectively)[8,9]. In their analysis on the bleeding risk associated with continuation of aspirin therapy perioperatively, Burger et al. note that aspirin therapy is associated with a 1.5-fold increase (median, interquartile range: 1.0–2.5) in the baseline bleeding risk associated with different surgical interventions [9,] whereas Payne et al. note a 3.4-fold prolongation of bleeding time (from 7.6±3.4 minutes to 17.5±8.6 minutes, $p < 0.05$) with use of aspirin plus clopidogrel [11,12]. Both of these measures translate to an overall increased risk of blood loss when undergoing surgery. This poses a management dilemma when such a patient requires intervention during the first year following stent placement. The risks are further compounded when a patient requires procedures that involve a closed compartment, such as an intracranial, spinal, or intra-ocular space, where bleeding could be disastrous[12,13]. In these cases, using short-acting intravenous antiplatelet agents has been proposed to minimize the risk of stent thrombosis without greatly increasing the risk of perioperative bleeding as a means of preoperative "bridging therapy" [12].

We report the case of a patient undergoing spinal surgery who was treated perioperatively with the intravenous

Received August 27, 2011
Revised January 11, 2012
Accepted January 12, 2012
Published online January 31, 2012

administration of eptifibatide (Integrilin), a glycoprotein IIb/IIIa receptor inhibitor as bridging therapy after the discontinuation of treatment with oral clopidogrel. We also present a review of the current literature regarding bridging therapy.

CASE

A 61-year-old woman with coronary artery disease and chronic back pain presented with complaints of acute worsening of her low back pain accompanied by new lower extremity weakness; she did not report loss of bowel or bladder function.

Physical examination showed a marked decrease in the patient's reflexes, strength, and sensation in both of her lower extremities. Urgent magnetic resonance imaging (MRI) of the lumbosacral (LS) spine demonstrated acute disc herniation and extrusion at L4–L5 with cranial disc migration resulting in severe central canal stenosis. It also showed a significant mass effect on the right-sided nerve roots at the L4 level. Coincidentally, an MRI of the LS spine had been obtained three weeks prior to presentation for evaluation of the patient's chronic low back pain. This showed degenerative anterolisthesis (anterior slippage of a vertebra) at L4 with acquired severe central canal and subarticular recess stenosis, without signs of acute disc herniation or migration.

These findings indicated that the patient required urgent laminectomy to prevent further neurologic compromise. In this case, however, the risks of surgical intervention were heightened by the fact that the patient had experienced a myocardial infarction within the previous 3 months and that drug-eluting stents (DES) had been placed in both the distal left circumflex artery and the posterior obtuse marginal branch. Since that time, the patient had been treated with aspirin and clopidogrel.

Given the long half-life of aspirin and clopidogrel, it was judged that the patient needed to be converted to a bridging antiplatelet therapy with a shorter half-life in order to minimize the risk of intraoperative bleeding. Thus, she was placed on high dose steroids to reduce the degree of neuronal swelling and allow time for preoperative antiplatelet modification. Clopidogrel and aspirin were held five days prior to surgery at the request of the neurosurgeons. To prevent stent thrombosis, she was placed on an eptifibatide drip as "bridging therapy" at a concentration of 2mcg/kg/min, or 0.75 mg/mL, and infused at a rate of 12 mL/hour. The eptifibatide was stopped approximately eight and a half hours prior to surgery. She then underwent a right L4 laminectomy with a L4 to L5 discectomy and decompression of the right L4-L5 nerve root. Six hours after surgery the patient began receiving aspirin again at a dosage of 81 mg/day. Fifteen hours after surgery, she received clopidogrel at a loading dose of 300 mg and then began taking this drug at a dosage of 75 mg/day. On postoperative day 3, she was discharged home. At follow-up two months later, she remained free of thrombotic complications.

DISCUSSION

The unpredictability of stent thrombosis makes it difficult to ascertain when it is safe to discontinue or interrupt antiplatelet therapy following placement of drug-eluting stents. Studies indicate that the risk of stent thrombosis is increased by the coexistence of a reduced left ventricular ejection fraction of less than 50%, renal insufficiency, diabetes, malignancy, and whether the segment of stented vessel is bifurcated[1,4,12]. The degree to which these factors increase the risk is uncertain, but there is general agreement that premature cessation of dual antiplatelet therapy before 12 months poses the greatest risk for stent thrombosis[2–4,7,12–14]. Although the mechanism is not well understood, it is thought that the abrupt termination of antiplatelet therapy may trigger a rebound prothrombotic state[13,15,16]. It is postulated that there is a pro-inflammatory response with an up-regulation of platelet biomarkers in patients after the removal of clopidogrel, aspirin, or heparin[13,15].

The potential for prothrombotic rebound to occur with cessation of dual antiplatelet therapy favors the use of bridging therapy, and it also supports the argument that the duration of dual antiplatelet treatment should be extended in patients with DES[5,6,16]. According to the literature, the highest incidence of thrombotic complications is seen in patients within the first 6 weeks after stent placement[1,13,17,18]. However, the patient reported here fell outside of the 6-week time frame but remained within the 12-month window when the exact risk of thrombosis is difficult to quantify. Although few sources in the general medicine literature address this issue, it is precisely in this group of patients seen by internists that the balance between the risk of stent thrombosis and the risk of intraoperative bleeding remains precarious and ill defined.

Few studies have actually followed patients through the entire first year of recommended dual antiplatelet therapy[12,19]. Those studies that have done so have shown that catastrophic events are relatively rare, but patients with drug-eluting stents are at a risk of long-term complications such as stent thrombosis even beyond 1 year due to delayed endothelization; thus, extended antiplatelet therapy remains the best prevention[4–6,13,17].

Table 1. Summary of Considerations in this Case

1. Patient presents with cord compression requiring urgent surgery:
   a. High risk / "closed-space surgery" (intracranial, spinal, ocular)
   b. Drug eluting stents placed less than a year ago. Patient still requiring antiplatelet therapy
2. Surgery cannot be postponed: Postponement may lead to permanent paralysis
3. Selecting appropriate bridging therapy—antiplatelet agent with:
   a. Easy reversibility/ transitory inhibitor
   b. Short half-life: eptifibatide or tirofiban
4. Hold dual antiplatelet agents, replace with bridging agent 5 days prior to surgery
5. Stop infusion of agent 5 half-lives prior to surgery:
   a. Eptifibatide 4–5 hours
6. Postoperatively restart aspirin and clopidogrel the day following surgery

The decision to continue aspirin with or without clopidogrel perioperatively is favored where an increase in bleeding risk is deemed "acceptable" by clinicians [12,13]. Since clopidogrel and aspirin cause irreversible inhibition of platelet aggregation, thereby necessitating new platelet formation in order for the reestablishment of normal coagulation, their usage perioperatively may vary from surgeon to surgeon. For "closed-space" surgeries in which any increased risk of bleeding is dangerous, the literature advocates the use of "bridging therapy" [12,13]. Ideally, in bridging therapy, one antiplatelet agent would be substituted for another, and preferably one with a shorter half-life to reduce the risk of intraoperative bleeding and minimize the duration that antiplatelet agents are held preoperativly. This excludes antithrombotic agents such as heparin, and favors the use of agents that prevent platelet aggregation by blocking the interaction between fibrinogen and the platelet GP IIb/IIIa receptor [12,20]. The selection of a GP IIb/IIIa inhibitor was substantiated by a handful of successful examples of bridging therapy using these agents in the context of non-cardiac surgery [7,21].

Agents that act on GP IIb/IIIa agents include abciximab, eptifibatide, and tirofiban. Abciximab is a permanent receptor inhibitor with a 7-day duration of action. In contrast, the other agents are reversible (transitory) receptor inhibitors [12,20]. Eptifibatide has a half-life of 50–60 minutes, tirofiban has a half-life of 2 hours, and each agent is administered as an infusion [10,19,20]. Of these two, eptifibatide was chosen in the case reported here due its availability at our institution and because its shorter half life permitted greater flexibility perioperatively.

When the infusion of eptifibatide is stopped, bleeding time normalizes within 30 minutes [19,20]. Platelet function returns in 2–4 hours without platelet transfusion or immediately with platelet transfusion [12,19,22]. In this case, surgery was scheduled eight hours after the cessation of eptifibatide. However in retrospect, it would have been acceptable to undergo surgery after 4–5 hours given that eptifibatide's half-life of 50–60 minutes. Of note, in a study by Dyke et al., 60% of GP IIb/IIIa platelet receptors remained inhibited at 4 hours after cessation, though this did not appear to increase the risk of hemorrhage [22].

In our patient, the decision to restart aspirin and clopidogrel after surgery with loading doses was based on a review of prior case reports involving patients with DES undergoing non-cardiac surgeries [7,12,21]. The goals were to reduce the risk of post-operative stent thrombosis from prothrombotic rebound and to minimize the risk of bleeding [Table 1].

CONCLUSION

As the use of drug eluting stents in patients with coronary artery disease continues to increase and as the recommended duration for dual antiplatelet therapy expands, it will become important to select an antiplatelet regimen that minimizes perioperative risks while maintaining stent patency. Abualsaud et al. stratify the concerns inherent in this process in their review of the literature regarding perioperative management in patients with coronary stents [12]. Although further study is needed regarding the use of short-acting GP IIb/IIIa inhibitors as bridging therapy, we found that eptifibatide's short half-life, reversibility with platelet transfusion, and the marginal prolongation of bleeding time made eptifibatide an optimal agent for use in our cardiac patient who required urgent spinal surgery during the period of mandated antiplatelet therapy.

Acknowledgement: *The authors thank Ms. Sharon Maddox for her editorial support.*

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

Corresponding Author: *Eira Roth, MD; Department of Radiology, University of Pittsburgh Medical Center, 200 Lothrop St, 3950 South Tower, Pittsburgh, PA 15213, USA (e-mail: rothes@upmc.edu).*

REFERENCES

1. **Grines CL, Bonow RO, Casey DE, et al.** 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. J Am Coll Cardiol. 2007;49:734–9.
2. **Yan BP, Duffy SJ, Clark DJ, et al.** Rates of stent thrombosis in bare-metal versus drug-eluting stents (from a large Australian multicenter registry). Am J Cardiol. 2008;101:1716–22.
3. **Roy P, Bonello L, Torguson R, et al.** Temporal relation between clopidogrel cessation and stent thrombosis after drug-eluting stent implantation. Am J Cardiol. 2009;103:801–5.
4. **Tin-Hay EL, Poh KK, Lim YT, et al.** Clinical predictors of stent thrombosis in the "real world" drug-eluting stent era. Int J Cardiol. 2009. doi:10.1016/j.ijcard.2009.05.038.
5. **Goy JJ, Urban P, Kaufmann U, Seydoux C, Benedetti ED, Berger A.** Incidence of stent thrombosis and adverse cardiac events 5 years after sirolimus stent implantation in clinical practice. Am Heart J. 2009;157:883–8.
6. **Ben-Dor I, Waksman R.** Bridging with GP IIb/IIIa inhibitors after abdominal surgery in a patient presenting with late stent thrombosis of a drug-eluting stent and who cannot receive oral antiplatelet treatment. J Invasive Cardiol. 2009;21:E73–6.
7. **Bhatt S, Hauser TH.** Very late stent thrombosis after dual antiplatelet therapy discontinuation in a patient with a history of acute stent thrombosis. Ann Pharmacother. 2008;42:708–12.
8. **Gerschutz PG, Bhatt LD.** The CURE trial: using clopidogrel in acute coronary syndromes without ST-segment elevation. CC J M. 2002;69:377–385.
9. **Yusuf S, et al.** Effects of clopidogril in addition to aspirin in patients with acute coronary syndrome without ST-segment elevation. The clopidogrel in unstable angina to prevent recurrent events trial incestigators. NEJM. 2001;345:494–502.
10. **Burger W, Chemnitius JM, Kneissl GD, Rucker G.** Low-dose aspirin for secondary cardiovascular prevention—cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation—review and meta-analysis. J Intern Med. 2005;257:399–414.

11. **Payne DA, Hayes PD, Jones CI, Belham P, Naylor AR, Goodall AH.** Combined therapy with clopidogrel and aspirin significantly increases the bleeding time through a synergistic antiplatelet action. J Vasc Surg. 2002;35:1204–9.
12. **Abualsaud AO, Eisenberg MJ.** Perioperative management of patients with drug-eluting stents. JACC Cardiovasc Interv. 2010;3:131–42.
13. **Newsome LT, Weller RS, Gerancher JC, Kutcher MA, Royster RL.** Coronary artery stents: II. Perioperative considerations and management. Anesth Analg. 2008;107:570–90.
14. **Schouten O, van Domburg RT, Bax JJ, et al.** Noncardiac surgery after coronary stenting: early surgery and interruption of antiplatelet therapy are associated with an increase in major adverse cardiac events. J Am Coll Cardiol. 2007;49:122–5.
15. **Angiolillo DJ, Fernández-Ortiz A, Bernardo E, et al.** Clopidogrel withdrawal is associated with proinflammatory and prothrombotic effects in patients with diabetes and coronary artery disease. Diabetes. 2006;55:780–4.
16. **Angiolillo DJ, Sabaté M, Fernández-Ortiz A, Macaya C.** Acute stent thrombosis after early withdrawal of platelet glycoprotein IIb/IIIa antagonists: potential rebound prothrombotic effect? Catheter Cardiovasc Interv. 2003;58:481–4.
17. **Wilson SH, Fasseas P, Orford JL, et al.** Clinical outcomes of patients undergoing non-cardiac surgery in the two months following coronary stenting. J Am Coll Cardiol. 2003;42:234–40.
18. **Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE.** Catastrophic outcomes of noncardiac surgery soon after coronary stenting. J Am Coll Cardiol. 2000;35:1288–94.
19. **Lecompte T, Hardy JF.** Antiplatelet agents and perioperative bleeding. Can J Anaesth. 2006;53:S103–12.
20. **Phillips DR, Scarborough RM.** Clinical pharmacology of eptifibatide. Am J Cardiol. 1997;80:11–20B.
21. **Broad L, Lee T, Conroy M, et al.** Successful management of patients with a drug-eluting coronary stent presenting for elective, non-cardiac surgery. Br J Anaesth. 2007;98:19–22.
22. **Dyke CM, Jennings LK, Maier G, Andreou C, Daly R, Tamberella MR 3rd.** Preoperative platelet inhibition with eptifibatide during coronary artery bypass grafting with cardiopulmonary bypass. J Cardiovasc Pharmacol Ther. 2007;12:54–60.