Antiplatelet medications and their surgical implications

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OBJECTIVES

At the completion of this PBLD the participant will understand the following:

1. Pharmacology of platelet inhibitors
2. Management of antiplatelet medications in patients with coronary stents during the perioperative period
3. Implications of perioperative use of antiplatelet medications for regional anesthetic techniques

STEM CASE

A 64-year-old, 70 kg man, is scheduled for an elective thoracotomy and right upper lobectomy for bronchial adenocarcinoma. His past medical history is significant for coronary artery disease, hypercholesterolemia, hypertension and COPD. He sustained an inferior wall myocardial infarction 4 years ago for which he underwent coronary angioplasty with placement of 2 paclitaxel eluting stents. Since then, he has been symptom free and has been able to perform moderate exercise. His medications included clopidogrel (Plavix) 75mg daily, aspirin 325mg daily, atorvastatin (Lipitor) 80mg daily, metoprolol (Lopressor) 100mg daily and quinalapril (Accupril) 20mg daily. He has discontinued the clopidogrel and aspirin 7 days ago. He previously smoked 1 pack-per-day for 30 years but quit 5 years previously. He currently consumes 3-4 beers per day. Preoperative vital signs include heart rate 66 bpm and blood pressure 107/64 mmHg. Physical examination revealed a normal airway, clear lung fields and regular heart sounds with no murmur, rub or gallop present. The preoperative 12 lead ECG showed normal sinus rhythm at a rate of 66 bpm with a first degree AV block. Preoperative laboratory values were all within normal limits.

At the time of his inferior wall myocardial infarction, the patient had a transthoracic echocardiogram which revealed normal functioning right and left ventricles with an estimated LV ejection fraction of 65%, no wall motion abnormalities and no valvular pathology. The patient’s cardiologist had ordered a stress-MIBI, as part of the preoperative evaluation, which was essentially normal. The patient was “cleared” for surgery.

QUESTIONS

1. How are drug eluting stents different then bare metal stents? How long do you need to wait after drug eluting stent placement before proceeding with surgery?
2. How do aspirin and clopidogrel work on platelet inhibition? Why is dual antiplatelet therapy required in patients with drug eluting stents?
3. Should aspirin and/or clopidogrel be discontinued? When? Are there any guidelines?
4. Are there any new antiplatelet medications which could alter the perioperative management?

The patient was brought to the OR. His initial vital signs were blood pressure (BP) of 140/80 mmHg and heart rate (HR) 80 bpm in sinus rhythm. A T7-T8 epidural was placed. General anesthesia was induced uneventfully with midazolam, fentanyl, thiopental and vecuronium. A double lumen tube and a radial artery catheter were placed. Hydromorphone 0.7 mg was given via the epidural catheter. Hemodynamics were well maintained during the entire case. Blood pressure ranged between 90/60 mmHg and 140/85 mmHg, heart rate varied between 60-75 bpm. During one lung ventilation oxygenation was well maintained on 100% FiO₂. The total fluid administered was 1200 cc crystalloid. The urinary output was 220cc/3 hours and the estimated blood loss was 100 cc. At the end of the procedure, for optimal post-operative analgesia, a total of 10 cc of bupivacaine 0.25% with 1/200000 epinephrine was given over 30 minutes. Subsequently the patient was breathing spontaneously with adequate tidal volume (500 cc) and respiratory rate (10 rpm). He was awake, following commands. Residual neuromuscular blockade was fully reversed. The vital signs were stable BP 140/67 mmHg HR 70 bpm, SaO₂ 100% and T 36.7C. The hematocrit was 36%. The patient was extubated in the OR and transferred to the PACU. Initial vital signs were: HR 66 bpm, BP 96/50 mmHg, SaO₂ 100% (on 40% FiO₂ face mask) and T 36.6C. His PACU admission 12 lead ECG showed no change compared to the preoperative one.

Over the next 30 minutes the patient’s BP gradually declined to values of 80/45 mmHg. After few boluses of phenylephrine an infusion was started at a rate of 0.12 mcg/kg/min in order to maintain coronary perfusion pressure.

One hour after admission to the PACU the patient complained of slight substernal chest pain (3/10 pain score) radiating to the neck and was diaphoretic. The HR increased to 88bpm with a BP 90/60 mmHg. A repeat 12 lead ECG revealed 1 mm ST elevations in lead II, III and aVF and T wave inversions in V₂-V₃ as well as 1mm ST depressions in the same leads.

Nitroglycerin 0.5 mcg/kg/min and esmolol 20 mg IV x 3 doses were given. The phenylephrine infusion was discontinued as the BP was 120/65 mmHg. Metoprolol 5 mg IV in divided doses was administered. The cardiology service was consulted and the decision was made to transfer the patient immediately to the cardiac catheterization lab. The cardiologist consulted the anesthesia team regarding the management of the epidural catheter in view of the planned antiplatelet therapy.

The epidural catheter was removed and a 90 minute waiting interval was recommended before antiplatelet and anticoagulant therapy administration. In the cardiac catheterization laboratory the patient was found to have an in-stent thrombosis of the RCA. He was given eptifibatide (Integrilin) infusion at 1 mcg/kg/min and bivalirudin (Angiomax) IV. An angioplasty with thrombus removal was performed reestablishing good flow. The ST elevations present on the previous 12 lead ECG normalized and the patient was symptom free. The bivalirudin was discontinued at the end of the procedure and the eptifibatide was discontinued 2 hours thereafter.

QUESTIONS

5. What other antiplatelet medications are typically employed in the catheterization laboratory? What is their mechanism of action?
6. In case of post-procedure life-threatening bleeding what treatment options are available?
7. Should an epidural catheter be inserted in patients with DES? How should the catheter be managed if the patient requires immediate percutaneous coronary intervention?

DISCUSSION
1. How are drug eluting stents different than bare metal stents? How long do you need to wait after drug eluting stent placement before proceeding with surgery?

Coronary artery stents were introduced in 1993 as a solution for preventing acute coronary artery recoil encountered with balloon angioplasty. They were regarded as a major advance in the progress of percutaneous coronary interventions (PCI). However, shortly thereafter it was found that even after placement of intracoronary stents, the problem of reocclusion was not completely resolved. In-stent restenosis usually occurs within weeks to months after the placement of the stent but the process starts when the stent is deployed. The stent induces trauma to the media of the vascular wall and, together with the presence of the metallic stent itself, results in proliferation of vascular smooth muscle cells which promotes restenosis. However, in-stent restenosis usually ensues gradually thus allowing for collateral circulation to evolve and manifests as angina or non-fatal myocardial infarction (MI) as opposed to sudden death. The rate of in-stent restenosis for BMS is 20-30%.

Drug eluting stents (DES) were designed to prevent in-stent restenosis by inhibiting leukocyte activation and smooth muscle cell proliferation. These stents have a metallic mesh similar bare metal stents (BMS) but they are embedded in a polymer coated with anti-neoplastic or anti-inflammatory drugs. The drugs are released over a long period of time into the endothelium thus preventing smooth muscle cell proliferation. Due to their mechanism of action, as opposed to BMSs, these stents take a longer time to endothelialize.

Currently on the US market there are four types of DESs approved by the FDA. The first generations of stents are the Cypher and Taxus. The Cypher stent (Johnson & Johnson) elutes sirolimus, an antifungal, antimitotic and immunosuppressive agent. The Taxus stent (Boston-Scientific) elutes paclitaxel, a cytostatic agent. The Cypher stent completes the elution of sirolimus in 6 weeks and usually the stent is endothelialized in 3 months. The Taxus stent has a bimodal elution: 10% of the drug is eluted in the first 10 days and the rest over an indefinite period of time. In most cases the stent is endothelialized by 6 months. Recent literature has suggested that, in some patients, DESs may not be endothelialized even after a long period after their implantation. This renders the patient vulnerable to late stent thrombosis. Thrombosis is another pathophysiologic mechanism of occlusion in drug eluting stents and, as opposed to in-stent restenosis, thrombosis develops suddenly. Thrombosis occurring after 30 days from the time of stent deployment is defined as late stent thrombosis (LST) and is the most feared complication of DES. LST episodes manifest in most cases as sudden death or extensive myocardial infarction. The clinical incidence of LST in unknown but it is believed to be much higher than the angiographic incidence reported at below 1%. The causes of LST are unclear but several mechanisms have been hypothesized such as delayed endothelialization, hypersensitivity reaction to the polymer, or the development of neointimal hyperplasia with acute thrombus formation.

In an attempt to decrease the incidence of LST a second generation of DESs has been developed and released on the market in 2008. The Endeavor stent (Medtronic) elutes zotarolimus which is a semi-synthetic immunosuppressant. The Xience V stent (Abbott) elutes everolimus which is a similar type of substance. Both stents are supposed to have an improved risk/benefit profile as compared to the first generation ones.

But are DESs any better? Published data suggest no difference in myocardial infarction and mortality rates compared to BMSs. However, it appears that the reoclusion rate is lower then in BMSs (<10% versus 20%). The current consensus is that for large caliber arteries BMSs are better but for small caliber arteries and diabetic patients DESs
have a more favorable risk/benefit profile. However, for the anesthesiology community, the more interesting question is which stent has a higher risk of cardiac morbidity and mortality in the perioperative period. Two recent retrospective studies comparing the rate of major adverse cardiac events (MACE) in the perioperative period have been published. The results suggest that the BMSs have an initial higher rate of complications but this rate declines abruptly if the surgery is postponed for 6 weeks after stent placement. On the other hand, DESs maintain a fairly high rate of cardiac complications even if surgery is deferred for a long time after stent implantation.

2. How do aspirin and clopidogrel work on platelet inhibition? Why is dual antiplatelet therapy required in patients with drug eluting stents?

Aspirin is a cyclooxygenase (COX) inhibitor and thus irreversibly blocks the pathway of thromboxane A₂ platelet aggregation. It is considered a weak platelet inhibitor and for a more potent arrest of platelet aggregation clopidogrel needs to be added to the therapeutic regimen. Clopidogrel is a thienopyridine pro-drug which is metabolized by cytochrome P-450 to the active form. It irreversibly inhibits ADP-induced aggregation of platelets by binding to the platelet P2Y₁₂ receptor (fig.1, table 1). The platelets are inhibited for their lifespan. Clopidogrel and aspirin need to be discontinued for 5-7 days in order for circulating platelets to resume full functionality. The effects of clopidogrel can be reversed by platelets transfusions.

As previously mentioned, DESs may take a longer time to endothelialize the metallic mesh. In some situation the endothelialization does not occur even after a long time has elapsed since placement of the stent. The presence of the un-endothelialized stent is a potent stimulus for platelet aggregation, thrombus formation with subsequent coronary occlusion and myocardial infarction or death. The ability of any one antiplatelet agent to optimally inhibit platelet aggregation through one predominant mechanism of action may be overcome when multiple aggregation agonists are released from platelets and endothelial cells. Thus, in patients with DESs, it becomes of extreme importance to inhibit platelet aggregation via two pathways.

3. Should aspirin and/or clopidogrel be discontinued in view of the planned surgery? When? Are there any guidelines?

The initial recommendations for patients receiving DESs were to maintain dual antiplatelet medication (aspirin and clopidogrel) for at least 3 months for sirolimus stents and 6 months for paclitaxel stents. As opposed to this, BMSs require just 1 month of antiplatelet therapy. However, in light of the recent publications addressing the issue of LST in both types of stents, the current American Heart Association Guidelines for Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients with Coronary Stents recommend to maintain dual antiplatelet therapy for at least one year post insertion. Many cardiologists consider, in certain subset of patients, to prolong the dual antiplatelet therapy for a longer period and potentially indefinitely.

Discontinuation of dual antiplatelet therapy in the perioperative period for patients with DESs in place is a topic of debate. Several case reports addressed the fact that thrombosis of DESs is more likely in the perioperative period. The etiology of this problem is hypothesized to be related to the systemic inflammatory response and hypercoagulable state coupled with the discontinuation of dual antiplatelet therapy in the perioperative period. In addition, a recent retrospective study, demonstrated a clustering of adverse cardiac events in the first 90 days after clopidogrel discontinuation suggesting a possible rebound hypercoagulable phenomenon. This observation was valid in both medically treated as well as PCI-treated patients with acute coronary syndrome.
The management of the perioperative antiplatelet regimen should take into account the risk of stent thrombosis versus the risk of intraoperative bleeding. The recently published guidelines recommend maintaining both antiplatelet medications for 1 year and deferring elective surgery for this period of time. If the surgery is semi–urgent then the risks of bleeding from the surgical procedure and the risk of stent thrombosis need to be assessed. If the risk of bleeding is low and the patient is less then 1 year out from DES placement then dual antiplatelet therapy should be maintained. If the risk of bleeding is high but the risk of stent thrombosis is lower (patient has the DES in place for more then 1 year) then clopidogrel should be discontinued preoperatively and restarted as soon as possible after the surgery. Aspirin should be continued if possible through out the perioperative period. If the risk of bleeding is high and the risk of stent thrombosis is also high then dual antiplatelet therapy could be discontinued and the patient admitted to the hospital for bridging IV antiplatelet therapy (fig.2). Anesthesiologists should be prepared to handle both types of perioperative scenarios: bleeding or stent thrombosis.

4. Are there any new antiplatelet medications which could alter the perioperative management?

Prasugrel is a novel oral thienopyridine, similar to clopidogrel. Being a pro-drug, it requires conversion to an active metabolite before binding to the platelet P2Y\textsubscript{12} receptor and irreversible inhibiting the ADP-induced aggregation. The time to recovery of platelet function after discontinuation of the drug is 2 days, shorter compared to clopidogrel (5 days). It has received preliminary FDA approval. In a recently published clinical trial comparing clopidogrel and prasugrel in acute coronary syndromes, it appears that prasugrel has a greater antithrombotic activity but, as a consequence, has a higher risk of major bleeding including fatal bleeding. Three subsets of patients are at an increased risk of fatal bleeding: older than 75 years, weighing less than 130 lb and who have had strokes in the past.

Cangrelor, an ATP-derivative, is an IV, short-acting, potent competitive P2Y\textsubscript{12} receptor inhibitor. It exhibits a complete antiaggregatory activity with a significant greater antithrombotic effect as compared to clopidogrel or prasugrel. This drug is in more incipient forms of clinical trials (just started phase III trials). The time to recovery of full platelet activity after discontinuation of the IV infusion is 1 hour. This drug may significantly alter the perioperative management of patients with DESs requiring bridging antiplatelet therapy (table 2).

5. What other medications antiplatelet medications are typically employed in the catheterization laboratory? What is their mechanism of action?

There are various types of IV antiplatelet agents such as abciximab, tirofiban and eptifibatide (table 1). All of them have a similar mechanism of action. They are glycoprotein IIb/IIIa receptor antagonists. The glycoprotein IIb/IIIa receptor is involved in the final common pathway of platelet aggregation. These agents produce a maximal degree of platelet inhibition and could potentially generate significant postoperative bleeding. However, in rare scenarios, such as stent thrombosis caused by a lack of antiplatelet therapy for a long period of time, their usage may be considered. Eptifibatide and tirofiban are considered short acting glycoprotein inhibitors (GPI) and 50% of platelet function is recovered after 4 hours from discontinuation of the IV infusion. These IV antiplatelet agents could be considered for preoperative bridging therapy. Abciximab is a longer acting GPI and 50% of platelet function is recovered after 24 hours of discontinuation of IV infusion. This feature makes it a less desirable drug for the patient in the immediate post-operative period.
6. In case of post-procedure life-threatening bleeding what treatment options are available?

In case of major post-procedure bleeding the most important issue is to assess the main cause of bleeding: platelet dysfunction, left-over thrombin inhibitor effects or a combination of causes leading to DIC. Some assays are currently becoming available at point-of-care centers to test the platelet function. A thromboelastogram (TEG) could also be used. If the cause of bleeding appears to be secondary to a platelet dysfunction the effects of aspirin, clopidogrel and abciximab can be reversed by platelet transfusions assuming that the active anti-platelet drug is not circulating in large quantities. Platelet transfusions are not effective in the first hours after discontinuation of eptifibatide and tirofiban infusions. If the patient is in DIC and has received large amounts of blood products then it is reasonable to use recombinant factor VIIa. However, keep in mind that use of factor VIIa may cause stent thrombosis.

7. Should an epidural catheter be inserted in patients with DES? How should the catheter be managed if the patient requires immediate PCI?

The key problem is balancing the benefit of pain control via epidural anesthesia against the risk of an epidural hematoma in case the patient would thrombose the stent and require immediate PCI with loading doses of antiplatelet medications. If regional anesthesia is considered as part of the anesthetic plan it may be more prudent to avoid leaving catheters in place.

There is no consensus as to management of an epidural catheter placed in a patient who will receive various types of antiplatelet medications. As usually these patients will be on standing doses of antiplatelet medications post-procedure and, interrupting these medications may put them at additional risk for re-infarction, it may be advisable to remove the catheter before the PCI. The anesthesiologist and the interventional cardiologist should carefully evaluate the situation and make a plan which would take into account all the risk factors. Whichever care plan is elected one should monitor the neurological status of the patient for at least 24 hours after the epidural catheter removal and should promptly mandate a CT scan of the spine if any suspicion of neurological injury exists.
Fig. 1 Mechanism of action of various antiplatelet medications

Fig. 2: Managing preoperative antiplatelet therapy in patients with drug eluting stents
REFERENCES
### Antiplatelet Medications

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<tr>
<th>Medication</th>
<th>Mechanism of action</th>
<th>Effect</th>
<th>Duration of action after drug stopped</th>
<th>Reversability of effects</th>
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<tbody>
<tr>
<td>Aspirin</td>
<td>Irreversible inhibition of COX</td>
<td>Weak antiplatelet</td>
<td>7-10 days</td>
<td>Platelet transfusion</td>
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<tr>
<td>Clopidogrel Plivaix®</td>
<td>Irreversible inhibition of ADP receptor</td>
<td>Partial inhibition of activation and aggregation</td>
<td>5-7 days</td>
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<td>Nonselective inhibition of GP IIb/IIIa receptor</td>
<td>Inhibits aggregation</td>
<td>at 24 h 50% normal plts</td>
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<tr>
<td>Eptifibatide Integrelin®</td>
<td>Selective inhibition of GP IIb/IIIa receptor</td>
<td>Inhibits aggregation</td>
<td>at 4 h 50% normal plts</td>
<td>Platelet transfusion not effective in first hours</td>
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<tr>
<td>Tirofiban Aggrastat®</td>
<td>Selective inhibition of GP IIb/IIIa receptor</td>
<td>Inhibits aggregation</td>
<td>at 4 h 50% normal plts</td>
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### FUTURE ANTIPLATELET MEDICATIONS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Compound</th>
<th>Route of adm.</th>
<th>Onset of action</th>
<th>Anti-aggregatory activity</th>
<th>Anti-thrombotic activity compared to clopidogrel</th>
<th>Recovery PLT f(x)</th>
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<tr>
<td>Clopidogrel</td>
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<td>Partial</td>
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