“MANAGEMENT OF PATIENTS ON ANTIPLATELET DRUGS UNDERGOING SURGERY” TO STOP OR NOT TO STOP?

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INTRODUCTION

Perioperative management of patients on antiplatelet therapy involves assessing and balancing individual risks for thromboembolism and bleeding. Discontinuing antiplatelet therapy may be necessary for major surgery but increases the risk of thrombotic events. Perioperative management of antiplatelet therapy requires special care in patients with coronary stents; the timing of surgery relative to stent placement dictates management in these patients. We review briefly on this aspect.

PHYSIOLOGY OF PLATELETS:

Platelets lack the biosynthetic machinery to synthesize new protein as it does not have nucleus. The life span of platelet is 8-10 days.

ANTIPLATELET DRUGS CURRENTLY AVAILABLE AND THEIR MECHANISM OF ACTION:

1. Aspirin
2. Dipyridamole, Cilostazol
3. Clopidogrel, Ticlopidine, Prasugrel,
4. Abciximab, eptifibatide, and tirofiban:

MECHANISM OF ACTION OF ANTIPLATELET DRUGS:

Aspirin: Irreversibly acetylates the enzyme cyclooxygenase (COX). COX has two isoforms: COX-1 and COX-2. Aspirin selectively inhibits COX-1 over COX-2 by 166-fold. The antithrombotic action of aspirin is mainly due to inhibition of platelet COX-1, which prevents the synthesis of thromboxane A2. This would inhibit platelet aggregation. T ½ of aspirin is 20 min. Still once a day dosing is effective because inhibitory effect of aspirin is cumulative. Daily administration of low dose aspirin results in virtually complete suppression of platelet thromboxane biosynthesis within 5 – 7 days. The defect induced by aspirin cannot be repaired during their life span of platelets.1

Dipyridamole and cilostazol: Increase concentrations of cyclic adenosine monophosphate (cAMP) in the platelet by inhibiting phosphodiesterase, stimulating prostacyclin production, and reducing cellular uptake of adenosine. Dipyridamole may also directly enhance prostacyclin-mediated platelet inhibition and inhibit thromboxane A2. They reversibly inhibit platelet aggregation induced by ADP, collagen, arachidonic acid, epinephrine, thromboxane A2, platelet-activating factor, and shear stress. Half life of Dipyridamole is 14 hours.

Clopidogrel, Ticlopidine and Prasugrel: Clopidogrel and Ticlopidine inhibit ADP activity by preventing its binding to the platelet receptor P2Y 12. ADP stimulates expression of the GP IIb/ IIIa receptor and may mediate release of other aggregation agonists and enhance platelet binding of von Willebrand factor. Hence, the end result of ADP inhibition is impairment of platelet aggregation and fibrinogen-mediated platelet crosslinking. After a single, oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The half-life of the active metabolite is about 30 minutes.
So platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective. Prasugrel is a prodrug and its active form binds irreversibly to the adenosine diphosphate (ADP) P2Y12 receptor on platelets for their lifespan, thereby inhibiting their activation and decreasing subsequent platelet aggregation. It has a greater antiplatelet effect than clopidogrel because it is metabolized more efficiently.

**Abciximab, eptifibatide, and tirofiban:** The GP IIb/IIIa receptor antagonists block the final common pathway in platelet activation. Abciximab is a monoclonal antibody that binds nonspecifically to the glycoprotein IIb–IIIa receptor. It can also bind to the vitronectin receptor on vascular smooth muscle cells and the integrin alphaMbeta2 receptor (Mac–1) on monocytes. Abciximab binds rapidly after a bolus infusion, leaving little free drug in the plasma. The most important difference between abciximab and the other glycoprotein IIb/IIIa inhibitors is duration of the antiplatelet effect. Due to the high-affinity binding of abciximab to the target receptor, the antiplatelet effects of the drug persist for 24–48 hours. Residual platelet inhibition can remain as high as 50-60% for 24 hours after the infusion is ended. Thus the effective half-life of abciximab is an estimated 12-24 hours or longer.2

Eptifibatide and tirofiban are both small–molecule glycoprotein IIb–IIIa inhibitors. They bind to the glycoprotein IIb–IIIa receptor with high specificity but low affinity, and this binding is competitive and rapidly reversible. Eptifibatide and tirofiban have a biologic half-life of about 1.5 to 2.5 hours each and rapidly dissociate from the receptor. Platelet aggregation returns to baseline within 4 hours after the infusion is ended. At steady state, a large amount of free drug continues circulating in the plasma, which can have implications for potential bleeding risk in these patients.

**ANTIPLATELET THERAPY IN PATIENTS AT RISK FOR CORONARY STENT THROMBOSIS UNDERGOING NON CARDIAC SURGERY**

Percutaneous interventions (PCIs) have become the most commonly performed coronary revascularization procedures, accounting for approximately 60% revascularizations.3 At the same time, there is an increased likelihood that patients with (recently implanted) intracoronary stents will need to undergo (urgent) surgery. Two serious consequences may emerge from this situation: stent thrombosis in relation to discontinuation of ant platelet therapy and major bleeding in relation to continuation of antiplatelet therapy.

The stress response to surgery includes sympathetic activation that may trigger adverse cardiovascular outcome.4 Furthermore, the surgical patient is in a hypercoagulable state due to an increase in plasma clotting factors while fibrinolysis is decreased. This alteration in hemostasis, which occurs during the peri-operative period, may also increase the risk of intracoronary stent thrombosis.

Premature discontinuation of clopidogrel after stent placement, because of non-cardiac surgery, can have fatal consequences. Discontinuation of aspirin therapy in patients treated with either Bare metal stent (BMS) or Drug eluting stent (DES) has been identified as an independent predictor of stent thrombosis.5

The best solution to overcome the risk resulting from surgery performed in patients after stent implantation is to postpone the surgery until after re-endothelialization of the vessel surface is complete. As only approximately 5-10 % of surgeries are performed as an urgent procedure, this could be a significant way to increase the safety of non-cardiac surgical procedures following stent implantation.6

**Recommendations**

- **Timing of surgery:** Guidelines recommend delaying non cardiac surgery for at least 6 weeks and optimally up to 3 months after bare metal stent implantation.7 After DES implantation, the elective surgery should not take place until after at least 12 months of dual antiplatelet therapy.8 The need for surgery in relation to its timing and the specific pathology should be balanced against the risk of stent thrombosis and “case by case” consideration is advisable.

- **Antiplatelet therapy:** It is recommended that 3 months after BMS PCI and 12 months after DES PCI, patients can be sent for non-cardiac surgery with continuation of aspirin therapy.9-10 Aspirin should only be discontinued if the bleeding risk outweighs the potential cardiac benefits. Discontinuation of aspirin should be considered in those in whom hemostasis is difficult to control during the operative procedure (for e.g. Neurosurgery/posterior chamber of eye surgery/Transurethral resection of prostate (TURP)).

Difficult decisions regarding antiplatelet management arise when a patient who is still receiving dual antiplatelet therapy with aspirin and a P2Y12 antagonist (mostly clopidogrel) is required to undergo a surgery that cannot be postponed. There is no realistic universal recommendation for this situation. Aspirin should be continued if possible; neither observational nor randomized study data are available regarding continuation of monotherapy with clopidogrel in this situation. If discontinuation of clopidogrel therapy is necessary, a P2Y12 antagonist should be resumed if there is adequate hemostasis after 24 hours post-surgery. In patients who require temporary interruption of aspirin or clopidogrel, or both, it is recommended that this treatment be stopped at least 5 days, preferably 10 days, prior to procedure.7 Heparin therapy, either unfractionated or low molecular weight,
Continuation of dual antiplatelet therapy is justified if the risk of stent thrombosis outweighs the risk of peri-operative bleeding complications. In recently published observational analysis, the incidence of surgical bleeding was low despite the high rate of dual antiplatelet therapy. For patients receiving antiplatelet therapy with excessive peri-operative bleeding, transfusion of platelets and administration of pro-hemostatic agents is recommended. Thus, non-cardiac surgery in patients following intracoronary stent implantation involves the risk of stent thrombosis, especially if surgery has to be performed when dual antiplatelet therapy is necessary. Awareness, prevention and early treatment of peri-operative complications in these patients are best achieved by collaborations between surgeons, anaesthesiologists and cardiologists.

PRE-OPERATIVE ANTIPLATELET THERAPY IN PATIENTS UNDERGOING CARDIAC SURGERY

Pre-operative aspirin taken within 5 days preceding coronary artery bypass grafting (CABG) is associated with significantly lower in-hospital mortality without increased risk of re-operation for bleeding or need for blood transfusion. In patients who have had off-pump CABG (OPCAB), it does not increase bleeding related complications, mortality rate, or other morbidities.

The risk versus benefit of pre-operative administration of clopidogrel remains unresolved with various studies giving conflicting results. Pre-operative clopidogrel is an independent risk factor for transfusion requirements and prolonged ICU and in-hospital length of stay. Among in-hospital referral patients, pre-operative clopidogrel administered within 5 days of CABG has been shown to increase early mortality and morbidity and risk of death is greatest when drug is given within 48 hours of surgery. On the other hand pre-operative use of clopidogrel has also been shown not to be associated with increased major or life threatening bleeding, need for surgical re-exploration or higher risk of blood transfusion after CABG. The ACUITY trial concluded that clopidogrel therapy in acute coronary syndrome in patients who underwent early CABG led to less ischemic events after surgery with no increase in bleeding.

It is recommended that surgery in patients receiving clopidogrel be performed with standard heparinization and anti-fibrinolytic strategies; platelets transfused before chest closure have beneficial effect on hemostasis. Aprotinin may reduce bleeding and transfusion requirements of packed red blood cells, platelets and total blood units in patients receiving clopidogrel who need urgent or elective CABG. Recent use of clopidogrel before OPCAB is associated with greater risk for bleeding with similar mortality rate. However, discontinuation of clopidogrel 3 days (72 hours) before the operation demonstrated a similar blood loss pattern compared with a control group.

According to American college of cardiology recommendations, in patients taking thienopyridine, in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow dissipation of the antiplatelet effect. The period of withdrawal should be at least 5 days in patients receiving clopidogrel and 7 days in those receiving prasugrel, unless the need of revascularization and/or the net benefit of thienopyridine outweigh the potential risk of excess bleeding.

ANTI-PLATELET THERAPY AFTER PERCUTANEOUS CORONARY INTERVENTION (PCI)

In patients without allergy or increased risk of bleeding, aspirin 162 to 325 mg daily should be given for at least 1 month after bare metal stent (BMS) implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which long term aspirin use should be continued indefinitely at a dose of 75 to 162 mg daily.

The addition of platelet P2Y₁₂ receptor antagonist like clopidogrel and prasugrel, to aspirin is essential for prevention of stent thrombosis until re-endothelialization of vessel surface is complete. For all “elective” PCI patients who receive a drug eluting stent (DES), clopidogrel 75 mg daily should be given for at least 12 months if patients are not at high risk of bleeding.

In patients of STEMI and Unstable angina/NSTEMI undergoing PCI, the duration of thienopyridine therapy should be as follows:

- In patients receiving a stent (BMS or DES) during PCI for ACS, clopidogrel 75 mg daily or prasugrel 10 mg daily should be given for at least 12 months.
- If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, early discontinuation should be considered.

In patients in whom subacute thrombosis may be catastrophic or lethal (unprotected left main or bifurcating left main, or last patent coronary vessel), platelet aggregation studies may be considered and the dose of clopidogrel increased to 150 mg/day if less than 50% inhibition of platelet is demonstrated.
Continuation of clopidogrel or prasugrel beyond 15 months may be considered in patients undergoing DES placement.

**GLYCOPROTEIN IIb–IIIa INHIBITORS**

**Bleeding Risk.** Some patients who have been treated with glycoprotein IIb/IIIa inhibitors for acute coronary syndromes and during percutaneous coronary intervention subsequently need a surgical intervention. A major concern regarding these patients is the potential for increased surgical morbidity and mortality secondary to significant bleeding. The rate of emergent CABG required after percutaneous coronary intervention was 2–4% in large trials evaluating the glycoprotein IIb–IIIa inhibitors.²

**Options for Minimizing Bleeding Risk.** Clinical experience demonstrates that emergent or urgent CABG surgery after abciximab therapy is associated with increased blood loss, use of blood products, and chest tube drainage; in some reports it is correlated with increased surgical mortality. Due to the prolonged platelet inhibition that results from abciximab therapy, surgery should be delayed 24 to 48 hours whenever possible. When emergent or urgent CABG is necessary, every effort should be made to delay surgery by at least 12 hours, since the increased bleeding risk appears to be most prominent during the first 12 hours after abciximab discontinuation.¹⁹ If surgery cannot be delayed without significant risk for the patient, other management strategies to limit bleeding risk...
**Decision making algorithm for patients undergoing cardiac surgery**

**Initial check list**
- a) Type of antiplatelet therapy used dual/single
- b) Urgent/elective (can wait for 1 week) surgery
- c) Co-morbidities in the patient (DM/Renal failure/EF)

**Urgent previously on dual antiplatelet therapy**
- Stop Clopidogrel
- Give Platelet rich concentrate intraop
- Continue Aspirin

**Elective (can wait for 1 week) On dual antiplatelet therapy**
- Stop Clopidogrel 5 days prior to surgery, continue Aspirin

**Recommended duration of antiplatelet therapy after percutaneous interventions (PCI)**

**Type of stent**

**Bare metal stent (BMS)**
- Aspirin 162-325mg daily for at least 1 month
- Clopidogrel 75mg minimum for a month and ideally for 12 months

**Drug eluting stent (DES)**
- Sirolimus stent: Aspirin 162-325mg daily for at least 3 months
- Paclitaxel stent: Same dose for 6 months
- Clopidogrel 75mg at least for 12 months until re-endothelialization occurs.

- Aspirin 75-162mg daily to be continued indefinitely
- Use of Clopidogrel thereafter would be after weighing the risk of bleeding, should be considered to be continued on a long term basis in patients with DES.

must be considered. Eptifibatide and tirofiban have posed minimal bleeding risk when discontinued 4 hours before surgery.

In the setting of percutaneous revascularization, protocols of reduced dose heparin combined with glycoprotein IIb–IIIa inhibitors have resulted in decreased frequency of major bleeding events. Transfusions of blood products are a logical treatment for reversing the effects of glycoprotein IIb–IIIa inhibitors. However, platelet transusions are less effective in reversing the effects of small-molecule glycoprotein IIb/IIIa inhibitors (eptifibatide or tirofiban) due to the large amount of free drug in the plasma at steady state. The free drug can
bind to the newly infused platelets and result in little or no net benefit in reversing platelet inhibition.20

Abciximab therapy results in a relatively small amount (<5%) of free drug available to bind to new platelets. Platelet transfusions before, during, and after cardiopulmonary bypass surgery have been useful in diminishing the amount of blood loss and subsequent need for blood products in abciximab–treated patients. Prophylactic platelet transfusions will be a reasonable approach in abciximab–treated patients who are undergoing cardiopulmonary bypass.

The timing and amount of platelets transfused should be determined based on each patient’s bleeding risk and coagulation profile if possible. Platelets should be given after termination of cardiopulmonary bypass when possible to avoid the deleterious effects of the procedure on the newly transfused platelets. After the initial prophylactic transfusions, additional transfusions should be given based on the usual clinical and laboratory indicators, and only after a surgical cause and inadequate heparin reversal have been excluded as precipitating factors. The role of antifibrinolytic agents in the setting of glycoprotein IIb–IIIa inhibitor treatment has not been well defined.

KEY POINTS:

• When balancing risks of bleeding versus thrombotic events, the relative consequences of each event again must be considered. Bleeding is rarely life-threatening in comparison with the potential consequences of stent thrombosis.

• Abrupt discontinuation of antiplatelet therapy can lead to a rebound effect marked by an inflammatory prothrombotic state, increased platelet adhesion and aggregation, and excessive thromboxane A2 activity.

• Surgery further increases the prothrombotic and inflammatory state, which, combined with incompletely endothelialized drug-eluting stents, can lead to stent thrombosis and, consequently, myocardial infarction and/or death.21

• The US Food and Drug Administration recommends that dual antiplatelet therapy be continued for at least 3 months after placement of a sirolimus-eluting stent and at least 6 months after placement of a paclitaxel-eluting stent. Recent data suggest, however, that this duration of antiplatelet therapy may not be sufficient and that at least 1 year of therapy may be needed.8

REFERENCES


