Antiplatelet Drugs - Perioperative Management - Full Clinical Guideline

Reference no.: CG-ANAES/2017/010

Introduction

Platelets play a major role in thrombus formation with complex activation via multiple receptors and pathways. They are therefore central in the pathogenesis of atherosclerosis and thrombotic diseases. As a result, increasing numbers of antiplatelet agents are being used in both the prevention and treatment of coronary, cerebral and peripheral vascular diseases. This presents a significant challenge when these patients present for surgery, when the inherently increased risk of bleeding has to be carefully weighed against the potentially devastating complications of withholding antiplatelet therapy. There are no specific reversal agents and bleeding during antithrombotic therapy is associated with high morbidity and mortality.

Aim and Scope

This guideline provides a rational, evidenced based approach for the perioperative management of patients taking antiplatelet agents who present for surgery at Derby Teaching Hospitals NHS Foundation Trust. It aims to reduce unnecessary delays in getting patients to theatre, avoid the administration of inappropriate platelet transfusions and, above all, minimise patient harm. It covers the newer antiplatelet agents with which some clinicians may not be quite so familiar and on which current evidence is limited.

This guideline is of particular relevance to anaesthetists, surgeons, haematologists and cardiologists.

Major Characteristics of Antiplatelet Agents

Drug (route)	Mechanism of action	Platelet inhibition	Time to recover platelet function after drug withdrawal
Aspirin (PO)	COX-1 inhibition	Irreversible	5-7 days
Dipyridamole (PO)	Phosphodiesterase inhibitor	Reversible	24 hr
Clopidogrel (PO)	ADP receptor inhibitor	Irreversible	5-7 days
Prasugrel (PO)	ADP receptor inhibitor	Irreversible	5-7 days
Ticagrelor (PO)	ADP receptor inhibitor	Reversible	3-5 days
Abciximab (IV)	GP IIb/IIIa receptor inhibitor	Reversible	24-48 hr
Eptifibatide (IV)	GP IIb/IIIa receptor inhibitor	Reversible	4-8 hr
Tirofiban (IV)	GP IIb/IIIa receptor inhibitor	Reversible	4-8 hr

Aspirin

Aspirin is the most commonly used antiplatelet agent. It irreversibly inhibits cyclo-oxygenase 1 and 2 enzymes thereby preventing formation of Thromboxane-A2 (TXA-2), a potent vasoconstrictor and platelet activator. It's antithrombotic effect is maintained for the lifespan of the platelet (7-10 days). It has a short half-life of 15-20 mins and is therefore cleared after 2 hr in most circumstances. Platelet aggregation returns to baseline levels within 5 days of discontinuation.

Aspirin increases the risk of surgical bleeding 1.5 fold but does not increase the severity of bleeding for most procedures and it's withdrawal in patients with Ischaemic Heart Disease (IHD) may significantly increase the risk of a Major Adverse Cardiac Event (MACE).

Aspirin should be continued perioperatively in most circumstances. It may need to be withheld for certain operations which carry a high risk of bleeding e.g. intracranial surgery, posterior eye chamber surgery or transurethral resection of the prostate (TURP), in which case it should be stopped 7 days prior to surgery.

Dipyridamole

Dipyridamole is a phosphodiesterase inhibitor which prevents the degradation of cAMP and cGMP, causing vasodilatation and impairing platelet activation. It is mainly given in combination with aspirin for secondary prevention of cerebrovascular events in patients unable to take clopidogrel.

ADP Receptor Inhibitors

Irreversibly bind to ADP receptors on the platelet surface to prevent ADP-mediated platelet aggregation.

Clopidogrel and **Prasugrel** are thienopyridine prodrugs which require hepatic conversion to an active metabolite. They do not require dose adjustment in moderate renal or hepatic disease. Prasugrel is more effective and faster than clopidogrel at achieving platelet inhibition.

Ticagrelor is a non-thienopyridine, reversible, non-competitive antagonist of the ADP receptor which has a more rapid onset and is more potent than the latter 2 drugs. It has a plasma half life of 8-12 hours and requires twice daily administration. Ticagrelor, unlike Clopidogrel, is not affected by response variability due to genetic polymorphism and has a better safety profile than Prasugrel.

In elective patients at low risk of thrombotic complications:

- Clopidogrel and Prasugrel should be discontinued for 7 days preoperatively
- Ticagrelor should be discontinued for 5 days preoperatively
- All ADP receptor inhibitors should be restarted as soon as possible post-operatively and certainly within 48hr

Dual AntiPlatelet Therapy (DAPT)

ADP receptor inhibitors are mostly given alongside aspirin as part of a DAPT regimen in patients with ischaemic heart disease. The duration of therapy depends on the indication and type of any coronary stents implanted.

In brief, DAPT is recommended for
- at least 1 month after bare metal stent (BMS) implantation in stable coronary artery disease
- 6 months after new generation drug-eluting stent (DES) implantation and
- up to 1 year in patients after an acute coronary syndrome (ACS) irrespective of revascularisation strategy
- in all these patients, aspirin should continue lifelong

Premature cessation of DAPT in patients with recent coronary stents is the most powerful predictor for stent thrombosis. Perioperative stent thrombosis carries a mortality of up to 20%.

Ideally, elective surgery should be delayed until completion of DAPT. When surgery cannot be delayed, there needs to be careful discussion between the surgeon, cardiologist and anaesthetist regarding risk of bleeding versus risk of stent thrombosis.

Bleeding risk in non-cardiac surgery

Surgical haemorrhagic risk	Blood transfusion requirement	Type of surgery
Low	Usually not required	Peripheral, plastic & general surgery biopsies Minor ortho, ENT & general surgery Endoscopy Eye anterior chamber Dental extraction & surgery
Intermediate	Frequently required	Visceral surgery Cardiovascular surgery Major ortho surgery ENT Urological surgery Reconstructive surgery
High	Possible bleeding in a closed space	Intracranial neurosurgery Spinal canal surgery Eye posterior chamber

Low risk of bleeding
- continue DAPT perioperatively.

Intermediate risk of bleeding
- DAPT should be continued if possible
- where the risk of bleeding outweighs the risk of thrombosis, stop ADP receptor blocker preoperatively as detailed above
- restart ADP receptor blocker as soon as possible postoperatively - no sooner than 6 hours and certainly within 48 hours
- Aspirin should be continued throughout

High risk of bleeding
- Stop ADP receptors preoperatively
- Restart ADP receptor blocker as soon as possible postoperatively - no sooner than 6 hours and certainly within 48 hours
- continue aspirin where possible

For patients with a very high risk of stent thrombosis (eg recent insertion, previous stent thrombosis, unfavourable coronary anatomy), bridging therapy with intravenous glycoprotein IIb/IIIa

inhibitors (see below), should be considered. These are effective in achieving platelet inhibition similar to that of the oral ADP receptor inhibitors, with rapid onset and offset of action. Of note, unfractionated heparin (UFH) makes platelets more reactive to activation resulting in a prothrombotic effect and low-molecular-weight heparin does not have platelet inhibitory effects. The use of UFH or LMWH for bridging in these patients should therefore be avoided.

Glycoprotein IIb/IIIa Receptor Inhibitors

These agents prevent platelet cross-linking and aggregation by reversible inhibition of the GP IIb/ IIIa receptor on the platelet surface. They are intravenous drugs, currently used as an adjunct in the treatment of patients with ACS or undergoing percutaneous coronary intervention (PCI).

Abciximab is a monoclonal anti-GP IIb/IIIa antibody which binds rapidly to platelets and has a plasma half-life of 10 mins. It dissociates slowly from the receptors and platelet function recovers over 48 hr. It is not excreted in the urine. May cause significant thrombocytopenia. As minimal drug is available in the blood it's effects can be rapidly reversed by platelet transfusion.

Eptifibatide and **Tirofiban** inhibit platelet aggregation in a dose dependent manner and rapidly dissociate from platelets on discontinuation of infusion. They are excreted unchanged in the urine with a half-life of around 2 hr and require dose adjustment in renal impairment. Thrombocytopenia is uncommon and in the absence of renal impairment the bleeding risk diminishes rapidly after cessation of treatment. Unbound drug is available in the plasma and therefore platelet transfusions are unlikely to reverse the effects while active circulating drug is present. Reversal therefore relies primarily on stopping the drug.

Antiplatelets and regional anaesthesia (adapted from AAGBI guidelines)

NB. These recommendations relate primarily to neuraxial blocks and to patients with normal renal function. Risks associated with other regional techniques (plexus/peripheral nerve blocks) will vary depending on the type of block and rely on individual clinical judgement and expertise. Catheter techniques may carry a higher risk than single shot blocks.

Drug	Acceptable time after drug for block performance	Administration of drug while spinal/epidural catheter in place	Acceptable time after block performance or catheter removal for next drug dose
Aspirin	No additional precautions	No additional precautions	No additional precautions
Dipyridamole	No additional precautions	No additional precautions	6 hr
Clopidogrel	7 days	NOT recommended	6 hr
Prasugrel	7 days	NOT recommended	6 hr
Ticagrelor	5 days	NOT recommended	6 hr
Abciximab	48 hr	NOT recommended	6 hr
Eptifibatide	8 hr	NOT recommended	6 hr
Tirofiban	8 hr	NOT recommended	6 hr

Aspirin and other NSAIDs, by themselves, represent no significant risk for the development of spinal haematoma in patients having central neuraxial anaesthesia. For all other antiplatelet agents, platelet function should ideally be allowed to recover before neuraxial block is performed. However, these recommendations should be taken in context with regard to the risk of regional versus general anaesthesia for individual patients. There is little or no evidence that Clopidogrel alone increases the risk of vertebral canal haematoma in patients receiving spinal or epidural anaesthesia. However, extreme caution is advised and neuraxial block should be avoided in patients on DAPT.

Major bleeding

In the case of major bleeding in patients on antiplatelet therapy, management should consist of the following:

- Early activation of the ***major haemorrhage protocol***
- Local haemostatic measures
- Fluid resuscitation and red cell transfusion as indicated
- Exclude any co-existing coagulopathy e.g. DIC
- Document the timing and amount of the last drug dose and presence of pre-existing renal or hepatic impairment
- Estimate the half-life and length of functional defect induced by the antiplatelet drug
- Platelet transfusion (1-2 adult doses) should be considered for critical bleeding (see below)
- Consider Tranexamic acid IV (15mg/kg)
- Seek haematology advice

Platelet Transfusions

The efficacy of platelet transfusions are reduced in the presence of ADP receptor inhibitors. The active metabolite of Clopidogrel remains in the circulation for up to 18 hours and permanently inhibits any platelets during this time. If possible, emergency surgery is best delayed for 24 hours after the last dose of clopidogrel when the response to platelet transfusion will be improved. Platelet transfusions are unlikely to be effective within 6 hours of a loading dose of Prasugrel and 4 hours of a maintenance dose. The active compound of Ticagrelor has a half life of 12hr and therefore any platelet transfusion given within this time may be ineffective. If surgery cannot be adequately delayed and the bleeding risk is high, a platelet transfusion may be considered preoperatively or at least platelets should be immediately available in case of major bleeding intraoperatively.

Aspirin inhibits TXA-2 formation but not the TXA-2 receptor. Thus, aspirin-inactivated platelets can be recruited by TXA-2 which is generated by transfused platelets. Platelet transfusion is therefore effective at restoring platelet function in patients taking aspirin alone but is rarely indicated. It should only be considered for severe intra- or post-operative bleeding clearly related to aspirin.

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Review Date:	June 2020 – Extension agreed April 2024
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