TRIPOM
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Perioperative Management of anticoagulant medications

Multiple Choice Questions
Please select each statement as true or false

1 New Oral Anticoagulant Drugs (NOACs)

a) Have longer half-lives than warfarin
b) Have no specific reversal agents
c) Should be withheld for at least 24 hours prior to surgery
d) Can be restarted within 12 hours of surgery
e) Have no effect on prothrombin time (PT), thrombin time (TT) or activated partial thromboplastin time (APTT)

2. With regards to antiplatelet agents.

a) All ADP receptor blockers should be withheld for 7 days prior to major surgery
b) Dual Antiplatelet Therapy (DAPT) has a higher bleeding risk peri-operatively than monotherapy
c) Aspirin is a reversible COX inhibitor
d) Platelet transfusions should not be given within 12 hours of aspirin therapy due to likely de-activation of transfused platelets
e) No additional precautions are required for patients on maintenance NSAIDs or aspirin prior to performing spinal or epidural anaesthesia.

3. With regards to performance of central neuro-axial blockade

a) Clopidogrel and Prasugrel should be stopped 7 days prior to blockade
b) Ticagrelor should be stopped 5 days prior to blockade
c) The time taken between last dose of Rivaroxaban and spinal or epidural performance depends on the indication for Rivaroxaban
d) It is recommended to wait 6 hours post performing blockade or removing epidural catheter before restarting warfarin
e) It is advisable to have a normal APTT ratio or wait 4 hours after administering intravenous or subcutaneous unfractioned heparin before performing spinal or epidural

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4. With regards to antiplatelet agents.

a) In patient with a history of recent acute coronary syndrome who require surgery, it is advisable to continue at least 1 DAPT if possible

b) Patients with a high risk of cardiac thrombosis who have stopped one or more antiplatelet agents, can have bridging therapy with intravenous glycoprotein 2b/3a inhibitors

c) Tranexamic acid has been shown to increase thrombotic risk when given pre-operatively prior to cardiac or trauma surgery

d) Both agents in the commonly used DAPT regimen of aspirin and clopidogrel are irreversible COX inhibitors

e) Dipyridamole has a longer half life than clopidogrel and aspirin and therefore needs to be stopped for longer prior to surgery or block performance

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Key points:

- There are increasing amounts of people on anticoagulants and their risk of thrombosis and risk of bleeding needs to be assessed to make a sensible decision regarding their anticoagulation in the peri-operative period [1].
- Patients with a high risk of thrombosis who are having a major procedure may require bridging therapy with low molecular weight heparin or unfractionated heparin. The newer oral anticoagulants have a much shorter onset and offset time than warfarin making bridging therapy either unnecessary or shorter in duration [2].
- For some operations with a low bleeding risk such as, dental procedures, pacemaker insertion, cataracts and some endoscopic procedures it may be possible to continue anticoagulation if the bleeding risk is acceptable [3,4,5].
- Patients that have a high surgical bleeding risk can be treated with pre-operative parental tranexamic acid in cardiac and trauma surgery without an increased thrombosis risk [2].

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Introduction

An increasing number of patients are now taking anti-coagulant medications or antiplatelet agents. This means there is increased risk of significant haemorrhage in the peri-operative period and care needs to be taken regarding choice of surgical and anaesthetic technique [1].

Historically aspirin was the mainstay of antiplatelet treatment with warfarin the most commonly used oral anticoagulant. This is no longer the case as there are also newer agents in use currently [2].

For elective patients the role of the peri-operative team is; to establish the reason for the antiplatelet or anticoagulant medication, make an appropriate plan to continue, withhold or use bridging therapy, and to make a safe and effective anaesthetic and surgical plan for that patient.

In emergency situations it may even be necessary to reverse the anticoagulant medication rapidly to allow live saving surgery to take place. In this situation there is always a risk versus benefit decision and it is important to choose an appropriate reversal method and seek haematology advice when required.

Anticoagulant Medications

Warfarin

Warfarin is a coumarin derivative that has been used as an anticoagulant since the 1950s, it remains popular but is being replaced by newer oral anticoagulant medications. It has multiple drug interactions which may need to be kept into consideration when patients have deranged coagulopathy [6,7]. It works by inhibiting vitamin K synthesis, this limits production of vitamin K dependent clotting factors – 2,7,9,10 as well as protein C and protein S. It has a long half life of 36 hours as new clotting factors are synthesised by the liver to restore normal clotting function [2].

Current guidance for elective surgery is to discontinue warfarin 5 days prior to surgery and to check the International Normalised Ratio (INR) the day before major surgery, aiming for an INR of < 1.5. For dental procedures and minor surgery, an INR of < 2.5 may be acceptable [2,3].

Some patients may have a significant risk of thrombo-embolic disease and thus stopping their anticoagulation is not desirable. Bridging therapy with either unfractionated or low molecular weight heparin can therefore be considered. British

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Society of Haematologists suggest bridging therapy is considered in patients in the following 3 groups.

Previous venous thrombo-embolism (VTE) – VTE within last 3 months, previous VTE on therapeutic anticoagulation

Atrial Fibrillation (AF) – stroke of transient ischaemic attack (TIA) in last 3 months, previous stroke and TIA and 3 or more of (hypertension, congestive cardiac failure, age > 75 years, diabetes mellitus)

Mechanical Heart Vales – All mechanical heart valve patients except those with a bileaflet aortic valve and no other risks factors [2].

In the emergency setting or in case of unexpected high INR it may be necessary to reverse warfarin therapy. There are two commonly used methods to reverse warfarin in the emergency setting, if it is possible to delay surgery for 6-8 hours; Phytomenadione at a dose of 5mg can restore vitamin K dependent factors. However a repeat INR is still required prior to surgery. In more severe emergencies 25-50 units/kg of four- factor prothrombin complex can be given, it is still recommended to check the INR prior to surgery [2]. In all cases haematology advice can be sought locally.

Mechanical Heart Valves and Warfarin

All patients with mechanical heart valves require lifelong warfarin anticoagulation, and some patients with mitral or tricuspid bioprosthetic valves may also require temporary warfarinisation [8,9].

For those requiring warfarin the target INR depends on the surgery, the cardiac surgeon and the type of valve. For instance, an isolated aortic valve replacement patient without other thrombotic risk factors using a low risk mechanical valve e.g ON-X, can aim for a median INR of 2.5. Whereas a patient with mitral / tricuspid valve replacement or an aortic valve replacement with other thrombotic risk factors, will need to aim for a higher median INR depending on the thrombogenic risk of the valves used, usually between 3.0 and 4.0 [9,10].

As previously mentioned, all patients with mechanical valves undergoing major surgery will require bridging therapy. Bridging therapy for mechanical valves should be with unfractionated heparin (UFH) rather than low molecular weight heparin (LMWH), due to the faster onset and offset of UFH and the ability to reverse UFH with protamine. Local guidelines should be reviewed or discussion with a local cardiologist considered when

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making a peri-operative anticoagulation plan for patients with mechanical heart valves [9,10].

New Oral Anticoagulants (NOACs) also known as Direct Oral Anticoagulants (DOACs)

NOACs act either by direct thrombin inhibition (Dabigatran) or inhibition of factor Xa (Rivaroxaban, Apixaban). All of these drugs have quicker onset and shorter half life than warfarin with no standard monitoring tests such as the INR [7].

NOACs are approved for use for treatment of VTE and prevention of stroke prevention in non-valvular atrial fibrillation in the US since 2009. Warfarin is still the preferred anticoagulant for patients in the US with stage 5 renal impairment (creatinine clearance < 15ml/min) and mechanical heart valves [11,12]. NOACs have a quicker onset and offset than warfarin, which precludes the need for bridging therapy but also necessities strict adherence to dosing by the patient. The NOAC agents also have less drug interactions and a lower bleeding risk than warfarin, however there is no method to objectively measure NOAC activity and there are no specific reversal agents available yet for the NOACs except for dabigatran [8,12].

As mentioned routine coagulations studies do not demonstrate the activity of NOACs and a normal PT and normal APTT does not signify that there is no NOAC activity ongoing. However a normal thrombin time (TT) is a good marker for ruling out any dabigatran activity [13]. Therefore it is advisable not to perform neuro-axial blockade unless the anticoagulant effect of NOACs can be excluded (a normal TT for a patient on Dabigatran is satisfactory) [2,13]. All NOACs are cleared renally and thus renal impairment can affect their duration of action, more so for dabigatran than the Xa inhibitors [7].

Except for Dabigatran there is no specific reversal for these agents currently on the market. Praxbind (Idarucizumab) is a monoclonal antibody that is a specific reversal agent for Pradaxa (Dabigatran)[14].There is currently a reversal agent for direct Xa inhibitors undergoing clinical trials, (Andexanat alfa) which the British Society of Haematologists have recommended for use for emergency reversal of Direct Xa inhibitors rivaroxaban and apixaban once it has been approved [2,15].

Previously fresh frozen plasma, prothrombin complex concentrates (PCC) and fibrinogen containing concentrates have been used to reverse direct Xa inhibitors, with some effect however is an un-validated technique and discussion with a haematologist should occur prior to giving activated PCC to reverse direct Xa inhibitors [16].

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Current recommendations are that patients with normal renal function should avoid NOACs for 24 hours for low risk procedures and 48 hours for high risk procedures. NOACs should be recommenced 6-12hours post low risk procedures and 48 hours post high risks procedures. The British Society of Haematologists also advises that a prophylactic dose of low molecular weight heparin can be given between surgery and restarting NOACs for patients with a high VTE risk [2,16].

Tranexamic Acid is recommended to reduce bleeding in patients undergoing emergency surgery on NOACs or patients who have excessive surgical bleeding due to NOAC activity [2].

Antiplatelet agents

Aspirin

Aspirin remains the most commonly used antiplatelet medication for primary and secondary prevention of cardiovascular disease (CVD) [17]. Aspirin is an irreversible COX inhibitor in the platelet, therefore its effects last the lifespan of the platelet (7-10 days). Aspirin acetylates cyclo-oxygenase thus preventing the production of prostaglandins and thromboxane [18]**.** Recommendations from the British Society of Haematology regarding aspirin are;

"When being used for secondary prevention of cardiovascular disease

aspirin monotherapy can be continued for most invasive non-

cardiac procedures (including neuroaxial anaesthesia) but, if the perceived

bleeding risk is high, aspirin can be omitted for day -3 to day +7 with no net detriment".

"Aspirin can be continued both before and after coronary artery bypass surgery" [2].

Adenosine Diphosphate Receptor (ADP) receptor blockers

These drugs work by blocking the P2Y12 receptor (an ADP receptor) on the platelet's surface which prevents platelet aggregation and reduces platelet interactions with procoagulant substances in the plasma. The most commonly used ADP receptor blockers are clopidogrel and ticagrelor [19]. These drugs are thienopyridine derivates that are irreversible and often used as dual antiplatelet therapy (DAPT) for CVD or monotherapy for peripheral vascular disease (PVD) or following a stroke or transient ischaemic attack (TIA) [20,21].

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Clopidogrel is the most commonly used ADP receptor blocker, as DAPT with aspirin for acute coronary syndrome (ACS) or monotherapy for vascular disease, as it is irreversible its effects last the lifespan of the platelet [19]. For (ACS) a loading dose is required for rapid platelet inhibition. This is usually followed by a maintenance dose as part of DAPT, which for ACS should be continued for 6-12 months particularly if coronary stenting has occurred [22]. British Society of Haematology recommends withholding clopidogrel for 5 days pre-operatively in preparation for elective procedures [2].

Recent data has shown that emergency hip surgery for patients on clopidogrel as a single antiplatelet agent do not have a significant increase in post-operative bleeding. However, patients on DAPT do show a significant increase in post-operative bleeding following early hip surgery [23,24]. Therefore, the British Society of Haematologists recommends that patients on clopidogrel as a solo antiplatelet agent can have early hip surgery using normal local protocols and to consider carefully the management of hip fractures requiring surgery on patients on DAPT [2,23].

Ticagrelor is also an irreversible ADP receptor blocker that is used either as DAPT for ACS with aspirin or monotherapy for vascular disease. It is recommended to stop ticagrelor for 5 days prior to elective surgery [2,20].

Prasugrel is also an irreversible ADP receptor blocker that is less commonly used than clopdiogrel and ticagrelor as it has been shown to have a higher bleeding risk when used as DAPT with aspirin [25]. It has a longer drug metabolic half-life that clopidogrel and ticagrelor and therefore it is recommended to be stopped 7 days prior to surgery whenever possible [26,27].

Glycoprotein 2b/3a Inhibitors

Glycoproteins 2b and 3a are present on the surface of platelets in abundance. Inhibitors of these receptors block fibrinogen adhering to the activated platelets, therefore preventing the building of a cross linked platelet plug. Commonly used agents are abciximab, tirofiban and eptifibatide in the setting of ACS. Tirofiban and eptifibatide are short acting agents and can even be used as bridging therapy for patients on DAPT whom have a high thrombotic risk and a require emergency cardiac surgery. Abciximab is longer acting and has been shown not to increase bleeding risk during coronary surgery [28].

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Dipyridamole

Dipyridamole is an antiplatelet agent that works mainly by inhibition of platelet cAMP-phosphodiasterase [20]. It is a second line antiplatelet agent for prevention of vascular disease, commonly prevention of stroke or TIA. It can be used either alone or in combination with aspirin if clopidogrel is not tolerated or if clopidogrel is contraindicated as part DAPT. Dipyridamole is also used as monotherapy for patients for whom aspirin and clopidogrel are not tolerated or contra-indicated [20]. It has almost no activity 24 hours after administration and therefore only needs to be stopped 24 hours prior to surgery and can be restarted 3-4 days post operation [29,30].

Dual Antiplatelet Therapy

Some patients on aspirin are on dual antiplatelet therapy (DAPT) which poses an increased bleeding risk for surgery and anaesthetic procedures [24]. DAPT therapy is particularly important in patients with recent acute coronary syndrome or recent cardiac stents. In these cases it is recommended to continue medications if the operation has a low bleeding risk; or in elective surgery with a high bleeding risk to postpone surgery if possible. If the bleeding risk is considered high but the surgery cannot be postponed then the recommendations from the British Society of Haematologists is to consider continuing aspirin and stopping the adjuvant antiplatelet agent [2].

For emergency surgery with high bleeding risk it is not possible to stop the antiplatelet medication prior to surgery or to delay the operation. In these circumstances it is recommended to use tranexamic acid either pre-operatively or during the operation, and if that does not provide satisfactory haemostasis, consider platelet transfusion of 2 pools of donor platelets as well as resuscitation with other blood products as required [2]. As these agents are irreversible it is recommended to wait at least 2 hours after last aspirin dose or 12-24 hours after the last clopidogrel dose before giving a platelet transfusion to avoid any active drug in the plasma deactivating the transfused platelets [2].

Neuro-axial blockade in patients on Antiplatelet and Anticoagulant medication.

The main concern regarding central neuro-axial blockade and anticoagulation is the risk of spinal or epidural haematoma leading to compression of the spinal cord. Although these are rare events with reported incidence in the United States of <1 in 150,000 for epidural anaesthesia and <1 in 220,000 for spinal anaesthesia [31]. In

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National Audit Project 3 (NAP 3) the incidence of vertebral canal haematoma was 0.85 per 100,000 [32]. Few incidences of spinal haematoma have been shown to be related to antiplatelet therapy and therefore aspirin and non-steroidal anti-inflammatory agents (NSAIDs) are regarded as safe to continue, however due to limited evidence regarding neuro-axial blockade and ADP receptor blockers, it is advisable to stop these prior to spinal or epidural anaesthesia [32,33].

There is little data regarding the safety of performing peripheral nerve blocks whilst on anticoagulant medication and thus there is no clear guidance for each peripheral block [34]. The guidance from UK and US anaesthetic groups pertains mainly to spinal / epidural anaesthesia. However the AAGBI states that certain factors may affect the bleeding risk of peripheral nerve blocks. These are mainly; deeper blocks are higher risk than superficial nerve blocks, leaving an indwelling catheter increases the bleeding risks, using ultrasound guidance by experienced clinicians reduces the risks, altered coagulation increases the risk. The risk of harm also depends on the site affected and complications thereof, for example bleeding causing airway compression or bleeding to a non-compressible site have increased risk of harm compared to superficial bleeding [35].

The Association of Anaesthetists of Great Britain and Northern Ireland (AAGBI) have produced clear guidance on the timing of neuro-axial blockade and removal or epidural catheters with respect to antiplatelet medications. For patients on maintenance aspirin therapy (75mg-100mg per day) no additional precautions are required prior or post to performing neuro-axial blockade unless unforeseen complications occur. Dipyridamole can also be continued for performance of neuro-axial blockade but doses should only given 6 hours or more post removal of a catheter or performing block [35].

For patients on clopidogrel and prasugrel it is recommended to discontinue 7 days prior to performing neuro-axial blockade, to withhold these medications whilst a catheter is in situ and to restart at least 6 hours following removal of epidural catheter or performing block [35].

For patients on ticagrelor it is recommended to discontinue 5 days prior to performing neuro-axial blockade, not to give if catheter in situ and to wait at least 6 hours post catheter removal or performing block before restarting [35].

Due to the shorter half lives of the glycoprotein 2b/3a inhibitors, it is recommended that neuro-axial blockade can be performed 8 hours or more after administration of tirofiban or eptifibatide. These medications again should not be given whilst a catheter in situ and can be safely restarted 6 hours post block performance or catheter removal.

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Abciximabs longer half life means it should be withheld for 48 hours post block performance but otherwise follows the same guidelines as tirofiban and eptifibatide [35].

With regards to anticoagulant medications, the AAGBI recommend that warfarin be stopped 3-5 days prior to neuroaxial blockade and INR checked regularly. Central neuro-axial blockade can be performed when INR less than or equal to 1.4, warfarin should be withheld whilst a catheter is in situ and can be restarted once the catheter has been removed or after the block has been performed [31,35].

For patients on bridging therapy due to high risk of thrombosis on intravenous or subcutaneous Unfractionated Heparin (UFH) it is recommended that the drug administration is avoided 4 hours prior to performing central neuroaxial blockade or the patient has a normal APTT ratio prior to spinal or epidural. Caution is advised if the patient requires heparinising whilst a catheter is inserted and it is recommended to wait 1 hour post blockade or post catheter removal to restart subcutaneous UFH and 4 hours for intravenous UFH [35].

For patients on Low Molecular Weight Heparin (LMWH) AAGBI recommends waiting 12 hours post dose if on prophylactic dosing and 24 hours post dose if on treatment dosing before spinal or epidural. These agents can be started 4 hours post blockade or removal of an indwelling catheter it is not recommended to give treatment dose LMWH if a catheter is in situ [35,36].

Of the NOACS, dabigatran is most affected by renal function therefore the time taken from last dose to spinal or epidural performance is either 48, 72 or 96 hours depending if the creatinine clearance is > 80, >50 or between 30-50ml/min respectively [2,37].

Of note it is not recommended to give any NOACs whilst a catheter in situ following central neuro-axial blockade and current recommendations state that all NOACs can be restarted 6 hours after spinal or epidural performed or after removal of indwelling catheter.

Rivaroxaban can be given as either treatment dose for acute VTE or maintenance dose for prevention of VTE in differing doses [38]. Patients with a creatinine clearance > 30ml/min should wait 18 hours post last dose if on maintenance dosage and 48 hours post last dose if on treatment dose rivaroxaban prior to neuroaxial blockade [35].

Apixaban is recommended to be withheld 24-48 hours prior to neuro-axial blockade [35].

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MCQ answers

2 FFTTF
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