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Perioperative anaesthetic management of anticoagulation

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Patients who present for surgery while taking anticoagulants present challenges related to the underlying condition that requires anticoagulation as well as requiring a careful assessment of the risks of bleeding and thrombosis. Commonly used drugs include low-molecular-weight heparins (LMWH), direct-acting oral anticoagulants (DOACs) and warfarin. Patients taking warfarin who have a high risk of thrombosis and are undergoing surgery with a high risk of bleeding require bridging therapy with LMWH.

Keywords: indications and drugs used for anticoagulation, perioperative management of anticoagulation, bridging, general and regional anaesthesia

Introduction

Patients taking anticoagulants who present for surgery pose significant anaesthetic challenges. Aside from considerations about the underlying conditions that require anticoagulation, these patients are at risk of thromboembolism, excessive bleeding and concerns regarding the use of regional anaesthesia.

When faced with a patient taking anticoagulants, the anaesthetist should ask the following questions:

1. Why is the patient taking anticoagulants?
2. What type of anticoagulant is the patient taking?
3. What type of surgery is planned?
4. How should the anticoagulation be managed perioperatively?
5. Is regional anaesthesia desirable or required?
6. Does the patient require emergency surgery/is the patient bleeding?

Reasons for anticoagulation

The commonest reasons for anticoagulation are:

Venous thromboembolism

Deep vein thrombosis (DVT) and its complication, pulmonary venous thromboembolism (VTE), are the third commonest cause of cardiovascular disease worldwide.[1] DVTs are caused by a complex interaction between genetic predisposition and acquired risk factors causing a venous thrombosis, with risk of embolisation to the pulmonary circulation.

A South African meta-analysis of 21 studies[2] revealed that DVTs occur in 14% of medical patients; in 2.4–9.6% of postoperative patients, and in approximately 0.5% of pregnant patients. The prevalence of VTE in hospitalised medical patients ranged between 17.5 and 61.5%, with a mortality rate between 40% and 69.5%, higher than rates quoted in Western countries.

Atrial fibrillation

The presence of atrial fibrillation (AF) is associated with a risk of ischaemic stroke and death.[3,4] The validated prediction scores $CHADS_2$ and CHA_2DS_2-VASc[5] provide a reliable risk stratification for the risk of stroke in the presence of AF.

The risk of stroke increases according to the point score per year: a $CHADS_2$/CHA_2DS_2VASc score of 0 to 2 is associated with a lower

Table I: Risk stratification models

Condition	$CHADS_2$	CHA_2DS_2.VAsc	Points
Congestive cardiac failure/left ventricular systolic dysfunction	C	C	1
Hypertension (BP > 140/90 or treated hypertension on medication)	H	H	1
Age > 75 years	A	A	1
Diabetes mellitus	D	D	1
Stroke/TIA or thromboembolism in history	S2	S2	2
Vascular disease (peripheral vascular disease, myocardial infarction, aortic plaque)	Not applicable	V	1
Age > 65 years	Not applicable	A	1
Sex (female)	Not applicable	Sc	1

BP – blood pressure, TIA – transient ischaemic attack

(1.9–4%) risk of stroke, and a score of 3 and greater represents a higher risk (5.9–18.5%) of stroke per year.

Patients with prosthetic heart valves

Patients with mechanical heart valves in the mitral or aortic positions, patients with more than one artificial heart valve and patients with intra-cardiac thrombus require lifelong anticoagulation.

Patients with intravascular stents

Patients with coronary, intravascular, or intracerebral stents are usually placed on dual antiplatelet therapy. This is particularly important during the first 12 weeks of stent insertion.

Drugs used for anticoagulation

Heparins

Unfractionated heparin[6,7]

Heparin binds to antithrombin, inactivating Factor IIa and Xa and blocking the conversion of fibrinogen to fibrin. Factor Xa is the rate-limiting step for escalation of the coagulation cascade to thrombin activation.

Common uses of unfractionated heparin include the prevention and treatment of acute thrombotic events and anticoagulation for dialysis and cardiopulmonary bypass.

For thrombosis, a bolus dose of 80 units/kg, followed by a continuous infusion of 18 units/kg/hr IV or subcutaneously, is given. Heparin-induced thrombocytopaenia occurs in 30% of patients.

Monitoring of effect is with the active partial thromboplastin time (aPTT) and the activated clotting time (ACT). Anti-factor Xa activity levels can also be monitored.

Low-molecular-weight heparins: enoxaparin, dalteparin[8]

Low-molecular-weight heparins (LMWHs) potentiate the action of antithrombin III indirectly, irreversibly inactivating factor Xa. They have a quick onset of action with 90% bioavailability when given subcutaneously. The dose for treatment of thrombosis is 1 mg/kg 12 hourly. Dosing modifications are required for obese patients and those with renal failure. They are used both for prophylaxis and treatment of venous thrombosis and when 'bridging' patients on oral anticoagulants prior to surgery.

Monitoring of the anticoagulant effect is difficult as the aPTT, prothrombin time (PT) and international normalised ratio (INR) are variably or not affected. Anti-Xa activity assays can be performed but take time and are not always useful in bleeding emergencies.

Warfarin[9]

Warfarin competitively inhibits the vitamin K epoxide reductase complex 1, reducing the synthesis of coagulation factors II, VII, IX and X, as well as the coagulation regulatory factors proteins C and S. Oral administration results in complete absorption, with an onset of action of 24–72 hours and a duration of effect from two to five days.

Warfarin remains commonly used for the prevention of thrombosis in patients with prosthetic heart valves, AF, DVTs and in off-label use for secondary prevention of recurrent stroke.

Warfarin has a narrow therapeutic window, with a large inter-individual variation in effect and interacts with many drugs. Warfarin use requires regular monitoring with the PT/INR tests.

Direct-acting oral anticoagulants[10]

Rivaroxaban, apixaban, edoxaban and betrixaban bind directly to factor Xa or factor II without complexing to antithrombin.

Good oral bioavailability, a shorter half-life (important for periprocedural and bleeding events), fewer drug interactions and stable pharmacodynamic responses at fixed doses make management of anticoagulation easier than with warfarin.

No long-term monitoring of anticoagulation is required. The effect of direct-acting oral anticoagulants (DOACs) on screening tests (INR, PTT, aPTT) is directly related to reagent composition and clotting time is different, depending on the reagent.

The direct inhibitor of factor IIa, dabigatran,[11] inhibits the formation of fibrin from fibrinogen. The prodrug is predominantly metabolised by hydrolysis (non-CP450 mechanism), limiting drug interactions. Anticoagulant effects are dose-dependent and predictable, with a peak within two hours and a half-life of 14 hours.

At clinical doses, dabigatran has little effect in aPTT and INR; effect is monitored by the thrombin clotting time (tt), which directly assesses the activity of thrombin, and the ecarin clotting time, which specifically assays for thrombin generation.

Approved indications for use for DOACs are DVT/PVE treatment/prophylaxis and non-valvular AF. 'Off-label' indications include DVT prevention after total knee replacement and after percutaneous coronary interventions with AF. The RE-LY[12] trial showed that in AF, dabigatran has similar efficacy and lower rates of major haemorrhage than warfarin.

The RE-ALIGN trial[13] showed that DOACs are contraindicated as anticoagulation for mechanical heart valves, with excess thromboembolic and bleeding events.

Fondaparinux[14]

Fondaparinux is an indirect factor Xa inhibitor, binding reversibly to antithrombin. It has a longer half-life (17 hours) than heparin and does not interfere with platelet function. It is administered subcutaneously once a day, usually in place of heparins in patients who develop thrombocytopaenia and is as effective as these agents in the treatment and prophylaxis of VTE and acute coronary syndromes.

Antiplatelet agents[15]

Antiplatelet drugs are used for the prevention of atheromatous strokes and thrombosis in peripheral vascular disease, for stable angina and acute coronary syndromes, after insertion of devices to close atrial and ventricular defects, and after coronary and endovascular stenting.

Aspirin

This irreversible cyclo-oxygenase 1 and 2 inhibitor prevents the formation of prostaglandin A2, a potent vasodilator and inducer of platelet aggregation. The effect lasts for the lifetime of the platelet (8–9 days). After stopping, a 10% return of platelet function per day is usual.

Thienopyridines and non-thienopyridines

Clopidogrel, ticlopidine and prasugrel inhibit the P2Y12 receptor on platelets, which promotes the stabilisation of platelet clots through fibrinogen bonds. The non-thienopyridines, ticagrelor and congrelor, cause reversible, non-competitive platelet P2Y12 receptor aggregation inhibition.

Glycoprotein IIb/IIIa inhibitors

The glycoprotein IIb/IIIa inhibitors abciximab, eptifibatide and tirofiban are only available in intravenous form and used to reduce ischaemic cardiac events in combination with heparin, and in combination with tissue plasminogen activator in acute ischaemic strokes.

What type of surgery is the patient coming for?

According to the principles of perioperative management for patients on long-term anticoagulation set out by the American Heart Association and the American College of Cardiology,[16,17] the following guidelines are suggested:

1. *Oral anticoagulants should not be interrupted for procedures with low bleeding risks.*

- *The following procedures are amenable to uninterrupted anticoagulation:*

  Endoscopies, including biopsies.

  Percutaneous endovascular and coronary interventions.

  Electrophysiological cardiac studies and pacemaker insertion.

  Cataract surgery.

  Dermatological surgery.

  Dental extractions.

  Laparoscopic cholecystectomy.

  Bronchoscopy.

  Abdominal hernia repair.

- *The following procedures have a high risk of bleeding, and the anticoagulation should be stopped:*

  Resection of colonic polyps.

  Endoscopic retrograde choledochal-pancreatic duct and sphincterotomy.

  Abdominal surgery involving spleen, liver, and kidney.

  Cardiac surgery.

  Intra-cranial neurosurgery, spinal surgery.

  Major orthopaedic surgery is a risk factor for both bleeding and postoperative VTE.

  Reconstructive plastic surgery.

  Surgery lasting for more than 45 minutes.

2. *Patients at high risk for thromboembolism should be bridged periprocedurally with LMWH. The following conditions present a high risk of thromboembolism perioperatively:*

   i. Patients with mitral valve prostheses, mechanical aortic valve prostheses, or with more than two prosthetic cardiac valves and those with intracardiac thrombus or placement of a coronary stent within last 12 weeks.
   ii. Patients with a cerebrovascular accident (CVA) or transient ischaemic attack (TIA) within the last six months.
   iii. Patients with a single, non-provoked DVT/VTE within the last six months.
   iv. The presence of AF with a CHA_2DS_2-VASc score 5 or greater, or with associated rheumatic valvular disease.
   v. Patients with known thrombophilia syndromes.

- *Patients who are at moderate risk of thromboembolic events:*

   i. Patients with bi-leaflet aortic valves with congestive cardiac failure and/or diabetes.
   ii. Atrial fibrillation with CHA_2DS_2-VASc score of 4 or less.
   iii. VTE within last 12 months with associated cancer, protein C, S, deficiency, anti-phospholipid syndrome.

3. *Intermediate- and low-risk cases should be assessed for risk-benefit on a procedure-specific basis.*

Perioperative management of anticoagulation

Perioperative management of patients at risk of bleeding and on unfractionated heparin

Heparin should be discontinued 6 hours prior to surgery and the aPTT should be checked. Heparin should be restarted 6 to 12 hours postoperatively.

Perioperative management of high-risk patients taking warfarin[18,19]

'Bridging' refers to the perioperative substitution of warfarin for an LMWH to limit the time that sub-therapeutic anticoagulation occurs.

How to bridge warfarin

Discontinue warfarin five days prior to surgery. When INR < 1.5, start LMWH at therapeutic doses. Surgery can proceed when the INR < 1.5.

The following guidelines also apply to patients taking low-molecular-weight heparin at therapeutic doses

Discontinue LWMH 24 hours prior to surgery.

Postoperatively, if patient is able to tolerate oral fluids, restart warfarin 12–24 hours after surgery. If there is a low risk of bleeding, restart therapeutic LWMH 24 hours after surgery. If there is a high risk of bleeding, restart LWMH 48–72 hours after surgery. Stop LMWH when the INR > 2.

Perioperative management of patients taking direct-acting oral anticoagulants

Bridging therapy is generally not required for patients taking DOACs. In the BRIDGE[20] trial, it was shown that foregoing bridging anticoagulation in patients with low CHA_2DS_2-VASc scores is non-inferior to bridging with LMWH for prevention of thromboembolism and is superior to bridging with respect to major bleeding.

DOACs should be stopped prior to surgery according to the following table and restarted after 24 hours in patients with low bleeding risks and after 48–72 hours in those with a high bleeding risk. If the risk of embolism is high, consider using LMWH prophylactically postoperatively.

The risks of bridging

The ORBIT-AF[18] trial was a prospective, observational study recording the incidences of temporary interruptions of DOACS. Bridging was used in 24% of cases and these patients were at higher risk of bleeding and adverse events. Patients at particular risk were those with HASBLED scores > 3 and those with mechanical heart valves. 0.4% of patients overall suffered thromboembolic complications.

The HAS-BLED[20,21] score is a reliable predictor of bleeding associated with bridging anticoagulation. One point is allocated for each associated factor:

1. Hypertension
2. Abnormal liver or kidney function
3. Stroke
4. History of bleeding
5. Labile INR values (warfarin)
6. Elderly
7. Drugs – nonsteroidal anti-inflammatories, alcohol, herbal remedies, ginkgo biloba, ginger, garlic, aspirin

Perioperative management of patients taking antiplatelet drugs

Patients on antiplatelet drugs do not require perioperative bridging. Patients on combination antiplatelet drugs and/or other anticoagulants are at high risk of bleeding. Procedures with a high risk of bleeding include spinal, intracranial extra-ocular, major reconstructive surgery and resection of the prostate. Aspirin should be stopped five days prior to this surgery. Other agents should be stopped at least seven days prior to the procedure and ticlopidine must be stopped 14 days before surgery.

Regional and neuraxial anaesthesia[18,22]

Bleeding is a potential complication of neuraxial and peripheral blocks. If the consequences of block-induced bleeding are significant, or the management of bleeding is difficult, and these techniques are assessed as being required for the surgery, withdrawal of antithrombotic therapy is always recommended.

These techniques include stellate ganglion blocks, infra-clavicular blocks, epidural and spinal anaesthesia/analgesia, paravertebral blocks, lumbar plexus blocks, sympathectomies, psoas blocks, quadratus lumborum, pericapsular nerve group (PENG) and sciatic blocks.

If the consequences of bleeding are relatively minor, and bleeding is amenable to compression, the recommendation is that anticoagulation is not stopped. This includes occipital, peribulbar, interscalene, upper limb blocks, erector spinae plane blocks, transversus abdominis plane blocks; ilioinguinal, rectus sheath, femoral and genitofemoral blocks, as well as adductor canal and popliteal sciatic blocks, fascia iliaca blocks and lateral cutaneous nerve of thigh blocks.

Neuraxial anaesthesia

There is a black box warning that epidural or spinal haematomas leading to permanent paralysis may occur in patients who receive neuraxial anaesthesia while on LMWHs. Factors that increase risk are placement of indwelling epidural catheters, concomitant use of other anticoagulants drugs, traumatic or repeated epidural or spinal punctures and spinal deformity/surgery. The use of ultrasound may reduce vascular complications and is recommended. The use of warfarin and DOACs is a contraindication to the use of neuraxial anaesthesia.

If neuraxial anaesthesia is required for patients taking warfarin, bridging to LMWH should be undertaken and the LMWH stopped according to Table III.

Table II: Guidelines for stopping DOACs pre-operatively[16]

Drug	Low bleeding risk surgery timing of last dose prior to surgery	High bleeding risk surgery
Dabigatran, rivaroxaban normal renal function	24 hours	48–72 hours
Dabigatran, rivaroxaban with creatinine clearance 30–50 ml/min	48 hours	72 hours

Table III: Clinical excellence guidelines[18]

Drug	Before catheter insertion	While epidural catheter is in place	Prior to catheter removal	After catheter removal
Therapeutic LMWH	Withhold dose 24 hrs prior	Only administer dose 12 hours after insertion	Withhold dose for 24 hours	Recommence after 4 hours

Aspirin and nonsteroidal anti-inflammatories drugs (NSAIDs) alone do not significantly increase the risk of spinal haematoma but should be regarded as a risk factor if combined with other antiplatelet or anticoagulants.

Emergency reversal of anticoagulation[23,24]

Warfarin

If bleeding is minor or non-urgent, stop drug and give vitamin K 1–10 mg IV/po.

In an emergency with serious bleeding, give vitamin K 10 mg intravenously slowly and prothrombin complex concentrate (PCC), infusing over one hour in the following amounts:

If the INR is 2–4 x normal: PCC 25 IU/kg

If INR between 4–6 x normal: PCC 35 IU/kg

If INR > 6; give 50 IU/kg of PCC

Alternatively, give fresh frozen plasma (FFP) in a dose of 10–20 ml/kg

In patients with trauma, give tranexamic acid 1 g, repeat 1 g eight hourly.

Unfractionated heparin

Effects can be reversed with protamine (1 mg of protamine reverses 100 IU of heparin) or with the use of FFP or PCC.

Low-molecular-weight heparin

The duration of effect of LMWH is 25–48 hours. Protamine (maximum 50 mg) incompletely reverses the effect of LMWH with an approximate 60% efficacy.

Direct-acting oral anticoagulants

PCC is the first-line treatment, although whether this is effective is controversial.

Rivaroxaban and apixaban can be reversed with andexanet alfa (a recombinant-modified human factor Xa decoy protein which is given as a bolus and an infusion and dabigatran can be reversed with the monoclonal antibody Idarucizumab.

Conclusion

The risks of thromboembolic complications and the risks of bleeding require consideration for every patient taking anticoagulants who presents for surgery. Each patient needs careful consideration for the best strategy for management of anticoagulation perioperatively. Conditions in which surgical bleeding is a major concern and stopping anticoagulation poses a significant risk for thromboembolism require bridging with LWMH perioperatively.

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