Perioperative management of adult patients with a history of stroke or transient ischaemic attack undergoing elective non-cardiac surgery

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ABSTRACT

It is increasingly common for physicians and anaesthetists to be asked for advice in the medical management of surgical patients who have an incidental history of stroke or transient ischaemic attack (TIA). Advising clinicians requires an understanding of the common predictors, outcomes and management of perioperative stroke. The most important predictor of perioperative stroke is a previous history of stroke, and outcomes associated with such an event are extremely poor. The perioperative management of this patient group needs careful consideration to minimise the thrombotic risk and a comprehensive, individualised approach is crucial. Although there is literature supporting the management of such patients undergoing cardiac surgery, evidence is lacking in the setting of non-cardiac surgical intervention. This article reviews the current evidence and provides a pragmatic interpretation to inform the perioperative management of patients with a history of stroke and/or TIA presenting for elective non-cardiac surgery.

KEYWORDS: Anticoagulation, Antiplatelet, non-cardiac surgery, perioperative, stroke

Introduction

Increasing numbers of older patients with multimorbidity are undergoing elective and emergency surgery. Unsurprisingly, physicians and anaesthetists are increasingly asked for medical advice to support the management of such surgical patients. Often these requests relate to patients with cerebrovascular disease, given that the incidence for stroke is approximately 152,000 per year and around 46,000 people experience a transient ischaemic attack (TIA) for the first time in the UK each year.[1,2] Although stroke incidence increases with age, approximately 25% of strokes occur in people under the age of 65 years.[3] Following an initial stroke, patients are at a significantly higher risk of a further stroke compared with the general population.[1,4] The highest risk of a recurrent event is within the first month.[4]

Perioperative stroke is a well-recognised complication of cardiac, carotid and neurological surgery; however, it is also a significant consequence of other types of surgery. Studies investigating the risk of perioperative stroke associated with non-cardiac procedures are largely retrospective analyses of administrative databases (Table S1). The reported incidence of perioperative stroke in non-cardiac surgery ranges from 0.1–4.4%, which may be an underestimation as minor strokes and TIAs are likely to be under-reported.[5–14]

The most consistently reported independent predictor for perioperative stroke is a previous stroke and, therefore, the perioperative management of this cohort of patients needs to be carefully tailored to minimise risk.[15,16] In addition, perioperative withdrawal of antiplatelets or anticoagulants and postoperative immobility can aggravate a surgery-induced hypercoagulable state thus increasing the risk of a perioperative cerebral thrombotic event. Other intraoperative risk factors include perioperative arrhythmias or intraoperative hypotension resulting in watershed territory cerebral infarction. Perioperative stroke has been strongly associated with poor outcomes: increased rates of postoperative respiratory and cardiac complications, increased length of stay, greater rates of institutionalisation and increased mortality.[12–16] Mortality rates associated with stroke following non-cardiac surgery are reported in the range of 18–32%[12–14] and are even higher in those with a previous history of stroke.[8]

This review aims to provide a practical, evidence-based approach to the management of patients with a history of stroke or TIA undergoing elective non-cardiac, non-carotid surgery.

Timing of elective surgery following a recent stroke

There are limited studies specifically addressing the optimal timing of elective surgery following a stroke; however, it is helpful to consider the pathophysiological factors associated with an acute event. In the days following a stroke, cerebral autoregulation is impaired and cerebral perfusion is therefore very sensitive to even modest changes in blood pressure.[17,18]

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The duration of this failure of autoregulation is uncertain but it has been postulated that it may last 1–3 months.[17–19] Furthermore, the area of infarcted cerebral tissue undergoes inflammatory processes and softens, rendering this area vulnerable to the haemodynamic stresses of anaesthesia and surgery.[19] Following a stroke, a sufficient time period should be allowed before elective surgery for the patient's neurological and haemodynamic status to stabilise and cerebral autoregulation to be restored to minimise the risk of a further stroke or worsening of the initial stroke. A 2014 cohort study has investigated the association between the timing of elective non-cardiac surgery following a stroke and the risk of a major cardiovascular event.[20] This found that, compared with patients who had never experienced a stroke, a prior history of stroke – especially within the preceding 3 months of surgery – was associated with a higher risk of major cardiovascular events (odds ratio 14.23, 95% CI 11.61–17.45) and also a higher 30-day mortality rate (odds ratio 3.07, 95%CI, 2.30–4.09). In patients who have had a recent stroke or TIA, current evidence suggests that it would be safer to delay elective surgery for 3 months.[8,15,19,20] This will need to take into account the urgency of surgery and an individualised approach to the risk and benefit of proceeding with early surgery will need to be made. For example, in the case of non-urgent surgery – such as an elective joint replacement – waiting the full 3 months would be prudent, whereas in cancer surgery the likely mortality benefit from urgent surgical treatment may outweigh the stroke risk and early surgery may be considered.

Preoperative carotid artery revascularisation

The 2014 European Society of Cardiology (ESC)/European Society of Anaesthesiology (ESA) guideline on non-cardiac surgery highlights the absence of specific studies investigating the benefits of carotid revascularisation in patients with symptomatic carotid disease undergoing elective non-cardiac surgery.[21] It recommends following the 2011 ESC guideline on the management of such patients in the non-surgical population.[22] The guidelines emphasise that the benefit of carotid revascularisation is highest within the first 2 weeks of symptoms and generally should be performed within 12 weeks, after which the risks of the procedure outweigh any stroke risk reduction benefit.[21–23] A pooled analysis of 5,893 patients reported that the number needed to treat to prevent one ipsilateral stroke in 5 years was five for those randomised within 2 weeks after the ischaemic event versus 125 for patients randomised after 12 weeks.[23] Therefore, it is reasonable to recommend that all patients with a history of TIA and/or stroke within the preceding 12 weeks should undergo carotid imaging. Patients with symptomatic carotid stenosis of greater than 50% should be referred for consideration of revascularisation within 12 weeks of the event prior to undergoing elective non-cardiac surgery.[21–23] In asymptomatic patients with no neurological symptoms or signs, routine carotid imaging is not recommended and the benefits of revascularisation are questionable compared with best medical therapy.[22]

Perioperative management of antiplatelet agents

The withdrawal of antiplatelet therapy used for stroke secondary prevention has been associated with an increased risk of perioperative stroke.[24–26] This may be due to the resultant rebound hypercoagulability characterised by increased thromboxane production and decreased fibrinolysis aggravating the pro-thrombotic state associated with surgery.[24] Conversely, continuing antiplatelet therapy throughout the perioperative period has implications on both surgical site bleeding and anaesthetic decision making, particularly with respect to the use of neuraxial techniques such as epidural or spinal anaesthesia.

Aspirin

There is considerable variability in clinical practice with regard to the perioperative management of aspirin.[27] Observational and retrospective studies suggest that the perioperative withdrawal of aspirin is associated with a significantly greater thrombotic risk, which outweighs the bleeding risk.[24,28] One double-blinded randomised controlled trial compared the effects of using low-dose aspirin during the perioperative period with placebo in patients with at least one cardiac risk factor undergoing elective non-cardiac surgery. A total of 220 patients were randomised to receive either aspirin or a placebo drug 7 days prior to surgery and continued on the study drug for 3 days postoperatively. They found that the 30-day postoperative incidence of stroke or TIA was significantly lower in the aspirin group: three patients (2.7%) in the aspirin group compared with ten patients in the placebo group (9%) (p=0.049); however, this study was found to be underpowered to evaluate bleeding complications.[29] A larger, more recent trial randomised 10,010 patients undergoing non-cardiac surgery to receive aspirin or placebo (patients already taking antiplatelet agents had to stop them 3–7 days prior to surgery and restart at the study dose just before surgery).[30] This demonstrated that aspirin use did not reduce the rate of death, myocardial infarction or stroke. Stroke occurred in 16 patients (0.3%) in the aspirin group and in 19 patients (0.4%) in the placebo group (hazard ratio, 0.84; 95% CI, 0.43–1.64; p=0.62). Conversely, major bleeding was significantly more common in the aspirin group than in the placebo group (4.6% versus 3.8%, respectively; hazard ratio 1.23; 95% CI 1.01–1.49; p=0.04). Based on the results of this study, the 2014 ESC/ESA guidelines and the 2014 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines both conclude that the perioperative management of aspirin should be based on a comprehensive individual risk-benefit assessment, weighing the perioperative bleeding risk associated with both the type of surgery and patient factors against the thrombotic risk.[21,31] The American College of Chest Physicians has suggested thrombotic and bleeding risk stratification strategies and bleeding risk scores such as HAS-BLED can also be used (Tables 1 and 2).[32–34]

Other antiplatelet agents

There are limited data investigating the risk of perioperative stroke associated with clopidogrel or dipyridamole withdrawal; however, the bleeding risk associated with clopidogrel is well established.[35,36] In the CURE (clopidogrel in unstable angina to prevent recurrent events) trial, a significantly higher rate of bleeding occurred in patients in whom clopidogrel was discontinued ≤5 days before surgery (9.6% in the clopidogrel group versus 6.3% in the placebo group, p=0.06) in patients due to undergo cardiac surgery.[35] Extrapolating from such

Table 1. Bleeding risk associated with different types of surgery

Moderate to high risk	Low risk
> Neurosurgery	> Minor dermatological surgery, eg skin biopsy
> Spinal/epidural surgical procedures	> Cataract or glaucoma surgery
> Urologic surgery and procedures	> Dental procedures, eg simple extractions
> Vascular surgery	> Laparoscopic cholecystectomy
> GI surgery – major intra-abdominal	> Biopsy of a compressible site
> Orthopaedic joint surgery	> Joint aspiration/ injection
> Breast surgery	
> Thoracic surgery	
> Invasive ophthalmic surgery	
> Reconstructive plastic surgery	
> Pacemaker/ICD implantation	
> Liver biopsy	

ICD = Implantable cardioverter defibrillator; GI = gastrointestinal
Adapted with permission from Douketis *et al.*[33]

studies, and based on the current practice for safe spinal anaesthesia, the consensus remains that clopidogrel should be stopped 7 days prior to non-cardiac surgery. In patients with a high thrombotic risk, it may be advisable to substitute clopidogrel with aspirin during the perioperative period.

Perioperative management of oral anticoagulants

Temporary discontinuation of oral anticoagulant therapy during the perioperative period requires careful management. The potentially increased risk of stroke during interruption of anticoagulation needs to be balanced against the risk of bleeding associated with surgery and the inability to use neuraxial anaesthesia in anticoagulated patients.

Vitamin K antagonists

In procedures with low bleeding risk, continuation of warfarin therapy has not been associated with a significant increase in bleeding.[37,38] A systematic review demonstrated that the rate of major bleeding in patients who continued a therapeutic dose of warfarin was 0.2% for dental procedures and 0% for cataract surgery, arthrocentesis, upper endoscopy and colonoscopy.[38] However, in patients who are at higher risk of bleeding (Table 1) one strategy commonly used is to 'bridge' the time off warfarin with low molecular weight heparin (LMWH) to minimise thrombotic risk. In an analysis of data from observational studies, the relative risk reduction for thromboembolism with bridge therapy was estimated to be 66–80%; however, this finding is offset by the reported higher risk of major bleeding compared with no bridging.[37,39–42] Until recently there have been no robust studies aimed at answering the fundamental question of when perioperative bridging is required during the interruption of anticoagulation.[43,44] A large randomised controlled trial of nearly 2,000 patients with chronic atrial fibrillation or flutter on warfarin for at least 3 months, and at least one of the following CHADS2 stroke risk factors (congestive cardiac failure, hypertension, age of 75 years or older, diabetes or previous stroke or TIA), assigned patients to receive either bridging with the LMWH, dalteparin, or placebo injections.[43] They found that stopping anticoagulation without bridging was non-inferior to the use of bridging with LMWH in preventing arterial thromboembolism and there was a much greater risk of major bleeding in the bridging group (3.2% versus 1.3%, RR 0.41; 95% CI, 0.20–0.78; p=0.005). It must be noted that this study excluded patients with mechanical heart valves and those with a stroke or TIA within 12 weeks of the surgery, and the majority of the patients included had a low CHADS2 score (mean score 2.6), ie low thrombotic risk. It would be wise, therefore, to adopt an individualised approach in those patients deemed to have a high thrombotic risk. The PERIOP 2 study is currently underway investigating

Table 2. Thrombotic assessment

	Thrombotic risk		
	High	**Moderate**	**Low**
Mechanical heart valve	> Any mechanical mitral valve > Older mechanical valve model aortic valve (caged ball/tilting disc) > Recently placed mechanical valve (<3 months) > Recent stroke or TIA (within 6 months)	Bi-leaflet aortic valve and one of the following: > AF, > previous stroke/TIA, > hypertension, > diabetes, > heart failure, > age >75 years.	> Bi-leaflet aortic valve without AF and no other risk factors for stroke
Atrial fibrillation	> With mechanical heart valve > With rheumatic fever > With recent stroke or TIA (<3 months) > CHADS score 5 or 6	CHADS score of 3 or 4	> CHADS score 0–2 (no previous TIA/ Stroke)
Venous thromboembolism	> VTE with previous 3 months > With severe thrombophilia (Protein C, S or Antithrombin III deficiency, Homozygous factor V Leiden mutation)	> VTE 3–12 months ago > Recurrent VTE > With non-severe thrombophilia (Heterozygous factor V Leiden mutation)	> Single VTE >12 months ago and no other risk factors

AF = atrial fibrillation; CHADS = congestive cardiac failure, hypertension, age of 75 years or older, diabetes or previous stroke or TIA; TIA = transient ischaemic attack; VTE = venous thromboembolism.
Adapted with permission from Douketis *et al.*[33]

Table 3a. Properties of non-vitamin K oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mode of action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Peak onset	2 hours	2–4 hours	3–4 hours	1–2 hours
Half-life	12–14 hours	5–13 hours	8–15 hours	10–14 hours
Elimination	80% Renal	66% Renal	25% Renal	50% Renal
	20% Biliary	33% Biliary	75% Biliary	50% Biliary
Adjust dose for renal failure	Yes avoid if eGFR <30 mL/min	Yes avoid if eGFR <30 mL/min	Yes avoid if eGFR <15 mL/min	Yes avoid if eGFR <15 mL/min

eGFR = estimated glomerular filtration rate

the effectiveness and safety of LMWH bridging in high-risk patients (those with a mechanical heart valve or atrial fibrillation/flutter and a high stroke risk).[44]

Non-vitamin K oral anticoagulants

The new oral anticoagulants – dabigatran, rivaroxaban, apixaban and edoxaban – are prescribed for stroke prevention in patients with non-valvular atrial fibrillation.[45,46] As these drugs have relatively short half-lives, and drug concentrations decline rapidly in patients with normal renal function (Table 3a), bridging therapy is not considered to be necessary during the perioperative period.[45,46] The 2013 European Heart Rhythm Association guidelines provide recommendations on the timing of stopping non-vitamin K oral anticoagulants prior to elective surgery.[46] This is dependent on renal function as the majority of these drugs are renally excreted, and also on the specific bleeding risk of the surgical procedure (Table 3b).

Intraoperative and postoperative considerations

Intraoperative hypotension

The pathophysiology of perioperative stroke in patients undergoing non-cardiac surgery is not well defined. An analysis of nine studies involving 301 patients reported that 68% of non-cardiac surgery perioperative strokes were due to cerebrovascular thrombosis, 16% were due to emboli and 5% were due to intracerebral haemorrhage.[14] This is in contrast to cardiothoracic surgical patients in whom the majority of strokes are embolic in nature. Interestingly, very few non-cardiac perioperative strokes have been reported to be related to hypoperfusion. Nevertheless, intraoperative hypotension in the setting of carotid artery stenosis is a risk factor for watershed infarcts.[47] The maintenance of adequate cerebral perfusion in this group of patients is therefore extremely important. There is a lack of consensus regarding optimal perioperative blood pressure targets; however, it has been suggested that mean or systolic blood pressure should be maintained within 20% of the patient's baseline preoperative blood pressure.[15,16]

Perioperative atrial fibrillation

Perioperative atrial fibrillation (AF) is the most common perioperative arrhythmia and is often due to electrolyte imbalances and intravascular volume shifts that may occur during surgery.[16,48] It has previously been considered transient; however, a recent retrospective study has demonstrated a significant association between the occurrence of perioperative AF and the long-term risk of stroke, especially in the setting of non-cardiac surgery.[49] Unfortunately, this study was unable to determine the duration of the AF episodes; thus the findings may be related to patients with persistent AF rather than a transient postoperative episode. Further studies are required to establish the long-term risk of stroke in this group of patients

Table 3b. Timings of when to stop NOACs prior to elective surgery according to surgical bleeding risk and renal function

	Dabigatran		Apixaban		Rivaroxaban	
If no clinically important bleeding risk, then perform surgery at trough level (ie ≥12 hours or ≥48 hours after last intake, depending on once daily or twice daily regimen)						
			Bleeding risk			
Renal function	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 mL/min	≥24 hours	≥48 hours	≥24 hours	≥ 48hours	≥24 hours	≥48 hours
CrCl 50–80 mL/min	≥36 hours	≥72 hours				
CrCl 30–50 mL/min	≥48 hours	≥96 hours				
CrCl 15–30 mL/min	Not indicated		≥36 hours	≥ 48hours	≥36 hours	≥48 hours
CrCl <15 mL/min	Not indicated					

NOAC = non-vitamin K oral anticoagulant
Adapted from the European Heart Rhythm Association recommendations.[46]

Table 4. Framework for preoperative assessment of patients with a prior history of stroke or TIA

History of stroke and/or TIA	> Date it occurred > Type of stroke (infarction or haemorrhage) > Secondary prevention medications, eg antiplatelets, anticoagulants, anti-hypertensives, statins > Residual deficit from the stroke > Previous stroke-related investigations, eg brain imaging carotid Doppler ultrasound, ECG, echocardiography
Decide upon the timing of surgery in relation to the stroke/TIA	> Delay elective surgery for 3 months unless mortality benefit from urgent surgical treatment likely to outweigh stroke risk
Formulate a perioperative management plan for patients taking antiplatelet agents and/or anticoagulation	> Perform a comprehensive individual assessment of thrombotic risk of stroke versus bleeding risk of surgery
Identify potential perioperative complications	
Communicate the individualised management plan to all healthcare professionals involved in the surgical pathway in agreement with the patient	

ECG = electrocardiogram; TIA = transient ischaemic attack.

and the need for long-term anticoagulation. Nonetheless, the National Institute for Health and Care Excellence recommends the initiation of anti-thrombotic therapy with heparin for patients with postoperative AF following non-cardiothoracic surgery until a full risk-benefit assessment can be undertaken.[50] The American College of Chest Physicians also recommends consideration of heparin therapy in high-risk patients who develop perioperative AF – particularly in those with a history stroke or TIA – and to continue anticoagulation therapy for 30 days after the return of a normal sinus rhythm.[31]

Preoperative assessment of patients with a prior history of stroke or TIA

Given the evidence on timing of surgery, management of antiplatelets and anticoagulants, and the lack of guidelines, Table 4 outlines a pragmatic approach to preoperative assessment to provide the patient with an individualised perioperative plan.

Discussion

The perioperative management of patients with a history of stroke is complex and requires careful attention to detail to minimise adverse outcomes in this high-risk population. The timing of surgery is particularly important and current evidence suggests that non-urgent surgery should be delayed by at least 3 months following a stroke or TIA because of alterations in autoregulation. The withdrawal of antiplatelet and anticoagulant agents prior to surgery should be guided by an individualised assessment of bleeding and thrombotic risk. Consensus opinion, however, supports continuing aspirin for all surgical cases, with the exception of specific surgery types (eg closed space surgery: intracranial, posterior eye chamber, etc). Prior to elective surgery, clopidogrel should be stopped for 7 days, warfarin for 4 days and non-vitamin K oral anticoagulants should be discontinued between 1 and 4 days preoperatively according to renal function and surgical bleeding risk. For patients deemed to have a high thrombotic risk and a high bleeding risk, an expert multidisciplinary opinion should be sought.

Patients with a history of stroke or TIA are at a higher risk of a perioperative stroke and subsequent poor clinical outcomes. Recognition of this risk and employing the perioperative strategies described in this article are crucial components of the safe management of this group of patients. ■

Conflicts of interest

The authors declare no conflicts of interests.

Supplementary material

Additional supplementary material may be found in the online version of this article at www.clinmed.rcpjournal.org/:

S1 – Incidence of perioperative stroke associated with non-cardiac non-carotid surgery.

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