PERIOPERATIVE ISCHAEMIC STROKE: STRATEGIES FOR PREVENTION AND MANAGEMENT
Aruna T. M1, Dinesh G2, Gurudatta C. L3

INTRODUCTION: Stroke can be a catastrophic outcome for patients undergoing non-cardiac, non-neurologic surgery and is associated with an adjusted 8-fold increase in mortality.1 One-third of those patients who survive a stroke require assisted care for living. Thus, although perioperative stroke is an uncommon occurrence, it has a large impact on the patient and their family and community.1 Unlike stroke in the community setting, the mechanistic cascade leading to perioperative stroke has a discrete and highly-predictable origin: surgical intervention.2 Stroke after non-cardiac and non-neurologic surgery is relatively understudied and there is a need for clarifying the clinical management of surgical patients at high risk for the complication.2

Definition of Stroke: “Perioperative stroke” is defined as a brain infarction of ischaemic or haemorrhagic aetiology that occurs during surgery or within 30 days after surgery.3

Patients at high risk of Stroke: In order to prevent perioperative stroke, it is critical to identify those at high risk for the complication. The incidence of stroke in a broad surgical population (Excluding cardiac, carotid, major vascular and neurologic surgery) is approximately 1 per 1000 cases and approximately 6 per 1000 cases after major vascular surgery below the diaphragm.4 The significant majority of perioperative strokes are ischaemic rather than haemorrhagic.5,6 Three of the most consistent risk factors for perioperative stroke identified in the literature are advanced age, renal failure, and a history of stroke or transient ischaemic attack.1 In general terms, all patients presenting for surgery with a history of cerebrovascular compromise should be regarded as high risk for perioperative stroke.1

When Surgery to be done after Stroke?: Patients with acute or recent stroke have impaired cerebrovascular autoregulation and chemoregulation for months. This will make them dependent on mean arterial pressure and passive perfusion. This dependence is going to create a particular risk for cerebral hypoperfusion, especially during general anaesthesia and the physiologic disturbances of surgery such as haemorrhage, anaemia, hypotension. It has been suggested that elective surgery should be delayed from 1 to 3 months after a stroke in order to prevent a secondary cerebrovascular event.7,8

To prevent perioperative stroke in patients with a history of recent cerebrovascular insult, it is recommended to identify the cause of the initial stroke by conducting investigations such as carotid imaging, magnetic resonance angiography, or echocardiogram. Known carotid disease should be treated based on current guidelines9,10 The decision to proceed with surgery should be undertaken balancing the risks of perioperative stroke and the risks of delaying surgery further.
Patients on Anti-coagulants and Antiplatelet Drugs: There are two common clinical scenarios in which management of anticoagulants or antiplatelet drugs can be linked to risk of perioperative stroke. The first is management of anticoagulants for patients with atrial fibrillation, a major risk factor for perioperative stroke, and the second is the management of aspirin in patients with cardiovascular or cerebrovascular disease (e.g., for primary or secondary stroke prevention). The clinical dilemma relates to balancing the risks of excessive perioperative bleeding and the risk of rebound hypercoagulability in the setting of the prothrombotic state induced by surgery.

Recently, the Peri-Operative Ischemic Evaluation (POISE)-2 trial demonstrated that perioperative aspirin did not reduce the incidence of death or nonfatal myocardial infarction after noncardiac surgery, but did increase the risk of major bleeding. Of note, patients who had aspirin therapy that was initiated in the course of the study had a reduced incidence of stroke compared to placebo; patients who were continuing aspirin therapy showed no reduction in stroke incidence. Stroke was not a primary outcome of the study and the authors acknowledged that the findings in the initiation group could be spurious. However, the results suggest that some patients at risk of stroke may benefit from preoperative initiation of aspirin therapy, but this must be balanced against the now well-documented risk of significant increases in bleeding and must be demonstrated in a larger trial.

Mashour G A et al. in their Consensus Statement from the Society for Neuroscience in Anesthesiology and Critical Care recommends that (1) atrial fibrillation should be medically managed and continue anticoagulation in patients with atrial fibrillation for minor surgeries or those in which high blood loss is unlikely. Discontinue anticoagulation in surgical patients at high risk of bleeding (with appropriate bridging strategies as indicated), but resume as soon as the risk of surgical bleeding is considered to be low, and (2) There is no evidence to suggest that continuation of aspirin in patients at risk for vascular complications reduces the risk of stroke after noncardiac surgery.

Preoperative Beta Blockers and Statins in prevention of Perioperative Stroke: The original POISE trial, which evaluated the cardio protective effects of metoprolol in 8351 noncardiac surgery patients, demonstrated that patients receiving high dose metoprolol had a significantly higher risk of stroke. Current guidelines endorse the perioperative continuation of beta blockers in surgical patients who are already taking this class of drug. To avoid perioperative stroke, anaesthesiologists should not apply high-dose beta-blockers immediately before the operation. To treat intraoperative tachycardia with beta-blockers, it has to be excluded that tachycardia is caused by hypotension, anaemia, or pain.

As with beta blockers, discontinuation of statins in the perioperative period may have adverse consequences. With respect to non-operative stroke, discontinuation of statins in individuals with acute ischemic stroke was associated with a high risk of early neurologic deterioration. Statins have also been shown to reduce the incidence of atrial fibrillation and other adverse outcomes that may be associated with postoperative stroke. However, there are no data to suggest that starting statins in the preoperative period can prevent stroke around the time of non-cardiac, non-neurologic and non-carotid surgery.

Mashour G A et al. in their Consensus Statement from the Society for Neuroscience in Anesthesiology and Critical Care recommends (1) Metoprolol or other beta blockers should only be started in the preoperative period with careful titration and (2) Continue beta blockers and statins throughout the perioperative period in patients already taking them.
INTRAOPERATIVE RISK FACTORS FOR PERIOPERATIVE STROKE: There is controversial evidence regarding the intraoperative events as a cause of postoperative stroke. Various factors like intraoperative management of anesthetic technique, ventilation strategy, fluid and blood transfusion, glycemic control and blood pressure may influence the incidence of perioperative stroke.

TECHNIQUES OF ANAESTHESIA: A recent retrospective review of 57,000 patients revealed no difference in stroke risk between regional and general anesthesia in noncardiac patients. A large database study (>200,000 patients) focusing on knee and hip arthroplasty found that neuraxial anesthesia was associated with a lower incidence of stroke (0.07%) compared to combined neuraxial/general anesthesia (0.12%) and general anesthesia (0.13%, p=0.006). Good anaesthetic technique will definitely have a major role in reducing the incidence of perioperative stroke. This should also include proper positioning of the head and neck, and the early management of hypotensive episodes. Patients at risk should be ideally kept euvolumic throughout the perioperative period.

VENTILATORY MANAGEMENT: Intraoperative hyperventilation has multiple systemic deleterious effects like 1. Increased intrathoracic pressure which in turn decreases the venous return and there by reduces the cardiac output; 2. Reduced myocardial oxygen supply (Coronary vasoconstriction); 3. Potential dysrhythmias due to respiratory alkalosis leading to hypokalaemia; and 4. reduced cerebral blood flow due to decreased carbon dioxide levels; It seems likely that hypocapnia, because of the reduction in cerebral blood flow, is undesirable in patients with risk factors for perioperative stroke and may be one of several factors that negatively affect outcome in those patients who suffer stroke perioperatively.

HAEMOGLOBIN CONCENTRATION: For non-cardiac, non-neurologic surgical patients already taking a beta blocker, a haemoglobin <9.0 gm/dl should be avoided in order to minimize risk of stroke. Haemodilution may help in prevention of stroke after ischaemic brain injury by improving the cerebral perfusion. Oxygen delivery has been shown to improve with a decrease in haematocrit to 30% via a reduction in viscosity. Unfortunately, current data do not support the routine use of haemodilution, except as an adjunct in the treatment of vasospastic ischaemia. Given the importance of haemoglobin in determining the oxygen carrying capacity of the blood, profound anaemia may contribute to cell energy dysfunction during cerebral hypoperfusion. Consequently, major perioperative haemorrhage is linearly associated with subsequent stroke in noncardiac and non-neurosurgical operations. Therefore, expert opinion suggests maintaining haemoglobin level of 10mg/dl or higher in all patients with a medium or high risk for perioperative stroke.

INTRAOPERATIVE GLUCOSE MANAGEMENT: Most authors recommend an intervention with serum glucose exceeding 150 mg/dL, with an absolute upper limit of 180 mg/dL, in hyperglycemic patients undergoing major surgery. Care should be taken to avoid hyperglycemia and hypoglycemia and to keep blood glucose concentration in an optimal range. It is suggested that insulin therapy should be started when blood glucose concentration exceeds 150mg/dl with an absolute upper limit of 180mg/dl. Mashour et al recommends that in patients at high risk for perioperative stroke undergoing surgery, glucose monitoring is recommended, with a target range of 60-180 mg/dL.
INTRA OPERATIVE HYPOTENSION: More recently, Bijker et al\textsuperscript{18} conducted a retrospective case-control study reviewing 48,241 consecutive non-cardiac and non-neurosurgical patients and found an overall stroke incidence of 0.09\% within 10 days of surgery. They determined that a decrease in intraoperative mean arterial pressure of more than 30\% below baseline was associated with postoperative stroke. However, the odds ratio of 1.013 reveals an effect size of unclear clinical significance. They concluded that the most widely proposed mechanism of a postoperative stroke is arterial embolism. Nonetheless, the results of the study supported the hypothesis that hypotension can influence the evolution of a postoperative stroke by compromising (Collateral) blood flow to ischemic areas.

In this context, hypotension is best defined as a decrease in mean blood pressure relative to a preoperative baseline, rather than an absolute low blood pressure value. Bijker et al\textsuperscript{18} opine that unrecognized or poorly quantified hypotension in the postoperative period may be more important to stroke genesis than hypotension during the highly monitored and regulated intraoperative period and suggest that intraoperative hypotension may be predictive of postoperative hemodynamic instability rather than an independent cause of postoperative stroke.

Mashour et al\textsuperscript{6} also found that, for median values in a 10-minute epoch, a <20\%, <30\% or <40\% decrease in mean arterial or systolic blood pressure is associated with stroke.

Postural hypotension may be an important risk factor for stroke after non-cardiac surgery. In 2005, Pohl and Cullen\textsuperscript{19} reported four cases of ischemic brain and spinal cord injury after shoulder surgery in the beach chair position. Since then, significant attention has been given to the risk of unrecognized reduced cerebral perfusion pressures and resultant neurologic injury in the beach chair position. Neurologic injuries have occurred in the beach chair position at recorded blood pressures that most anesthesiologists would consider acceptable.\textsuperscript{20} Assuming a 0.8mm Hg decrease in MAP for every 1 cm gradient, and a 15-30 cm gradient between the brachial artery (cuff measurement) and the brainstem, the MAP at the level of the brainstem could be 12-24mm Hg lower than the pressure measured by cuff on the non-operative arm. Clearly this relationship is greatly worsened if the cuff is placed on the lower extremity.\textsuperscript{21} This differential should also be kept in mind when leveling a transducer if invasive blood pressure monitoring is used.\textsuperscript{21}

It appears that there is an association between intraoperative hypotension and perioperative stroke, but the clinical significance of this association is not very well defined. Further prospective clinical studies are required to make strong evidence-based recommendations regarding intraoperative blood pressure management. It is probable that there are subsets of patients at increased risk for stroke who clearly are harmed by hypotension or low flow states. Some of these populations may include patients with unrecognized critical stenosis of carotid or intracranial arteries or congenital anomalies of the cerebral circulation.\textsuperscript{22}

As such, intraoperative hypotension should be avoided in patients at high risk of perioperative stroke. It is recommended by Mashour et al\textsuperscript{2} in their Consensus Statement from the Society for Neuroscience in Anesthesiology and Critical Care, that the blood pressure be maintained within 20\% of the patient’s normal range with a cerebral perfusion pressure greater than 70 mm Hg if possible. Intraoperative hypotension should be defined as a percent reduction from baseline blood pressure rather than an absolute value.\textsuperscript{2}

For surgery in the beach chair position, noninvasive blood pressure measurement by cuff should always be performed on the nonoperative upper arm (as opposed to lower extremity) and...
consideration should be given to the blood pressure gradient between the brachial artery and brain. Induced hypotension for shoulder surgery in the beach chair position should always be approached with caution, especially in patients at risk for stroke.

**Intraoperative Neuromonitoring:** Intraoperative neuromonitoring should be able to detect an insufficient supply of the brain with blood/oxygen before a stroke occurs. Noninvasive neuromonitors play an important role in reducing the perioperative stroke rate. The value of transcranial Doppler sonography (TCD) and electroencephalography (EEG) is already well established in high-risk operations such as carotid endarterectomy. It is essential to detect perioperative stroke as soon as possible and, thereby, treat the patient early. If the patient is awake after anaesthesia, the Face Arm Speech Time (FAST) seems to be sufficient to detect an acute stroke.

**Management of acute Stroke:** Techniques that are used to minimize the injury to the brain in the event of an ischemic insult can be thought of as having three broad purposes: to increase the supply of oxygen to the injured tissue, to reduce the metabolic demands, or to affect specific pathways in the ischemic cascade to reduce the production of unwanted metabolites.

In the event of an acute stroke, preventing secondary injury and achieving optimal outcome are based on rapid recognition, communication and management. Evaluation and treatment of acute perioperative stroke, which is typically ischaemic, should be consistent with the most recent American Heart Association Guidelines for the Management of Patients with Acute Ischemic Stroke.

Various physiologic, pharmacologic and pathologic factors in the postanaesthetic period can mask symptoms of intraoperative or postoperative stroke. Careful evaluation and resolution of pharmacologic contributions to a neurologic deficit is paramount to reduce delay in stroke diagnosis. Certain drugs that are commonly used during the intraoperative period can be reversed by administering definitive antagonists, including narcotics (with naloxone), benzodiazepines (with flumazenil), and neuromuscular blockers (with a cholinesterase inhibitor or sugammadex, where available). Although the presence of residual inhaled anesthetics can be quantified routinely in the operating room at the end of a surgical case, the effect of drugs such as propofol and dexmedetomidine cannot be conveniently measured in real time. Delayed emergence, altered mental status and/or the presence of new focal neurologic deficit in the absence of convincing confounders should raise suspicion for stroke.

Immediate diagnostic studies of all patients with suspected stroke should include non contrast computed tomography (CT) or magnetic resonance imaging (MRI) of the brain to determine whether the stroke is ischemic or hemorrhagic in origin and to correlate neurologic deficit with radiologic findings. The role of CT angiography and CT perfusion imaging is to provide supplementary information, especially in determining the need for urgent endovascular intervention. The presence of a large ischemic penumbra or thrombus in a major vessel (e.g., middle cerebral artery) would prompt consideration of endovascular therapy.

American Heart Association Guidelines for the Management of Patients with Acute Ischemic Stroke has the following recommendations:

1. The initial management of stroke is ideally done in a subspecialty acute care setting such as a neurocritical care or stroke unit. Maintaining appropriate physiologic stability is critical during acute stroke care.
2. Hypoxaemia is associated with poor neurologic outcomes and should therefore be monitored with pulse oximetry; supplemental oxygen should be used to maintain SpO2 saturation greater than 94%.

3. The airway should be secured in patients with depressed levels of consciousness (Glasgow Coma Scale <8), signs of brainstem dysfunction, or inability to protect the airway. Tracheal intubation and mechanical ventilation may also be helpful in the management of increased intracranial pressure or for those who have suspected malignant brain edema.

4. Patients with acute cerebral ischaemia should have cardiac monitoring for at least the first 24 hours, and any serious arrhythmia should be treated.

5. Every effort should be made to preserve cerebral perfusion pressure during the first 24 hours. Unless the patient is eligible for acute reperfusion intervention, systolic blood pressure is usually treated only if it is greater than 220mm Hg, and diastolic pressure is treated only if it is greater than 120mm Hg.

Intravenous recombinant tissue plasminogen activator (rtPA) is the pharmacological therapy of choice for thrombotic strokes, but it is contraindicated in a number of situations. Importantly, major surgery—with the exception of intracranial or spinal surgery—is a relative rather than absolute contraindication, but there is a paucity of literature regarding the management of stroke after a noncardiac, nonvascular or non-neurologic procedure.

**CONCLUSION:** Recognition of patients at high risk for stroke during or after non-cardiac, non-neurologic surgery is critical. Consistent risk factors include advanced age, renal disease and history of stroke or transient ischemic attack. Continuation of beta blockers and statins is important for prevention; Recent evidence suggests that continuation of aspirin in patients at risk of stroke after noncardiac surgery is not indicated and may increase bleeding risk. Intraoperative hypotension should be avoided in surgical patients at high risk of perioperative stroke and for those in the beach chair position.

For surgical patients manifesting symptoms or signs of stroke, timely neurology/stroke consultation and emergent neuroimaging are essential. Major non-cardiac, non-neurologic surgery is not an absolute contraindication to intravascular administration of rtPa; mechanical thrombolysis is also an option for those at high risk of surgery-related haemorrhage.

**REFERENCES:**

1. Mashour GA, Shanks AM, Kheterpal S. Perioperative stroke and associated mortality after noncardiac, nonneurologic surgery. Anesthesiology. 2011; 114: 1289–1296.

2. Mashour G A, Moore L E, Lele A V, Robicsek S A, and Gelb A W, Perioperative Care of Patients at High Risk for Stroke during or after Non-Cardiac, Non-Neurologic Surgery: Consensus Statement from the Society for Neuroscience in Anesthesiology and Critical Care J Neurosurg Anesthesiol 2014;00:000–000).

3. Talke PO, Sharma D, Heyer EJ, Robicsek SA and Gelb AW, Society for Neuroscience in Anesthesiology and Critical Care expert consensus statement: Anesthetic management of endovascular treatment of acute ischemic stroke. J Neurosurg Anesthesiol. 2014; 26: 95–108.)
4. Sharifpour M, Moore LE, Shanks AM, Didier TJ, Kheterpal S, Mashour; Incidence, predictors, and outcomes of perioperative stroke in noncarotid major vascular surgery. Anesth Analg. 2013; 116:424–434).
5. Ng JL, Chan MT, Gelb AW. Perioperative stroke in noncardiac, non-neurosurgical surgery. Anesthesiology. 2011; 115:879–890.
6. Mashour GA, Sharifpour M, Freundlich RE, Perioperative metoprolol and risk of stroke after noncardiac surgery. Anesthesiology. 2013; 119:1340–1346).
7. Landercasper J, Merz BJ, Cogbill TH, Perioperative stroke risk in 173 consecutive patients with a past history of stroke. Arch Surg. 1990; 125: 986–989.
8. Blacker DJ, Flemming KD, Link MJ, The preoperative cerebrovascular consultation: Common cerebrovascular questions before general or cardiac surgery. Mayo Clin Proc. 2004; 79: 223–229.
9. Hobson RW 2nd, Mackey WC, Ascher E, Management of atherosclerotic carotid artery disease: Clinical practice guidelines of the society for vascular surgery. J Vasc Surg. 2008; 48: 480–486.
10. Liapis CD, Bell PR, Mikhailidis D, Esvs guidelines. Invasive treatment for carotid stenosis: Indications, techniques. Eur J Vasc Endovasc Surg. 2009; 37: 1–19.
11. Devereaux PJ, Mrkobrada M, Sessler D, Aspirin in patients undergoing noncardiac surgery. N Engl J Med. 2014; 370: 1494–1503.
12. Bangalore S, Wetterslev J, Pranesh S, Perioperative beta blockers in patients having non-cardiac surgery: A meta-analysis. Lancet. 2008; 372: 1962–1976).
13. Blanco M, Nombela F, Castellanos M, Statin treatment withdrawal in ischemic stroke: A controlled randomized study. Neurology. 2007; 69: 904–910.
14. Chopra V, Wesorick DH, Sussman JB, Effect of perioperative statins on death, myocardial infarction, atrial fibrillation, and length of stay: A systematic review and meta-analysis. Arch Surg. 2012; 147: 181–189.
15. Memtsoudis SG, Sun X, Chiu YL, Perioperative comparative effectiveness of anesthetic technique in orthopedic patients. Anesthesiology. 2013; 118: 1046–1058).
16. Kamel H, Johnston SC, Kirkham JC, Association between major perioperative hemorrhage and stroke or Q-wave myocardial infarction. Circulation 2012; 126:207–212.
17. Engelhard K. Anaesthetic techniques to prevent perioperative stroke. Curr Opin Anaesthesiol. 2013; 26: 368–374.
18. Bijker JB, Persoon S, Peelen LM, Intraoperative hypotension and perioperative ischemic stroke after general surgery: A nested case-control study. Anesthesiology. 2012; 116: 658–664.
19. Pohl A, Cullen DJ. Cerebral ischemia during shoulder surgery in the upright position: A case series. J Clin Anesth. 2005; 17: 463–469.
20. Cullen DJ, Kirby RR. Beach chair position may decrease cerebral perfusion. APSF Newsletter. 2007; 22: 25–27.
21. Malhotra A, Cohen D, Syms C, Blood pressure changes in the leg on standing. J Clin Hypertens (Greenwich). 2002; 4: 350–354.
22. Drummond JC, Lee RR, Howell JP Jr. Focal cerebral ischemia after surgery in the “beach chair” position: The role of a congenital variation of circle of willis anatomy. Anesth Analg. 2012; 114: 1301–1303.
23. Whiteley WN, Wardlaw JM, Dennis MS, Sandercock PA. Clinical scores for the identification of stroke and transient ischaemic attack in the emergency department: a cross-sectional study. J Neurol Neurosurg Psychiatry 2011; 82: 1006–1010.

24. Gelb AW. Mechanisms of brain injury and potential therapies. Acta Anaesthesiol Belg 1999; 50:193–7.

25. Jauch EC, Saver JL, Adams HP Jr, Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American heart association/americam stroke association. Stroke. 2013; 44: 870–947.

26. Norris JW, Hachinski VC. Misdiagnosis of stroke. Lancet. 1982; 1:328–331.

27. Martin DP, Jankowski CJ, Keegan MT, Postoperative confusion and basilar artery stroke. Neurocrit Care. 2006; 4: 147–150.

28. Adams HP Jr, del Zoppo G, Alberts MJ, Bhat D L. Guidelines for the early management of adults with ischemic stroke: A guideline from the american heart association/americam stroke association stroke council, clinical cardiology council, cardiovascular radiology and intervention council, and the atherosclerotic peripheral vascular disease and quality of care outcomes in research interdisciplinary working groups: The american academy of neurology affirms the value of this guideline as an educational tool for neurologists. Circulation. 2007; 115:478–534.

29. Adams H, Adams R, Del Zoppo G, Goldstein LB; Stroke Council of the American Heart Association; American Stroke Association. Guidelines for the early management of patients with ischemic stroke: 2005 guidelines update: a scientific statement from the Stroke Council of the American Heart Association/American Stroke Association. Stroke. 2005; 36: 916–923.

AUTHORS:

1. Aruna T. M.
2. Dinesh G.
3. Gurudatta C. L.

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Anaesthesiology, Mysore Medical College and Research Institute, Mysore.
2. Assistant Professor, Department of Anaesthesiology, Mysore Medical College and Research Institute, Mysore.
3. Professor and HOD, Department of Anaesthesiology, Mysore Medical College and Research Institute, Mysore.

FINANCIAL OR OTHER COMPETING INTERESTS: None