Approach to Risk Management of Perioperative Stroke

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ABSTRACT

Aim of review: Perioperative stroke is a rare, but potentially devastating complication. This review is performed to draw attention of perioperative care providers to this complication and improve their understanding on the risk factors for perioperative stroke so that better management of patients with risk factors can be achieved.

Method: Literature was searched and reviewed to identify articles on risk factors of perioperative stroke and management of these risk factors.

Recent findings: Stroke rates are as high as 6% after cardiac, neurosurgical, and vascular surgery, and are lower (<1%) after general surgery. Perioperative stroke is mostly ischemic. Risk factors that are not modifiable include increasing age and female gender. Morbidities that increase the risk for perioperative stroke include renal failure, history of stroke or transient ischemic attack, diabetes mellitus, atrial fibrillation, congestive heart failure, smoking status, emergency surgery, carotid stenosis, and valvular cardiac disease. Modifiable factors for perioperative stroke during perioperative period include judicious use of antithrombotic therapy and beta-blockers, avoidance of hypotension and maintenance of normal blood glucose levels.

Summary: Many risk factors for perioperative stroke have been revealed. Careful management of the modifiable risk factors may reduce the occurrence of perioperative stroke.
Acute stroke can be divided into two subtypes: ischemic and hemorrhagic stroke. Cerebral ischemia can occur from reductions in blood flow; infarction can occur within 4-10 minutes with complete cessation of blood flow to the brain tissues (22). The majority of perioperative strokes are ischemic, rather than hemorrhagic, in nature (23, 24). Conditions for increased risk of perioperative ischemic stroke include cerebral atherothrombosis, atrial fibrillation, hypotension, hypercoagulability, paradoxical embolism, and cerebrovascular dissection (25). Hemorrhagic stroke includes intracerebral hemorrhage and subarachnoid hemorrhage (26). Patients with uncontrolled hypertension or on anticoagulants are at high risk of hemorrhagic stroke. Obesity, age, male gender, high alcohol intake, smoking behavior and diabetes are other risk factors for hemorrhagic stroke (26-28). Hemorrhagic stroke exerts its damaging effects either by pressure effects on surrounding tissue, or by direct toxic effects of blood on neuronal tissue (27).

Common etiologies of ischemic stroke include thromboembolism induced by surgery or secondary to atrial fibrillation, and cerebral hypoperfusion secondary to carotid stenosis. Atrial fibrillation likely contributes to acute stroke in two ways: either through embolism of cardiac thrombus, or through global hypoperfusion and cerebral ischemia induced by rapid ventricular response and hypotension (9). Less common causes of stroke have been reported to be air, fat, or paradoxical embolism, arterial dissection of neck arteries, cardiac valvular diseases, hypercoagulable states, and abrupt cessation of anticoagulation or antiplatelet therapies (7, 9). Watershed infarcts can occur in the absence of physical arterial obstruction at the junction between two major arterial distributions, and are thought to be secondary to decreased perfusion to the distal territory of the artery and resultant ischemia (29). In any case, the shared commonality is altered cerebral circulation resulting in neuronal cell injury or death. Transient ischemic attack (TIA) is a fleeting “version” of stroke, with no residual deficits.

Etiology for hemorrhagic stroke includes intracranial aneurysm and arteriovenous malformations. These vascular diseases weaken blood vessel walls that are easy to be ruptured. However, uncontrolled hypertension and illegal drug use can induce rupture of vessels without these changes (26, 27, 30).

### Risk Factors and Risk Optimization

Many risk factors for perioperative stroke have been identified (Table 2), although some of the most commonly identified ones are unfortunately unmodifiable. These unmodifiable factors include increasing age and female gender (5, 8, 9, 12, 24, 31, 32). Other independent risk factors include previous history of stroke or TIA, renal failure, diabetes mellitus, atrial fibrillation, congestive heart failure, smoking status, emergency surgery, and cardiac valvular disease (5, 8, 9, 12, 24, 31). Additional described risk factors include intraoperative complications including hypotension, cardiac arrhythmias or rate derangements, hyperglycemia, dehydration, and acute blood loss or anemia. We will focus our discussion on modifiable risk factors.

### Age

Bateman et al. (9) studied 371,641 patients identifying acute ischemic stroke (AIS) in the perioperative setting for non-cardiac and nonvascular surgery. The rate of AIS in all patients with hemicolectomy was 0.7%, total hip replacement was 0.2%, and lobectomy/segmental lung resection was 0.6%. These rates rose to 1.0%, 0.3%, and 0.8%, respectively, in patients older than 65.
years. Kikura et al. (31) identified a 4.7-fold increased risk of perioperative stroke after the age of 50, and a 23.6-fold increased risk of perioperative stroke after the age of 70, as compared with patients younger than 50 years old.

**Stroke History**

All patients with a history of cerebrovascular accident or TIA should be considered high risk for recurrent stroke. Patients with stroke history have a higher risk of perioperative stroke after coronary artery bypass grafting (CABG) (33). A cohort study of 1,426,795 patients undergoing major non-neurological surgery with a history of stroke within a 24-month period prior to their surgery found increased morbidity (pneumonia, sepsis, renal failure, acute myocardial infarction [MI], and pulmonary embolism) and 30 day in-hospital mortality (adjusted risk ratio [RR] 1.79, 95% confidence interval [CI] 1.61-1.99), especially in patients with previous intracerebral hemorrhage (RR 3.41, CI 2.97-3.91) and patients with stroke 1-6 months prior to surgery (RR 3.31, CI 2.91-3.71) (34). A Danish cohort analysis of 481,183 adults undergoing elective non-cardiac surgery found a dramatic increase in major adverse cardiovascular events, including ischemic stroke, acute MI, cardiovascular mortality, and all-cause mortality in patients with a history of stroke. This increase was most-

| Table 2. Identified Independent Predictors of Perioperative Stroke. |
|-------------------------|-----------|-------------|-----------|
| **Predictors** | **Odds ratio** | **Confidence intervals** | **Reference** |
| **Age** | | | |
| Age (per 10 years) | 1.43 | 1.35-1.51 | Bateman, 2009 (9) |
| Age (per additional year) | 1.02 | 1.01-1.04 | Sharifpour, 2013 (5) |
| Age 50-69 | 4.7 | 1.8-12.4 | Kikura, 2008 (31) |
| Age 70+ | 23.6 | 9.6-58.1 | Kikura, 2008 (31) |
| Age (per 10 years) | 2.5 | 1.01-3.2 | Biteker, 2014 (12) |
| Age ≥62 years | 3.9* | 3.0-5.0 | Mashour, 2011 (8) |
| **Renal disease** | | | |
| Renal disease | 2.98 | 2.52-3.54 | Bateman, 2009 (9) |
| Acute renal failure | 3.6* | 2.3-5.8 | Mashour, 2011 (8) |
| Dialysis dependence | 2.3* | 1.6-3.4 | Mashour, 2011 (8) |
| History of kidney disease (creatinine≥2) | 1.3 | 0.8-2.3 | Kikura, 2008 (31) |
| **History of stroke, TIA, cerebrovascular disease** | | | |
| History of previous stroke or TIA | 1.64 | 1.25-2.14 | Bateman, 2009 (9) |
| History of previous stroke or TIA | 3.6 | 1.2-4.8 | Biteker, 2014 (12) |
| History of cerebrovascular disease | 7.1 | 4.6-11.0 | Kikura, 2008 (31) |
| History of stroke, TIA, or hemiplegia | 1.72 | 1.29-2.30 | Sharifpour, 2013 (5) |
| Previous cerebrovascular disease | 12.57* | 2.14-73.7 | Limburg, 1998 (24) |
| **Gender** | | | |
| Female gender | 1.21 | 1.07-1.36 | Bateman, 2009 (9) |
| Female gender | 1.47 | 1.12-1.93 | Sharifpour, 2013 (5) |
| Female gender | 1.2 | 0.8-1.7 | Kikura, 2008 (31) |
| **Other diseases or history** | | | |
| Valvular disease | 1.54 | 1.25-1.90 | Bateman, 2009 (9) |
| Diabetes | 1.18 | 1.01-1.39 | Bateman, 2009 (9) |
| Current smoker | 1.5 | 1.1-1.9 | Mashour, 2011 (8) |
| History of cardiac disease | 1.42 | 1.07-1.87 | Sharifpour, 2013 (5) |
| Chronic obstructive pulmonary disease | 7.51* | 1.87-30.12 | Limburg, 1998 (24) |
| Peripheral vascular disease | 5.35* | 1.25-22.94 | Limburg, 1998 (24) |
| Hypertension | 1.5 | 0.9-2.4 | Kikura, 2008 (31) |
| Atrial fibrillation | 5.5 | 2.8-10.9 | Kikura, 2008 (31) |
| Atrial fibrillation | 1.95 | 1.69-2.26 | Bateman, 2009 (9) |
| History of ischemic heart disease | 2.3 | 1.3-4.1 | Kikura, 2008 (31) |

*Adjusted Odds Ratio
ly marked in patients with stroke less than 3 months prior to surgery, but was still elevated up to 12 months or more after stroke (35). Interestingly, these conclusions are contradicted by a study of patients undergoing total hip or knee replacement or abdominal aortic aneurysm repair within 6 months of recent stroke. This study found no relationship between timing of surgery after recent stroke and perioperative mortality (36).

It has been shown that after AIS, cerebrovascular autoregulation is deranged and may rely on systemic blood pressure to maintain adequate cerebral perfusion (37, 38). This impairment of autoregulation peaks within the first 5 days after stroke and with recovery over the next 3 months (37).

Renal Disease
Mashour et al. (8) identified acute renal failure as an independent risk factor for perioperative stroke in non-cardiac, non-neurologic surgeries (odds ratio [OR] 3.6, CI 2.3-5.8) as well as dialysis dependence (OR 2.3, CI 1.6-3.4). Bateman et al. (9) also identified renal disease as an independent risk factor for perioperative stroke (OR 2.98, CI 2.52-3.54). In patients undergoing carotid endarterectomy, moderate to severe chronic renal insufficiency is strongly associated with higher rates of both stroke and five-year mortality (39, 40). Postoperative blood urea nitrogen increase is found to be associated with perioperative stroke in cardiac surgical patients (41).

Atrial Fibrillation
Atrial fibrillation may be intermittent or continuous in nature, and has been found to be a comorbidity in 27.6% of the patients with postoperative strokes. It is associated with up to 5.5-fold increased risk of stroke (9, 31). Postoperative atrial fibrillation is the most consistent independent variable for stroke after CABG (42). New onset of perioperative atrial fibrillation has also been associated with an increased long-term (within 1 year) risk of subsequent stroke in patients with cardiac or non-cardiac surgery (9, 43). Anticoagulation in this population to reduce stroke risk is a common practice, and the benefit of continuing anticoagulation in the perioperative setting is offset by the risk of surgical site bleeding.

Symptomatic Carotid Stenosis
Carotid stenosis may be diagnosed on symptoms or clinical examination. In the non-operative setting, symptomatically severe carotid stenosis (>70% stenosis), the rate of recurrent stroke after onset of TIA or minor stroke is between 2-7.5% within the first month (44). It is reasonable to perform carotid endarterectomy or stenting in symptomatic patients (i.e. following ischemic stroke or TIA) within 6 months if the severity of internal carotid artery stenosis is greater than 70% by imaging, or more than 50% by catheter angiography. Asymptomatic patients with greater than 70% stenosis of the internal carotid artery are also candidates for intervention (45).

In general, optimization of other comorbidities is also important prior to elective surgeries, such as control of hypertension and hyperglycemia. Medical management to reduce risk factors for stroke includes smoking cessation, blood pressure control, anticoagulation for atrial fibrillation, and anti-hyperlipidemic medications.

Antithrombotic Therapy
Antithrombotic therapies (anticoagulants and antiplatelet drugs) are commonly prescribed medications. The risks and benefits of withholding these drugs perioperatively certainly need to be balanced against the probability of surgical bleeding, as well as the consequences of bleeding. For instance, specific surgeries may not tolerate even minimal amounts of bleeding, such as neurosurgical or certain ophthalmologic procedures. Conversely, stopping antithrombotic therapy can also result in untoward consequences. The withdrawal of antiplatelet medications or anticoagulants within 60 days preceding to an AIS accounted for 5.2% of strokes occurred in a community (46). Of these patients with withdrawal of the anticoagulants, 62.3% were first-ever strokes, and 47.4% occurred in the peri-procedural period.

Surgeries with high risk of bleeding include cardiac surgery (CABG and valvular replacement), intracranial surgery, intraspinal surgery, major vascular surgery (aortic aneurysm repair, peripheral artery bypass), major vascular orthopedic surgery, reconstructive plastic, major cancer surgery, urogenital surgery, and hip surgery. Surgeries with low risk of bleeding include den-
tal procedures, some ophthalmologic surgeries, and dermatology procedures (47, 48).

Anticoagulants are commonly used for prevention of stroke in patients with atrial fibrillation. The American College of Chest Physician (ACCP) recommendations for interruption of vitamin K antagonist therapy before elective surgery are dependent on balancing the risk of surgical bleeding with the thromboembolic risk of the patient. Specifically, in situations of high bleeding risk where cessation is required, the ACCP recommends cessation of vitamin K antagonist therapy 5 days prior to surgery. In the high-risk patient (known atrial fibrillation and CHADS score [a score system to estimate the risk for stroke in patients with non-rheumatic atrial fibrillation based on the existence of congestive heart failure, hypertension, advanced age, diabetes or stroke] >4, history of venous thromboembolism, history of stroke or TIA within 6 months, or mechanical heart valve on anticoagulation), bridging anticoagulation is recommended (47). Otherwise, in patients at low risk for thromboembolic events, no bridging is recommended. Resumption of anticoagulation therapy should occur as soon as is deemed safe from a bleeding risk standpoint.

Anti-platelet therapy is exceedingly common, particularly in elderly populations. These drugs are used in both the primary and secondary prevention of cardiovascular disease, and the use of aspirin has led to a 12% reduction in serious vascular events (mainly in reduction of non-fatal MI) and absolute reduction in serious vascular events (6.7% from 8.2% per year), respectively (49).

In patients at moderate-to-high risk of thrombotic events undergoing non-cardiac surgery, the ACCP recommends continuing aspirin perioperatively instead of stopping it 7-10 days prior to surgery (47). If interruption of anti-platelet therapy is required, expert guidelines have varying recommendations for cessation of aspirin and clopidogrel at 5 days or 7-10 days prior to surgery (45, 47, 50).

The PeriOperative Ischemic Evaluation (POISE)-2 trial studied the effect of low-dose perioperative aspirin as compared with placebo before non-cardiac surgery on perioperative death, nonfatal MI, and major bleeding. While the use of low-dose aspirin did not reduce the rate of death or nonfatal MI, it increased the risk of major bleeding (hazard ratio [HR], 1.23; 95% CI, 1.01 to 1.49) (51). The POISE-2 trial also found that discontinuing aspirin three or more days prior to surgery may decrease the risk of major bleeding, and that withholding aspirin after chronic use was not associated with an increase in thrombotic events (51). Resumption of anti-platelet therapy must be carefully considered to minimize the risk of surgical bleeding. In general, it is reasonable to restart aspirin after surgery when the risk of bleeding is significantly decreased. In one study, the absolute increase in risk of bleeding was 0.3% when aspirin was restarted at day 8 as compared with placebo (51).

Prediction Models of Perioperative Stroke
Charlesworth et al. (52) used data of 33,062 patients to develop a prediction model for stroke after CABG. The factors used to calculate the risk for perioperative stroke include age, gender, surgery urgency, diabetes, cardiac function, renal function and vascular disease. They came up a very accurate prediction formula for perioperative stroke. Goodney et al. (53) built up a prediction model based on the data of 3092 patients with carotid endarterectomy. The risk factors for perioperative stroke are age >70 years, contralateral internal carotid artery occlusion, congestive heart failure, emergency surgery and history of ipsilateral stroke. Patients with none or one of these risk factors have <1% chance of perioperative stroke or death. Patients who have three or more risk factors have nearly 5% chance of death or stroke.

Intraoperative Management

Hypotension
Cerebral autoregulation of blood flow is vital to maintain relatively constant cerebral blood flow over changes in arterial blood pressure. It is typically preserved when mean arterial blood pressures are between 50 to 150 mm Hg (54). The intraoperative period is known to have high rates of hypotension, but clearly, not every patient experiencing hypotension goes on to develop stroke. Surgery in the seated position is desir-
able for certain surgeries for better access and exposure to the surgical field, but can lead to cerebral hypoperfusion despite adequate systemic blood pressure. The consequences of this postural hypotension first attracted attention after a case series identifying four neurologic injuries with ischemic watershed brain infarcts after orthopedic surgery in the seated position (55). A subsequent prospective study of patients undergoing elective surgery in the beach chair position was performed, in which 60 patients were randomized to either general anesthesia or regional anesthesia with monitored anesthesia care. Baseline mean arterial pressure and cerebral oxygen saturations were measured during surgery, and both mean arterial pressure and cerebral oxygen saturations were found to be lower in the general anesthesia group as compared with the regional anesthesia and sedation group (56). Neuromonitoring can be considered for early detection of decrease in cerebral blood flow (57).

Neurologic injury secondary to cerebral hypotension is very rare. However, careful attention should be paid to both the systemic mean arterial pressure and also to cerebral perfusion pressure, which may be significantly different from systemic arterial pressure in certain surgical positions. Clinically significant hypotension, as defined by a decrease of more than 30% from baseline blood pressure (58), possibly plays a role in perioperative stroke (8, 59), although a case control study of 61 patients with ischemic strokes did not find any such association between intraoperative hypotension and development of ischemic stroke (24), and no ischemic stroke events occurred in a review of 4169 patients undergoing elective shoulder surgery in the seated position under general anesthesia and sedation, despite high rates of intraoperative hypotension (47%) and at least a 30% decrease in mean arterial pressure in 30% of patients (60).

Normoglycemia
Although intensive glucose control has not been conclusively identified as protective against stroke development (61), hyperglycemia is known to worsen brain injury and lead to increased mortality after periods of cerebral ischemia (62-64). A phase III multicenter trial, the Stroke Hyperglycemia Insulin Network Effect (SHINE), is currently underway to compare standard of care glucose control with intensive glucose control in hyperglycemic AIS patients (65). Current expert consensus recommends treating hyperglycemia greater than 150 mg/dl, with a target glucose range of 60-180 mg/dl (57, 66).

Anesthetic Technique
Patients undergoing certain surgeries may be eligible for either general anesthesia or neuraxial techniques with sedation. A study of 2,807 patients undergoing transfemoral aortic valve implantation under either local anesthesia or general anesthesia demonstrated no significant difference between rates of MI, major stroke, or in-hospital mortality. However, an observational study of 18,745 patients undergoing primary or revision total hip or knee arthroplasty, identified general anesthesia as an independent predictor of postoperative stroke (OR 3.54, 95% CI 1.01-12.39) (67). A multicenter analysis of 382,236 patients undergoing primary hip or knee arthroplasty identified neuraxial anesthesia as the anesthetic associated with the most favorable complication risk profile. The neuraxial group was associated with a stroke incidence of 0.07%, as compared with the combined neuraxial/general anesthesia group (0.12%) and the general anesthesia alone group (0.13%). Thirty-day mortality was also higher in the general anesthesia group as compared with neuraxial or neuraxial/general anesthesia group (adjusted OR of 1.83, 95% CI 1.08-3.1, and 1.70, 95% CI 1.06-2.74, respectively) (68).

Perhaps some of these findings can be explained by higher incidence of hypotension and decreased cerebral perfusion pressure and cerebral saturations (56), or by delayed detection of hypoperfusion to the brain under general anesthesia.

Volatile anesthetics have been demonstrated to provide neuroprotection against brain hypoxic-ischemic injury in animal models. However, no convincing clinical studies demonstrate this benefit in humans to date (69).

Beta-Blockade
The 2008 POISE trial associated continuation of
perioperative beta-blockers with reductions in MI, the need for coronary revascularization, as well as a reduction in the development of atrial fibrillation (59). However, there was an increased risk of clinically significant hypotension (HR 1.55, CI 1.38-1.74), and bradycardia, overall mortality (metoprolol group 129 [3.1%] vs. placebo group 97 [2.3%]), stroke (metoprolol group 41 [1%] vs. placebo group 19 [0.5%]) in spite of lower rates of atrial fibrillation. The risk and benefit of perioperative beta-blockade with metoprolol should be considered on an individual basis. Withdrawal of chronic beta-blockers is associated with increased risk of adverse cardiac outcomes (70), and continuation of beta-blockade in patients on beta-blocker therapy prior to admission has been identified as a Surgical Care Improvement Project (SCIP) Measure by the Joint Commission (71). One study of incidence of perioperative stroke in a group of 57,218 patients found approximately a 4.2-fold increase in perioperative stroke with preoperative metoprolol. However, the study did not find a statistically significant association of stroke with other beta-blockers (atenolol, bisoprolol, carvedilol, nadolol, propranolol, or sotalol), suggesting a metoprolol specific effect (72). The use of intraoperative metoprolol tartrate (intravenous, IV) was associated with a 3.3-fold increased risk of perioperative stroke; whereas IV esmolol or labetalol had no such association. Data suggests that preoperative beta-blockers should not be initiated in the immediate preoperative period, and initiation within 7 days prior to surgery may lead to increase in 30-day mortality (OR 1.49, CI 1.03-2.16) without an increase in 30-day ischemic stroke risk (50, 73).

Other Drugs
Angiotensin converting enzyme inhibitors are commonly used to treat hypertension. Continuous use of these agents, especially in combination with beta-blockers, can result in severe hypotension during surgery. This hypotension may not respond that well to vasopressors (74). Thus, angiotensin converting enzyme inhibitors may increase the risk of perioperative stroke. On the other hand, statins that are used to treat hyperlipidemia have been found to provide beneficial effects during the perioperative period. These effects include reducing perioperative stroke in patients after vascular surgery (74, 75).

### Unique Features of the Treatment of Perioperative Stroke

Early recognition is the key to have good neurological outcome after perioperative stroke (76). Patients under general anesthesia may not show any signs of stroke. Fortunately, the majority of stroke occurred after surgery when patients are not under general anesthesia. However, sedation can mask the presentation of stroke (77). Thus, minimizing sedation during perioperative period should facilitate the recognition of stroke.

Core treatment of ischemic stroke is supportive therapy and re-establishment of blood supply to the ischemic tissues (27, 30, 76). While supportive therapy, such as maintaining nutrition and avoiding hypotension, in the case of perioperative stroke should be the same as for other stroke patients, the use of intravenous tissue plasminogen activator to dissolve the clots in the vessels is relatively contraindicated within 14 days after a major surgery (30, 76). Using catheter to mechanically remove clots may be the method within this time window (30, 76). The treatment of perioperative hemorrhagic stroke may be similar to those measures used for hemorrhagic stroke that does not occur during perioperative period.

### Conclusions
Perioperative stroke is a relatively uncommon but debilitating event that is associated with high morbidity, mortality, as well as extraordinary intangible and financial costs. Although many of the most common risk factors are not modifiable, elective surgery after recent stroke should be postponed until cerebral autoregulation has improved, after a minimum of 3 months. All patients with history of stroke or TIA should be considered high risk for repeat stroke. Meticulous intraoperative management may mitigate the risk of perioperative stroke. Intraoperative hypotension should be treated, especially in patients at high risk for cerebral ischemia. Chronic beta-blocker therapy should be continued in the perioperative period. The deci-
sion to continue anti-platelet and anti-coagulation therapy should be based on the patient's individual thromboembolic risk and risk of surgical bleeding. Serum glucose levels between 60-180 mg/dl are ideal, with treatment recommendations for blood glucose levels >150 mg/dl.

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