Opinion

Perioperative Stroke Remains an Underappreciated Cause of Morbidity and Mortality

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The incidence of perioperative stroke has not changed over the last 2 decades despite overall improvements in medical and surgical care. Stroke in the non-cardiac, non-neurological procedure is more common than previously acknowledged and is an important cause of morbidity and mortality in the postoperative patient. Recognition of an acute stroke is difficult to recognize in the postoperative patient, but requires swift action to achieve optimal outcomes.

Perioperative stroke is an acute ischemic or hemorrhagic cerebrovascular event lasting at least 24 hours that occurs intraoperatively or within 30 days postoperatively. The reported incidence of stroke in non-cardiac, non-neurological procedures ranges between 0.05 and 7.4% (1). These studies likely underestimate the true incidence of perioperative stroke. The majority of these studies conducted between 1967 and 2009 are retrospective reviews of administrative data, which most likely included only clinically overt strokes. Minor strokes, transient ischemic attacks (TIA) and covert strokes are usually not captured as they go unnoticed by caregivers or are missed by billing code officers. In the postoperative setting, subtle neurological deficits are difficult to recognize given residual anesthetic effects, neuraxial anesthesia, postoperative opioid requirements and postoperative cognitive dysfunction. Furthermore, there are no dependable biomarkers of stroke, such as troponin or electrocardiographic findings in myocardial infarction, to aid in the diagnosis.

In addition, these studies used the 1970's WHO definition of stroke as a "focal or global neurologic deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours," (1). Given improvements in neuroimaging, the American Heart Association (AHA) and the American Stroke Association jointly in 2013 published a broadened definition to include "pathological, imaging or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution" (2). This updated definition introduced the concept of a silent or "covert" stroke, which is an asymptomatic ischemic event usually only detected by advanced neuroimaging techniques (3). Although asymptomatic at the time, the presence of covert strokes more than doubles the risk of subsequent strokes and dementia (4). In the prospective, multicenter Neurovision Pilot Study, 11.4% of the non-cardiac surgery patients age 65 years and older were found to have acute covert stroke on surveillance MRI despite lack of any symptoms or signs of neurologic injury (5).

There is increasing evidence that implicates surgical trauma and the associated inflammation in perioperative stroke pathophysiology. The data suggests that the inflammatory response triggered by surgery either initiates or exacerbates ischemic cerebral injury. Various cytokines, including interleukin-1, interleukin-6, tumor necrosis factor alpha, and C-reactive proteins, have been implicated in the postoperative inflammatory cascade (6, 7). Interleukin-6 appears to be a major mediator in non-operative strokes with peak concentrations correlating with both infarct volume and clinical outcomes (8). Peak plasma interleukin-6 concentrations above 30.5 pg/mL were associated with increased mortality at 12 months in a prospective study of 37 patients suffering acute stroke. In another study, a 1-unit increase in interleukin-6 predicted an 18% higher risk of dying during the hospitalization for acute ischemic stroke (9).

Given the association between surgery and acute strokes, it is important to understand the risk factors for perioperative stroke. Prospective identification of the risk factors of perioperative strokes in the non-cardiac population is limited, but large observational studies have helped to

Table. Risk Factors for Perioperative Stroke.	
Risk Factors	Odds Ratio
Advanced age	2-23
Atrial fibrillation	2-5.5
Peripheral vascular disease	8
Prior stroke or TIA	2-14
Renal disease	3

Independent risk factors consistently identified by large observational studies (1).

identify some risk factors (Table). Consistent independent predictors of perioperative stroke include advanced age, renal disease, peripheral vascular disease, atrial fibrillation and history of stroke or TIA (10, 11). Patients with prior strokes or TIAs should be considered high risk for subsequent strokes as they have evidence for existing cerebrovascular disease and may have areas of the brain with limited cerebral reserve. This is especially so within the first 12 months after the stroke as the risk of major cardiovascular event or stroke is increased approximately 10 times (12). Unfortunately, these risk factors are not easily modifiable.

The choice of anesthetic technique is generally regarded as not a contributing factor (13) although two recent retrospective analyses of patients undergoing joint arthroplasty found a lower stroke rate in those operated with regional anesthesia (14). The contribution of intraoperative hypotension, while seeming to be an obvious factor, is poorly defined because of lack of good quality prospective studies and no standardized definition of hypotension (15).

Perioperative stroke has a profound negative effect on outcomes after surgery, greatly increasing the odds of in-hospital mortality. Mortality associated with perioperative stroke is 2-3 fold the mortality in the nonsurgical setting (1). Compared to the 12.6% mortality rate associated with stroke in the non-surgical setting, mortality from perioperative stroke is 25-45% after general surgery (16). Perioperative stroke also increased the risk of requiring long-term care after discharge. In the Perioperative Ischemic Evaluation (POISE) trial, almost 60% of surviving stroke patients required long-term care with only 17% making a full recovery (17).

Rapid recognition is crucial in the management of acute stroke and achieving optimal outcomes. Symptoms and signs of stroke may be masked in the post-anesthetic period by pharmacologic agents used perioperatively. As such, stroke should be considered part of the differential diagnosis in the event of delayed emergence, altered mental status and/or the presence of new neurologic deficits, and staff should have a low threshold for neurologic consultation (10). In addition to ruling out other causes of neurologic deficits, a detailed neurologic examination should be performed. The National Institutes of Health Stroke Scale (NIHSS) helps to reproducibly quantify stroke severity and assess patient response to therapy. However for quick screening in the post-

anesthetic care unit, abbreviated tests such Face, Arm, Speech Test (FAST) or Melbourne Ambulance Stroke Screen (MASS) may be useful (18, 19). Urgent diagnostic studies, such as non-contrast computed tomography (CT) of the brain, should be conducted to distinguish between ischemic and hemorrhagic cause of neurologic deficit; however, most perioperative strokes are ischemic in origin. Additional studies, including CT angiography and CT perfusion imaging can help guide possible interventions (10).

Currently, no guidelines for the management of acute perioperative strokes exist, but therapeutic strategies in the nonsurgical setting may be helpful. There is a paucity of literature regarding the management of perioperative strokes after a non-cardiac, or non-neurological procedure. For the more common acute ischemic strokes, intravenous recombinant tissue plasminogen activator (rtPA) should be considered although major surgery within the previous 14 days is a relative contraindication due to hemorrhagic complications. Endovascular approaches have been increasingly used over the last decade and may be suitable for the immediate perioperative period (20).

Perioperative strokes have a significant impact on the surgical outcomes and occur more often than recognized. Because surgery and anesthesia are associated with increased risk of strokes, identifying patients at high risk for perioperative strokes is important with advanced age, renal disease, peripheral vascular disease and history of stroke or transient ischemic attack as the most

consistent risk factors. Additional prospective studies are needed to better define the incidence, risk factors and appropriate preventive measures. Early recognition, which is difficult in the postoperative setting due to residual anesthetic effects, postoperative opioid requirements and postoperative cognitive dysfunction, is essential in achieving optimal outcomes. Evaluations of simple, rapid clinical screening tests are needed. Intravenous rtPA should not be excluded as an option in the management of acute stroke after major surgery, but mechanical thrombolysis may be an attractive option despite lack of superiority.

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