Perioperative Stroke

Where Do We Go from Here?

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IN this issue of ANESTHESIOLOGY, Mashour *et al.* present an extensive analysis of the prospectively collected American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database. The authors investigated perioperative stroke in patients undergoing noncardiac nonneurologic surgery.[1] They analyzed more than 523,000 patients in the NSQIP database and developed a risk model to predict the occurrence of ischemic and hemorrhagic stroke. The model was derived from a cohort of approximately 350,000 patients and validated in a 173,000-patient cohort. The overall incidence of stroke in both cohorts was 0.1%. Perioperative stroke increased 30-day mortality by 8-fold (21% absolute risk increase of mortality in a comorbidity matched cohort).

Multivariate logistic regression revealed nine predictors of stroke and one protective factor. These 10 elements were used to create a risk model. The risk factors for stroke included: age 62 yr or older, myocardial infarction within 6 months of surgery, hypertension, history of stroke, history of transient ischemic attack, history of chronic obstructive pulmonary disease, dialysis, acute renal failure, and current tobacco use. Surprisingly, moderate obesity was protective (body mass index 35–40). There were no data regarding atrial fibrillation, other dysrhythmias, or hypotension in the NSQIP database, so these values could not be included. In the final unweighted model, stroke risk was 0.1% in patients with two or fewer risk factors, 0.7% in those with three or four risk factors, and 1.9% in the highest risk group with five or more risk factors. Despite the author's preference for a "simpler" unweighted risk classification, a *weighted* risk score would have been more precise, as the risk associated with the identified predictors varies considerably (hazard ratio range: 0.6–3.9).

How do we use these data? Even in the highest risk group identified by Mashour *et al.*, perioperative stroke was an uncommon adverse event (occurring in 1 in 50 patients) after noncardiac nonneurologic surgery. In fact, this high-risk population is elderly and sick and at risk for any of a large number of uncommon adverse events. The addition of atrial fibrillation to the risk assessment, if the data were available, would likely add predictive power but still not change the perioperative management of the individual patient. After all, any medically indicated anticoagulant and antiplatelet therapy should be restarted as soon as safely possible after surgery. Intraoperative hypotension should be treated aggressively. Thus, the anesthesiologist and surgeon are left with few practical options for preventing perioperative stroke beyond providing high-quality routine care.

So where do we go from here? Perioperative stroke is an uncommon complication with devastating consequences, as detailed by Mashour *et al.* Stroke is also a heterogeneous disease resulting from a multitude of etiologies.[2] Perioperative ischemic stroke can be caused by cardioembolism (from dysrhythmia or valvular disease), paradoxical embolism through a right to left cardiopulmonary shunt, artery-to-artery embolism, *in situ* thrombus formation in atherosclerotic cerebral vessels, or distal arterial watershed infarction from hypoperfusion. Venous infarction (ischemic or hemorrhagic) caused by cerebral sinus or cortical vein thrombosis can occur perioperatively in patients with hypercoagulability. Perioperative hemorrhagic stroke may be caused by hypertension or hemorrhagic transformation of an ischemic infarct, possibly exacerbated by antiplatelet or anticoagulant therapy. Finally, other neurologic outcomes such as cognitive dysfunction may be on a continuum with perioperative stroke, but there is insufficient evidence at this time to go beyond mere speculation.

Once again, where do we go from here? How do we prevent this serious uncommon complication that is multifactorial in etiology?

Better Data. First and foremost, this is a call for better prospective data gathering. The work of Mashour *et al.* illustrates the limitations of the NSQIP database, despite the laborious efforts of very dedicated nurses across the United States. Understanding uncommon events such as perioperative stroke will require detailed information on the entire spectrum of care from all surgical patients. The Centers for Medicare and Medicaid Services have mandated that electronic medical records meet meaningful use criteria and are providing financial incentives toward this end. This endeavor is currently accelerating the adoption of electronic medical records.* Although universal integration of various healthcare databases is likely decades away in the United

◆ This Editorial View accompanies the following article: Mashour GA, Shanks AM, Kheterpal S: Perioperative stroke and associated mortality after noncardiac, nonneurologic surgery. ANESTHESIOLOGY 2011; 114:1289–96.

Accepted for publication February 18, 2011. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

* Dolan PL. American Medical News. EMR adoption rates up, with small practices left behind. Available at: http://www.ama-assn.org/amednews/2010/11/22/bisb1122.htm. Accessed February 4, 2011.

 Anesthesiology 2011; 114:1263–4

States, large health systems should be able to accomplish this within the next 5 yr. Direct note entry by physicians, midlevel providers, and nurses into queryable informatics systems will allow researchers to create much higher level analyses. The NSQIP stroke patients undoubtedly saw a neurologist and underwent imaging studies, cardiac assessments, rhythm monitoring, and review of intraoperative hemodynamic variables and were on various regimens of antiplatelet, anticoagulant, antihypertensive, and statin therapies. However, none of these data are routinely obtainable for research. This information would have likely created a very different predictive model and conclusions regarding at risk populations.

With better risk assessments, patients at high risk of perioperative stroke (more than 10%, for example) could be studied prospectively in reasonably sized yet adequately powered trials investigating new preventive interventions. Statins, antiplatelet and anticoagulant regimens, and antiinflammatory and novel neuroprotectant therapies could be pursued. Intraoperative neuromonitoring, such as with cerebral oximetry, might show benefit in patients at high risk of stroke. Modest hypertension may be beneficial intraoperatively. The Perioperative Ischemic Evaluation Study Trial demonstrated an increase in stroke with indiscriminant β-blockade.[3] However, in that study, only 60 strokes occurred in the more than 8,300 patients at risk for atherosclerotic disease. This finding highlights the need to identify an even higher risk cohort for inclusion in future trials to achieve the necessary event rates.

Genomic, proteomic, and metabolomic studies hold great promise for identifying high-risk individuals and diagnosing acute stroke. However, this field is still in its infancy despite more than a decade of research.[4,5] Connecting genotype to phenotype depends on large cohorts of patients with well-defined stroke syndromes. Known modifiable risk factors, such as diabetes and hypertension, only explain approximately two thirds of the risk for stroke.[4] Genetic mechanisms of stroke are known only for a few rare stroke syndromes such as cerebral autosomal dominant arteriopathy with subcortical infarcts and dementia, commonly known by the acronym CADASIL.[4] Genetic polymorphisms causing hypercoagulability, such as factor V Leiden, increase the risk for cerebral sinus thrombosis[4] and deep venous thrombosis, but account for a small number of perioperative strokes. We are still a long way from understanding the genomics and proteomics of common stroke syndromes.

What About Now? For the time being, physicians need to maintain vigilance for perioperative stroke. Neurologic function can be assessed at the bedside on routine examination, even by simply observing the patient's movements, speech, and cognition during a brief postoperative visit. Neurologic signs or symptoms should trigger stroke codes and stroke teams that can emergently triage patients for acute interventions such as thrombolysis (intravenous or intraarterial) and/or endovascular clot removal.[6,7] Immediate treatment is paramount as outcomes worsen with time from ictus; "time is brain."[8]

We must continue to search for answers to stroke and neurocognitive complications in the perioperative period. Our current databases are largely insufficient, and new approaches are needed. We applaud the determination of investigators, such as Dr. Mashour, to see this work move forward. Robert Frost published "Stopping by Woods on a Snowy Evening" in 1923.[9] That same year he was a visiting fellow in Ann Arbor, not far from University of Michigan Hospital where Mashour *et al.* currently practice.† So it seems fitting to remind the anesthesiology community now, nearly a century later, that we have "promises to keep, and miles to go before (we) sleep."[9]

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