Postoperative Cognitive Dysfunction

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Cardiac surgery, and especially cardiopulmonary bypass (CPB), has been the poster child for postoperative cognitive morbidity. Over the past 10-15 years, however, it has become increasingly clear that disruption or decline in cognitive function is also fairly widespread among elderly non-cardiac surgical patients. The reasons are a matter of considerable controversy and this brief overview will recap current perspectives on the problem.

Delirium

Delirium, or acute brain dysfunction, is by far the most common cause of perioperative cognitive morbidity in elders. In fact, it may be the most common of all perioperative complications in older patients; the incidence is 15-55%, with orthopedic (hip fracture), major peripheral vascular, and cardiac surgery patients and at greatest risk. Prevalence approaches 100% among those requiring an ICU stay. Delirium is not just an annoyance. It is associated with prolonged hospital stay and expense, greater likelihood of discharge to a nursing home or other post acute-care facility, and higher 1-year mortality, with a hazard ratio of death in cardiac surgery patients not unlike that of postoperative stroke. It is also associated with prolonged decline in cognitive performance and may even be a marker for subsequent development of dementia.

Delirium is a clinical diagnosis; it is defined by an acute and fluctuating course and inattention along with either disorganized thinking and/or altered level of consciousness. Because it is so common and costly, hospitals are increasingly focused on identifying and managing delirium. Non-psychiatrists typically use the CAM (Confusion Assessment Method), a simple and well-validated bedside test, to diagnose delirium. However, delirium is under-diagnosed because the symptoms fluctuate, patients may simply appear sedated (hypoactive delirium), and its seriousness is underappreciated so caregivers may not look closely.

The neurobiological mechanisms of delirium are not known but the vulnerability and predisposing factors are well characterized. A leading hypothesis is that cognitive reserve and susceptibility to delirium are inversely proportional, such that a lesser insult is required to trigger acute brain dysfunction in a cognitively or medically fragile person. Given differences between the young and old brain, this would explain why elders are at higher risk. Age and co-morbid diseases are major vulnerability factors, and there may be genetic component as well; important predisposing factors include hypoxia, alcohol abuse, anemia, metabolic disturbances, and pre-existing emotional or mental disability (i.e. depression, executive dysfunction, dementia). Infection is also a notorious precipitator of delirium. This suggests that surgery, which produces an acute inflammatory response both peripherally and within the CSF, may trigger delirium. Indeed, delirium is more common after ‘big’, invasive procedures like cardiac surgery than minor ones but a causal relationship between cytokines and delirium remains speculative. Likewise, while it is tempting to implicate intraoperative microemboli in the pathogenesis of postoperative delirium, the data are inconclusive.

Drugs and drug interactions are a major factor, a point of considerable relevance to the OR and ICU. Drugs with anticholinergic activity, of which there are many besides atropine and scopolamine, are perhaps the most classic delirium promoting agents but many other drugs (including ketamine and benzodiazepines) do so as well. Curiously, the mode of anesthesia (spinal, epidural, general) seems to have little bearing, perhaps because use of sedatives and depth of hypnosis / anesthesia are not controlled. This is important for two reasons: there appears to be a relationship between deep sedation and delirium risk and procedural “sedation” often ends up being general.
anesthesia.20 The agent used may also make a difference. During prolonged sedation of patients in the ICU, the risk of delirium, or delirium plus ‘coma-free’ days, length of ICU stay, and 30 d mortality are all lower if dexmedetomidine is used instead of a benzodiazepine.21,22 Observations that are changing the way ICU patients are sedated.23 As far as postoperative pain management goes, most, but not all, studies indicate the effectiveness of pain control is more important than the specific agents or route of analgesia used.24-26 Pain itself is a cause of delirium so the main point is that analgesics should not be withheld in elderly post-surgical patients for fear of inducing delirium.

What can be done about perioperative delirium? First, identify the patient at high-risk and try to prevent it. Consider obtaining a geriatric consultation since a simple, low-tech, geriatrician-directed perioperative re-orientation program markedly reduces the incidence of delirium, particularly in high risk patients.27 Prophylactic administration of low-dose haloperidol should be considered in high risk cases, as it has been shown to decrease the duration and severity of delirium after hip surgery, albeit without reducing prevalence.28 Recent data suggest preoperative use of a statin decreases the risk of perioperative delirium by 46% after cardiac surgery but a large retrospective study found the opposite in non-cardiac surgery, so the role of these drugs remains controversial.29,30 During and after surgery, be especially meticulous about minimizing or avoiding delirium-inducing agents (e.g. anticholinergics, benzodiazepines) and managing potential precipitating factors (e.g. oxygenation, anemia). This is not always easy since many drugs have anticholinergic effects, so use drugs sparingly. Recognize also that delirium is often an early sign of serious underlying disease in the elderly.1 Because many factors contributing to delirium are not modifiable (e.g. age of patient, type of surgery), it is particularly important to identify and manage remediable causes such as hypoxemia, infection / sepsis, and pain. Maintaining a lighter plane of anesthesia might be useful but this remains controversial.31,32 Lastly, when prevention fails, pharmacological intervention for symptom management may be appropriate. There is no evidence benzodiazepines are effective and, as mentioned above, may actually make matters worse. Haloperidol is the agent of choice but its efficacy is largely unproven.33 It should be used sparingly and in low doses (0.5-1 mg iv initially) because of heightened sensitivity in advanced age, risk of QTc prolongation, and oropharyngeal dysphagia.

**Postoperative Cognitive Dysfunction (POCD)**

Many elderly patients experience cognitive dysfunction weeks to months after surgery.34,35 This POCD is manifest mainly as subtle deficits in memory and/or executive function that, unlike delirium, are diagnosed by performance on a battery of neuropsychological tests rather than by clinical criteria. POCD is present after non-cardiac surgery in 30-40% of patients in the 1st postoperative week regardless of age but 3 months later it is 2-3 times more common in aged patients (10-13%) than younger adult surgical controls or age-matched non-hospitalized controls (4-6%).36-38 Persons with POCD leave the workforce prematurely and, if they have POCD at both hospital discharge and 3 months postoperatively, are nearly 5-times more likely to be dead 1 year later.36,39 Thus, prolonged postoperative cognitive impairment is real, common, and associated with poor functional outcomes and higher 1-year mortality.

The key question, of course, is what causes it? The short answer is that no one is certain but the problem is almost certainly multifactorial. Advanced age clearly plays a role but it is not known whether this reflects loss of brain reserve, prevalence of comorbid diseases (especially cerebrovascular disease), lack of neurotrophic factors, poor reparative ability, etc. Although it is reasonable to speculate that poor baseline cognitive performance might identify patients at greatest risk for POCD, most trials have excluded such people in part because poor baseline performance makes decline difficult to detect.30 Genetic susceptibility may be a factor; a recent study found a strong association between the Apo E4 allele, a major susceptibility gene for Alzheimer’s disease and other types of cognitive decline, and POCD following inhalation but not intravenous anesthesia but previous work does not confirm greater vulnerability.41-43 Similarly, physiologic changes seem to contribute minimally or not at all to POCD. Investigation of perioperative hypotension (defined as MAP 45-55 mmHg or < 60% of baseline for ≥ 30 min) and/or hypoxia (SpO2 ≤ 80 for > 2 min) during non-cardiac surgery, for example, has found little evidence of an association with
POCD.\textsuperscript{17,38} Even the abnormal physiology of CPB does not explain late POCD, as comparison of on-pump and off-pump CABG reveal similar cognitive (and neurologic) outcomes.\textsuperscript{44-46}

This means we need to look elsewhere. Surgery itself is a good place to start, as surgery induces inflammation and inflammation can impair cognition. Consistent with this hypothesis, the incidence of POCD is higher after major inpatient than minor outpatient procedures, suggesting the magnitude of the surgical insult and inflammatory response play a role.\textsuperscript{40} Recent work in young animals shows that a surgical procedure disrupts the blood brain barrier, increases migration of macrophages into the brain, and produces transient neuroinflammation and learning impairment that is reversed by a cytokine antagonist or a nicotinic acetylcholine receptor agonist.\textsuperscript{47-49} Unexpectedly, however, isoflurane anesthesia alone also produces an inflammatory response in the brain.\textsuperscript{50} So, the neuroinflammation hypothesis is viable and may be as relevant for explaining anesthetic-induced cognitive impairment as it is for understanding surgically-induced cognitive deficits.

Could general anesthesia be the problem? Surely, among all the things that happen in the perioperative period, general anesthesia has the most obvious effect on the brain (i.e. coma). The data, however, are inconsistent. Several studies have found general anesthesia without surgery in old rodents induces prolonged changes in gene and protein expression and learning impairment that lasts days to weeks, implying either that the neurobiological machinery of memory is altered in an enduring way or that damage occurs.\textsuperscript{51-54} In addition, there is evidence that some volatile anesthetics promote processes implicated in the neuropathogenesis of Alzheimer’s disease\textsuperscript{55} including promoting formation and/or reducing clearance of $\beta\beta$, increasing $\beta\beta$ aggregation and oligomer formation, augmenting its neurotoxic qualities, and hyper-phosphorylating the microtubule protein tau (which also occurs with hyothermia).\textsuperscript{54,56,57-62} What this means clinically is unclear. Thus far, clinical studies reveal no difference in the risk of prolonged POCD between regional and general anesthesia\textsuperscript{63} and retrospective epidemiological studies report no link between general anesthesia (plus surgery) and the development or progression of Alzheimer’s disease.\textsuperscript{64,65} However, the studies are either underpowered or challenged on methodological grounds and should be interpreted cautiously.\textsuperscript{66} The fact that hospitalization for non-critical illness increases the risk of incident dementia\textsuperscript{67} makes it reasonable to worry that the same might be true for surgical illness, although it could also point to the importance of patient factors.

Indeed, what about the patient? Could it be they come to the OR with a cognitive deficit and we don’t know it? Absolutely! About 20\% of patients coming for elective total hip surgery meet criteria for MCI (mild cognitive impairment) and the incidence of cognitive impairment is probably twice that in patients having CABG surgery.\textsuperscript{68-70} These patients go undetected, however, because we don’t ordinarily perform a preoperative cognitive assessment.\textsuperscript{70,71} In addition, some studies indicate the type of surgery or anesthesia does not matter as far as POCD is concerned.\textsuperscript{72} Furthermore, when one examines the cognitive trajectory of patients with coronary artery disease who do or do not have CABG surgery, it turns out that over 5 years both groups decline but do so at the same rate.\textsuperscript{73,74} Therefore, the likelihood of experiencing cognitive impairment postoperatively may be determined more by preoperative cognitive status and comorbid conditions such as extent of cerebrovascular disease than the details of the surgery or anesthesia.

So, while we know a little about what it isn’t (e.g. cardiopulmonary bypass), we have no definitive answer for what causes perioperative cognitive morbidity. Patient, medication, and surgical factors are likely to interact in a way still poorly understood. What is clear is that like a “weak heart”, having a “bad brain” puts seniors at high risk for serious cognitive morbidity perioperatively—which is at least as debilitating and ominous as problems we worry about in other organ systems (e.g. low cardiac ejection fraction). Whatever the cause, the brain appears to take a ‘hit’ that manifests as volume loss in cortical gray matter and the hippocampus that lasts for several months.\textsuperscript{75} With this in mind, there is good reason for anesthesiologists and surgeons to be informed about the issue, as many of our elderly patients and their families are justifiably interested.
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Postoperative CNS Dysfunction: Stroke

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Stroke is an uncommon but potentially catastrophic complication in the perioperative period. A stroke is defined as a focal or global neurological deficit of vascular origin lasting more than 24 hours. A transient ischemic attack (TIA) lasts less than 24 hours and most less than a few hours. Because of the brevity we know nothing about the incidence of TIA after surgery. The frequency of stroke varies among surgical procedures: 0.08 - 0.7% after general surgery, 0.8 – 3% after peripheral vascular surgery, 2 – 5% after head and neck surgery, and 1.5 – 10% after cardiac surgery.

Important risk factors include age, previous stroke, vascular disease, hypercoagulable states, and atrial fibrillation. Fewer than 10% of strokes are apparent in the PACU. The majority manifests in a bimodal fashion, either in the first 24 hours or spread over the next days to weeks. Thus only a small percentage actually occurs intraoperatively. The etiology is not always clear because most of the current literature uses administrative databases to derive the incidence and the pathology is frequently not known or not documented. The vast majority when documented are embolic or thrombotic. The role of hypotension is hard to determine, as even watershed infarcts, the hallmark of hemodynamic strokes, are now believed to have an important embolic component. Hypotension is likely causative in some but is probably more often a compounding factor when it occurs. This applies to both intraoperative and postoperative strokes i.e. an embolic stroke associated with hypotension has a worse outcome. In a large stroke study, not an intraoperative study, every 10mmHg reduction in blood pressure below 150mmHg increased mortality by 18%.

The mortality from perioperative stroke ranges from 25 – 80%; the latter in patients with a previous stroke. The mortality from a stroke not associated with surgery is 10%. Delay in diagnosis is a likely contributing factor. Nurses are usually the first to detect neurological dysfunction but clinical neurological assessment is not a routine part of general surgical care. A further delay ensues between nursing informing the surgical team and the latter obtaining a neurological consultation. To address this, a growing number of hospitals have implemented a “code stroke” whereby nurses can get an immediate neurology assessment. Another important contributing factor is the fact that stroke is associated with a systemic inflammatory response and the greater the response, the greater the mortality. Surgery is also associated with a profound systemic inflammatory response and this presumably has a synergistic interaction with the similar response in stroke leading to a greater mortality.

There is no standard definition of hypotension in the anesthesia literature. Depending on the definition used, the incidence ranges from 5 to 99% of patients. This makes it difficult to determine the contribution of blood pressure to perioperative stroke and also the blood pressure threshold for treatment. Using the population lower limit of autoregulation is not recommended. The population average is approximately 70-80mmHg, which is much higher than shown in many current textbooks. Further the range is from 40 to 110mmHg making it impossible in any given patient to know their lower limit. A retrospective study by Bijker et al found a small but statistically significant relationship between a 30% reduction in mean blood pressure, but not systolic, from baseline and perioperative stroke. Using this threshold seems a reasonable approach.

A CT scan is the fastest way to confirm the diagnosis when perioperative stroke is suspected. The patient should be started on aspirin and moved to an ICU or intensive monitoring area. Many stroke patients die from cardiac arrhythmias so continuous monitoring and appropriate treatment are important. Most patients in the immediate postoperative period will not be candidates for intravenous thrombolysis with tPa. However they may be suitable for intracranial intra-arterial tPa if within 6 hours of the stroke and this should be discussed with the surgeon, stroke neurologist and interventional radiologist.

Further Reading:


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