Published in final edited form as:

Anesth Analg. 2011 May ; 112(5): 999–1001. doi:10.1213/ANE.0b013e3182160431.

Surgery and Anesthesia: Healing The Body But Harming The Brain?

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From the origins of surgical anesthesia in the 1840s through the late 1990s, the prevailing view has been that the brain emerged unscathed from the assault of surgery and the pharmacologic coma we call general anesthesia. Since then, the literature has been awash in studies suggesting that is not always the case and that sometimes, in an effort to heal the body, we might be harming the brain. However, when, why, and how this happens is a matter of considerable debate. That debate is winding up rather than down and is unlikely to be resolved anytime soon. In the spirit of fueling, if not resolving, the debate, the section on Neuroscience in Anesthesiology and Perioperative Medicine in this issue of *Anesthesia & Analgesia* pulls together a collection consisting of original work, reviews, a meeting summary, and an opinion piece that speak to various aspects of this subject. There is something here for everyone interested in the topic, and even for those who might just be curious, but before you dive into the specific manuscripts, we thought it would be useful to put them in the context of current themes/hypotheses about adverse perioperative cognitive outcomes.

The first theme has to do with the nature of the surgery or medication-induced brain dysfunction and whether it is clinically important. The brain, for all its complexity, has only so many ways to malfunction. Excluding stroke and seizures, which typically result from major physiologic or pathologic events, perioperative brain dysfunction manifests mainly as abnormalities in cognition/thinking. Postoperative cognitive dysfunction (POCD), a mild but possibly long-lasting cognitive foggiess that is "diagnosed" only by neurocognitive testing, is probably most familiar to the anesthesia community. Within the first week after surgery, 30–50% of patients have POCD, with no difference by age, and at 3 months after surgery about 10–15% do, but at this point the problem is limited to the elderly. (1,2) There is no consensus on the cause and, therefore, on whether the anesthesiologist can prevent or mitigate it. Indeed, because it is not a clinical diagnosis and the criteria used to define it are not uniform, there is debate about whether it even exists as a unique entity. Evered et al. (3) suggest in this issue of the Journal that POCD is, in fact, perhaps not a new or distinct entity because the incidence in older patients is similar after procedures of very different invasiveness/complexity (coronary artery bypass, elective hip replacement, and coronary angiography). Hence, they suggest the surgical experience just unmasks brain compromise that was already present preoperatively.

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The authors declare no conflicts of interest.

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Delirium, on the other hand, is a common and well-defined clinical syndrome. As reviewed in this issue of the Journal by Rudolph and Marcantonio (4) and Hughes and Pandharipande, (5) delirium occurs in up to 50–80% of elderly surgical patients, the criteria and tools to diagnose it are agreed upon, and it presages poor short- and long-term outcomes. Importantly, there is evidence that medication choices, depth of anesthesia, and treatment of pain can affect delirium risk. (4–7) Nonetheless, the anesthesia community has been somewhat inattentive to delirium, perhaps because it is erroneously believed to be a transient and unimportant condition. Nothing could be farther from the truth and the reviews by Rudolph and Marcantonio (4) and Hughes and Pandharipande (5) make it clear that there are opportunities to improve cognitive outcomes for patients at risk for delirium with seemingly small changes in patient management.

The cognitive consequences of surgical and anesthetic events in young children are the most enigmatic. That is because unlike the elderly, where cognitive syndromes (delirium and POCD) were identified first and animal studies looking at potential mechanisms followed, the sequence is reversed on the question of whether sedative and anesthetic agents are neurotoxic in young children. That worrisome story started with animal work and, because results of epidemiological studies examining an association between anesthesia and surgery during early childhood and learning disabilities later in life are few and conflicting, (8,9) it is not clear there is a clinical correlate. In essence, in the elderly we started with a victim (delirium, POCD) and are looking for a weapon whereas in children we started with a weapon (anesthetic/sedative drug-induced neurodegeneration in animals) and are searching for a victim (clinical problem).

Another major theme relates to the putative causes of adverse cognitive outcomes. There are three general theories: medications, surgery, and the patient. Evidence that our drugs are responsible is most consistent for developmental neurotoxicity. A major and consistent feature of the pathology in the developing animal brain following exposure to a variety of common sedative and anesthetic agents is both cell and synapse loss. (10–12) This has been convincingly demonstrated in cell culture models, rodents, and primates, even when systemic physiology is well-controlled, implying it is a direct effect of the medications. Learning and social deficits in adulthood have also been identified in animals exposed to sedative/anesthetic medications in the neonatal period.(10,13) As such, anesthetic-induced neurodegeneration is the prevailing theory driving concerns about general anesthesia in young children. However, even this is not straightforward; exposure to sedative/anesthetic medications after the peak of synaptogenesis increases synapse numbers (14) and, in *in vitro* work using human neuron-like cells and published in this issue of the Journal, Lin et al. challenge the idea that volatile agents injure neurons in humans.(15) There is also major disagreement about the ability of medications to cause long-lasting changes in the old brain. In mature brain, anesthetic-induced neuroapoptosis appears to be a minor event but accumulation of the neurotoxic proteins amyloid β and phosphorylated tau, both of which are implicated in the pathogenesis of Alzheimer disease, has been observed.(16,17) Likewise, persistent cognitive deficits have been reported in old animals after exposure to some common anesthetic agents. (18) However, as well-summarized by Eckenhoff in his report of the Second International Perioperative Neurotoxicity Workshop in this issue of the Journal, there is still considerable controversy about whether anesthetic agents contribute to development of POCD and dementia. (19) In contrast, as reviewed here by Rudolph and Marcantonio (4) and Hughes and Padharipande, (5) evidence is reasonably good that both specific sedative agents and depth of anesthesia can contribute to delirium.

The surgical theory of causation involves inflammation. This idea is obviously more appealing to anesthesiologists than accepting that our drugs are harmful. Moreover, there is ample evidence that under other circumstances inflammation can adversely affect cognitive

performance (consider the subtle cognitive cloudiness one often feels during a viral illness) and lead eventually to neurodegeneration. (20) Thus far, however, a relationship between surgery and subsequent cognitive dysfunction has been demonstrated experimentally mostly in young animals and over the short-term and the clinical story is circumstantial. Nor does the inflammation hypothesis exclude anesthetic agents as a potential cause of cognitive dysfunction because recent work indicates that some of these agents trigger neuroinflammatory changes in the brain. (21) It remains to be seen, therefore, whether inflammation explains cognitive dysfunctions that occur perioperatively but it is a viable hypothesis that deserves further study.

Perhaps the most intriguing recent theory about the cause of perioperative cognitive dysfunction in the older surgical patient is that it is their “fault” and has little to do with the surgeons or us. There is some face validity to this argument: even after the same surgery, delirium and persistent POCD are more common in old than young patients. And, it is not just about age alone. This is illustrated by manuscripts in this issue of the Journal by Leung et al. (22) and Jankowski et al. (23) showing, respectively, that preoperative frailty and cognitive impairment are independent risk factors for development of delirium postoperatively. Likewise, the report of Evered et al. (3) that shows a similar incidence of POCD in older patients after procedures of very different invasiveness points away from the surgical and anesthetic details and toward the intrinsic characteristics of the patient. This could have profound implications. If much of the cognitive dysfunction observed after surgery in elders is simply unmasking of a preexisting problem such as mild cognitive impairment, which afflicts about 1 in 5 community dwelling elders,(24) our terminology would have to change. POCD might be a misnomer because the condition may be neither “post” nor “operative.” “Illness-related cognitive dysfunction” may be a more accurate descriptor. More importantly, our focus would logically shift to identifying in advance those at risk. This is at the heart of a provocative Open Mind piece by Silbert et al. (25) in this issue. They essentially propose we use surgical preadmission test centers to screen patients for mild cognitive impairment or dementia much like we do for cardiovascular disease in at-risk groups. One approach would be to add cognitive evaluation to the routine preoperative assessment of elders, a course that would make good sense given the frequency and seriousness of perioperative cognitive morbidity in elders but that is not foolproof.(26) Another might be to take the lead on utilizing biomarkers to more accurately and reliably diagnose cognitive compromise (27) in order to make better informed clinical management decisions perioperatively. Regardless of what one thinks of these specific ideas, there is no disputing the general concept that with elders it is essential to explicitly consider the functional state of the brain both before and after surgery.

As the articles in the collection of this month’s issue of the Journal illustrate, there has been a remarkable transformation over the past 10–15 years in how we view the brain’s response to the duress of surgical illness, sedation, and general anesthesia. The spectre of cognitive dysfunction after noncentral nervous system surgery is alarming to patients, families, and anesthesiologists alike but it is also a strong motivator for learning more and doing better so our work to heal the body does not harm the brain. Please read, enjoy, and be stimulated by the articles in this month’s collection to do just that.

Acknowledgments

Funding: NIH RO1 GM088817 (GC) and KO8 GM077057 (DJC)

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