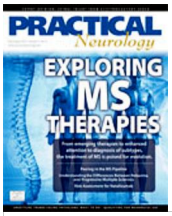

August 2012

Dementia Insights

Cognitive Complications of Elective Surgery and Anesthesia

By Ronald Devere, MD, FAAN

The first article in this series (see PracticalNeurology. net) discussed the cognitive changes that can accompany acute non-neurologic hospitalization. This second article will discuss the cognitive complications that can arise during elective general surgery and anesthesia (perioperative period).

As the aging population continues to increase, the frequency of elective surgery will continue to rise. It is important that clinical neurologists be aware of the potential cognitive complications that can arise from these surgeries and anesthesia. This is an important clinical concern because of its potential to cause morbidity to the patient and family and the challenge to the neurologist to determine if the cognitive impairment that develops is part of an ongoing degenerative brain disorder (MCI, Alzheimer's, etc.), or a likely resolving cognitive impairment.

Postoperative cognitive impairment was described in 1887 by George Savage, who said that this event can contribute to "mental insanity."[1] The most detailed studies to help address this disorder have only been in the last 15 years.[2,3] Post operative cognitive decline (POCD) has been recognized to occur in two patterns:

- Acute cognitive dysfunction (acute early post operative delirium)
- Chronic and more persistent POCD.

Acute post-operative delirium is characterized by inattention, disorganized thinking, and altered level of consciousness. Behavior may be hyperactive or hypoactive, the latter being more common. This post operative delirium is associated with increased mortality, greater dependency needs and cost, and prolonged hospitalization.[4,5] Increased risk for acute post-op delirium are: older age, male gender, preoperative depression, anxiety, tobacco use, alcohol and drug abuse, length of surgery, pain management, sleep deprivation and metabolic derangement.[1] Marcantonio, et al. developed a scoring system to predict onset of delirium before surgery is done, incorporating numerous risk factors.[6] They report a nine percent post-op delirium in elective non-cardiac, non-orthopedic surgery in the first five days. After orthopedic surgery, they report a 41 percent incidence of post op delirium.

The good news in general is that these acute cognitive changes, with or without delirium, are usually short lived, with preoperative cognitive function returning within days to weeks.

Chronic POCD is more prolonged, looks like a neurodegenerative disorder, and is best diagnosed by Neuropsychological testing. The testing frequently shows short- and long-term memory impairment, impaired executive function, impaired fine motor coordination, and depression. Chronic POCD also correlated with longer hospitalization and greater co-morbidities.[7] A large multicenter study on POCD in patients over 60 years reported memory loss in 26 percent of cases after one week, 10 percent after three months, five percent at six months, and one percent at 12 months.[3] This study however was not compared to a control group of surgical patients not having elective surgery. Johnson, et al.[8] in 2002 stated that 20 percent of middle aged patients experienced cognitive decline one week after non-cardiac surgery, compared to four percent in the non-surgical group used as a control. At three months, the incidence was six percent and control four percent—a non-significant difference. They also found that at three months, 29 percent of the post-op surgical patients had subjective-only cognitive complaints compared to the non-operative surgical group. This was felt to be due to depression. Their conclusion was that chronic POCD occurs not infrequently, but usually resolves to the preoperative level within three months. In 2008, Price, et al.[9] studied 308 patients 60 years of age or older undergoing elective major surgery. At three months, 14 percent experienced memory decline only, 8.5 percent had executive dysfunction only, and three percent showed decline in both. Sixty two patients were elective surgery candidates but served as controls without surgery.

TOP 5 ARTICLES FROM AUGUST 2012

TYSABRI AND MS: PUTTING THE ODDS IN THE PATIENT'S FAVOR
A recent analysis has created a better profile of who can receive Tysabri and when.
by Q&A with Robert J. Fox, MD

TRANSCRANIAL MAGNETIC STIMULATION BENEFICIAL IN MAJOR DEPRESSIVE DISORDER

RELAPSING AND PROGRESSIVE MULTIPLE SCLEROSIS: UNDERSTANDING THE DIFFERENCES
Accurate diagnosis is important in order to adjust treatment according to MS type as wells as individual response.
by Flavia Nelson, MD

EMERGING OPTIONS FROM THE MS TREATMENT PIPELINE
The MS pipeline is full of potential. Which therapies will be on the front line in tomorrow's battle against MS?
by Zac Haughn, Senior Associate Editor

BAPINEUZUMAB: DOWN BUT NOT OUT

In addition, this study looked at instrumental activities of daily living. Cognitive decline at three months after surgery impaired ADLs, especially in those cases with executive dysfunction and in those with memory and executive dysfunction in combination. The ISPOC1 study[3] drew a similar conclusion on ADLs. The patients needed help in 6/7 IADLs, such as commuting, shopping, meal preparation, housework, taking medicine, and handling finances. Monk, et al.[10] found that at three months after surgery, POCD was present in six percent of young patients, six percent in middle age, and 12 percent in the elderly. The prevalence of cognitive dysfunction in the age-matched controls was similar in the young and middle aged but significantly higher in the elderly. The study found independent risk factors for POCD at three months: increased age, lower educational level and history of stroke with no residual. The ISPOC13 study drew the same conclusion.

Cognitive Outcomes After Coronary Artery Bypass Surgery (CAB)

Studies have shown that many patients referred for CAB surgery are older and have more extensive extra-cardiac vascular disease.[11] Recent large prospective studies have not shown any reduced risk of complications using off pump surgery, a considerable concern 25-30 years ago as a cause of POCD. In an extensive review of this subject in 2012, Selnes, et al.[11] stated that contemporary studies have included control groups such as patients with and without risk factors for cerebral vascular disease who have and have not undergone CAB surgery, patients who have undergone percutaneous coronary intervention, those with off pump surgery and those who had no cardiac surgery. Preoperative cognitive studies in CAB surgery have found cognitive impairment in many patients that ranges from 20-40 percent that varies with age, presence of hypertension, and level of education. Preoperative MRI of the brain have shown small vessel ischemic disease and lacunar infarcts. These patients have shown to have worse post-operative cognitive impairment than those with normal preoperative findings. The general overall feeling at this time is that when POCD occurs in CAB surgery, it is not due to the use of cardiac pulmonary bypass or cardiac emboli, but the cause is poorly understood. The majority of patients who develop POCD can be reassured that this will resolve within one to three months based on neuropsychological testing. Subjective memory changes can still be present. Those with POCD who continue to have residual cognitive impairment and have been compared to non-operative controls have been shown to have increased risk and the presence of preoperative cerebral vascular disease. These risk factors need to be more seriously addressed if we want to reduce POCD in these cases. These risk factors include:

- Atheroma of the ascending aorta
- History of TIA and moderate to severe carotid stenosis
- History of Diabetes
- History of high blood pressure
- Smoking
- Intraoperative decreased blood pressure
- Cardiopulmonary bypass greater than two hours
- Post operative atrial fibrillation

Cause of Post-operative cognitive decline

In a very extensive review about POCD, Terrando, et al.[1]state, “Although age and surgery are consistently reported as important risk factors in the development of POCD, the etiology remains unclear and some question its significance. Studies exploring contributory factors have methodological problems including being underpowered and lacking appropriate controls. Furthermore, because of the differences in neurocognitive testing and threshold for diagnostic cognitive dysfunction, comparison of studies and hence prioritization of risk factors have been difficult.”

What do we know at this time about the possible causes of POCD? Is it the surgery or anesthesia or both? There is some evidence that in surgical cases, there is elevation of pro-inflammatory cytokines in the central nervous system and in the general circulation that may correlate to cognitive dysfunction.[1] Most surgeries, such as cardiac and orthopedic, can lead to considerable blood loss, and injury to tissue which can cause the immune system to muster an inflammatory response. In mice, increased expression of IL-1B (interleukin 1B) in the hippocampus after surgery is associated with cognitive decline. It has been shown that microglia (the resident immune competent cells) shift from a resting to a reactive state in the presence of inflammation. These activated microglia can release protective anti-inflammatory molecules, they also can secrete proinflammatory cytokines like IL-1 and tumor necrosis factor, excitotoxins like glutamate, and neurotoxins like amyloid precursor protein.

These activated microglia can also inhibit neurogenesis in the hippocampus, impairing synaptic function and repair. These changes after surgery are usually self limited. The reason why these changes can be enhanced and persistent in some patients is not clear. Perhaps this is due to advanced age or an underlying systemic disease. Even the normal inflammatory response after surgery may have long lasting detrimental effects in the presence of underlying neuropathology which is clinically present or not. There is some evidence that the neuro-inflammation that occurs after surgery likely has two phases: proinflammatory and anti-inflammatory.[1] If the proinflammatory response is unaccompanied by the anti-inflammatory response for some reason, this can lead to persistent cognitive decline.

What about the role of anaesthesia causing POCD?

Wang, et al. in 2011[11] devoted their whole paper to the inhibition of learning and memory by general anesthetics. Low concentrations of isoflurane (one fifth the concentration for immobilization) with or without nitrous oxide, servoflurane, and propofol each impaired immediate and delayed recall in healthy volunteers. Intravenous low doses of ketamine at various low doses reduced memory performance for word recall in healthy volunteers. Various amounts of low anesthetic dose can affect memory storage and memory encoding (immediate memory). Functional magnetic resonance imaging in humans has been shown to suppress memory-related regions, such as visual cortex, thalamus, hippocampus, and the supplemental motor area. The same has been shown in animal studies. In general, the older the human volunteers and animals were, the more pronounced memory deficits occurred.

Intermediate and long term memory depends on Long term Potentiation in the hippocampal neurons in addition to glutamate, NMDA and gamma amino butyric acid receptors, and the development of new proteins by the DNA of the neuron. General anaesthetics have been shown to target different parts of the memory system. For example, ketamine and nitrous oxide inhibit NMDA receptors but no effect on the GABA receptors. Propofol and barbiturates intravenously enhance the GABA receptor function similar to the volatile anaesthetics (isoflurane, sevoflurane, and desflurane). Memory impairment can last from 48-72 hours in these studies.

General anesthesia agents, like isoflurane and sevoflurane, have been shown to enhance Abeta oligomerization and accumulation in cultured cells in brain tissue of neonatal mice and Alzheimers disease transgenic mice, especially in the presence of nitrous oxide. This can lead to cell death, and along with anesthesia induced hypothermia can lead to tau phosphorylation. The anesthetic propofol can increase tau phosphorylation on its own. Other articles have suggested that anesthesia is not associated and does not promote neurodegeneration. This is supported by randomized clinical trials in older patients undergoing major non cardiac surgery, have reported the same incidence in POCD after regional or general anaesthesia. There is animal data that suggests that phosphorylated tau levels can impair axonal transport and Abeta as a copathogen to mediate neurotoxicity and cognitive impairment. This uncontrolled aggregation of these peptides ultimately disrupts brain homeostasis by limiting availability of nutrients and trophic factors to the neurons. This whole process of neuroinflammation, activation of microglial cells, and release of proinflammatory mediators contributes to disease development in Alzheimers disease. There however is not a definite link between anesthesia and Alzheimer's pathogenesis in humans.[11,12]

What does all this information really mean for clinical neurologists who see these patients in the immediate postoperative period and/or later in time, for problems with cognition? The answer is best summarized and quoted in Bittner's 2010 study[12]: "All the available evidence at this time suggests a possible association between anesthesia, surgery and long term cognitive effects. No study has confidently shown that general anesthetics administered at clinically relevant doses and for clinical relevant durations cause neurotoxicity in humans. There is no scientific basis for either recommending or contraindicating specific anesthetic agents or techniques on the basis of neurotoxicity or risk of cognitive morbidity in the elderly. The best steps clinicians should do is encourage our anesthesia colleagues to use the lowest possible effective doses and concentrations of anesthetics according to the individual patient needs. Encouraging regional anesthesia instead of general anesthesia is no better because POCD occurs equally in both types."

Future research in postoperative cognitive decline will benefit from future preclinical, clinical, and epidemiological experiments. In preclinical studies (animal models), it will be necessary to confirm that factors that increase the likelihood of POCD in humans, including advanced age and post-operative infections, are similar in animals. Animal models should reproduce the clinical setting by introducing sleep deprivation, addition of sedatives and analgesics that have their own cognitive effects.

How does diabetes and obesity affect POCD in animals? In the clinical studies, it will be important to confirm that any changes that occur in animal models also occur in surgical patients. In epidemiological studies, the contribution of ethnic, lifestyle and socioeconomic factors to the development of POCD is needed.

Conclusion

The incidence of POCD will continue to rise as more surgeries are required in the elderly. As Terrando, et al.1 state,"We are only now beginning to scratch the surface of the diagnosis, causation and prevention strategies to prevent and treat POCD. For POCD to be successfully counteracted, coordinated efforts will be required from experts in aging, neuro-degeneration, vasculopathy, inflammation, neuroimaging and the humane genome, working in conjunction with surgeons, anesthesiologists and primary care physicians. It is pivotal to establish multidisciplinary collaborations to confront a clinical problem with enormous patient suffering and societal consequences."

Dr. Devere has no relevant disclosures.

Ronald Devere, MD is Director of the Taste & Smell Disorders Clinic and Alzheimer Disease and Memory Disorders Center in Austin, TX.

1. Terrando, N, PhD; Brzezinski, M, MD, PhD; Degos, Vincent, MD,PhD, et al; Perioperative Cognitive Decline in the Aging Population, Mayo Clinic Proceedings, September 2011; 86(9): p885-893.
2. Rasmussen, LS, Johnson, T, Kuipers, HM et al; Does Anesthesia cause postoperative cognitive dysfunction? A Randomized study of Regional vs General Anesthesia in 438 Elderly Patients. Acta Anesthesiology Scandinavia, 2003;47(3); P2260-266.
3. Moller, JT, Cluitmans, P, Rasmussen, LS, et al; Long Term Postoperative Cognitive Dysfunction in the Elderly: ISPOCD1 Study. Lancet 1998; 351(9106): p857-861.
4. Fong, TG, Tulebaev, SR et al; Delirium in Elderly Adults: Diagnosis, Prevention and Treatment: Nat Rev Neurol. 2009;5(4):210-220.
5. Ely, EW, Shintani, A, et al; Delirium as A Predictor Of Mortality in Mechanically Ventilated Patients in The Intensive Care Unit. JAMA, 2004;291(14):1753-1762
6. Mercantonio, ER, Goldman, L. et al; A Clinical Prediction Rule for Delirium after Elective Non Cardiac Surgery. JAMA. 1994; 271(2):p134-139.
7. Steinmetz, J, Christensen, KB, Lund, T. et al, Long Term Consequences of Postoperative Cognitive Dysfunction. Anesthesiology 2009; 110(3): P 548-555
8. Johnson, T, Monk, T, et al; Postoperative Cognitive Dysfunction In Middle Aged Patients. Anesthesiology. 2002; 96 (6): p1351-1357.
9. Price CC, Garvan CW, Monk TG, Type and Severity of Cognitive Decline in Older Adults after Non Cardiac Surgery. Anesthesiology, 2008; 108 (1) p.8-17
10. Monk, Terri G., Weldon, Craig et al; Predictors of Cognitive Dysfunction after Major Noncardiac Surgery. Anesthesiology 2008; 108:p18-30
11. Gasparini M, Vanacore N, Schiaffini C. et al; A case control study of Alzheimer's Disease and exposure to anesthesia; Neurological Science 2002; 23: p 11-14
12. Bohnen N, Warner MA. Early and Midlife Exposure to Anesthesia and the Age of Onset of Alzheimer's Disease. International Journal of Neuroscience 1994; 77: p181-185.

Bryn Mawr Communications III LLC
1008 Upper Gulph Road, Suite 200
Wayne, PA 19087

Phone: 484.581.1800
Fax: 484.581.1818
Privacy/Legal Disclaimer

Subscription
Advertising

Website design by Sides Media Studio.