Revista Mexicana de Anestesiología

CONFERENCIAS MAGISTRALES
Vol. 33. Supl. 1, Abril-Junio 2010
pp S249-S253

Postoperative cognitive dysfunction

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Postoperative cognitive dysfunction (POCD) is a decline in a variety of neuropsychological domains, especially in memory and executive function, but also is characterized by a slowing of brain processing speed. POCD is a distinct entity from postoperative delirium. The hallmarks of delirium are an acute state of confusion with alterations in attention and consciousness. The literature is sometimes confusing in that the two terms are sometimes used interchangeably leading to imprecision in the discussion of etiologies and potential prevention or amelioration of POCD. Though POCD is a common finding after surgery and anesthesia there is currently no ICD-9 code for this disorder/syndrome.

Postoperative cognitive dysfunction affects both young and old who present for surgery; however, the elderly have an increased incidence of this disorder due to less plasticity in the aged brain. As the world population ages, the burden imposed by POCD will become increasingly more apparent. Twenty to thirty percent of those having surgery are over 65 and there are approximately 234 million operations per year worldwide, we can assume that some 50 million of those undergoing the knife will be aged. This number is staggering if we consider that some 10% of the elderly will exhibit persistent cognitive defects 3 months after surgery. Taking 50 million and multiplying that number by 10% will leave some 5 million elderly vulnerable to the effects of POCD. Those effects challenge the elderly with ability to perform activities of daily living, interfere with work responsibilities, and may lead in higher mortality rates in those with persistent cognitive changes.

One of the earliest publications on the issue of POCD and its attendant consequences was by PD Bedford[1] published in the journal *Lancet* in 1955. This publication was not a rigorous, randomized trial, but rather the personal observations of a single physician. The goal of the paper was to investigate the role played by general anesthesia in the development of dementia in the elderly after surgery. Dr. Bedford catalogued some 4,250 patients over the age of 50. 1,193 of these hospitalized patients had undergone an operation that employed the use of general anesthesia. Of the 1,193 patients, 410 patients, or one-third, had a near relative allege that the patient «had never been the same since the operation». The statement was considered «unjustified» by the author in 290 cases, leaving some 120 cases for further review. 29 of the patients developed extreme dementia in which the patient became a virtual «human vegetable». This publication was retrospective, based on personal observations. No sophisticated neuropsychiatric testing was performed nor was there any attempt at distinguishing dementia from a cerebrovascular event. The author stated that the catastrophe did not seem to be a direct function of the anaesthetic used, nor of the severity nor duration of a potential hypotensive state, but rather an individual's idiosyncratic reaction to many different factors. The author cautioned the elderly (those over 50) to avoid surgery.

The aging brain is vulnerable. The neuronal density decreases some 30 percent by the age of 80. The level of several important neurotransmitters such as acetylcholine, dopamine, and serotonin decrease as well as the concomitant increase in age-related diseases such as Alzheimer's, Parkinson's, and the increased incidence of cerebral arteriosclerosis as one ages.

Anesthetic agents such as ketamine and GABA agonists have been implicated in neuroapoptosis[2] in animal models, whereby the anesthetics affect translocation of Bax proteins in mitochondrial membranes, leading to increased membrane permeability, allowing extra mitochondrial leakage of cytochrome c, followed by activation of Caspase 3 and neuroapoptotic cascade.

A number of non-pharmacologic risks factors have been associated with POCD or delirium. These include patient related factors such increasing age, prior cognitive impairment, depression, and low educational level. Intraoperative factors can also impact POCD such as cardiac surgery and the implications of cardiopulmonary bypass on the brain as

well as longer anesthetic administrations. Postoperative factors have also been cited and these involve poorly controlled pain, respiratory complications and postoperative wound infections, as well as a reoperation within a week of the original procedure. Nonsignificant factors may be choosing between a general and regional anesthetic, and postoperative hypoxemia or hypotension[3].

A large number of medications have been implicated in POCD. These include opioid analgesics (meperidine, fentanyl, morphine), sedative agents (benzodiazepines and barbiturates), antihistamines (diphenhydramine and hydroxzine), and even nonsteroidal anti-inflammatory drugs. Drugs affecting cholinergic transmission within the central nervous system are prime causes of POCD and these include anticholinergic agents (atropine and scopolamine), antiparkinsonian agents (benztropine and levodopa), neuroleptics (clozapine, thioridazine, and chlorpromazine), tricyclic antidepressants (amitryptiline and imipramine), Class 1A antiarrhythmics (digoxin, beta-adrenergic antagonists), and H-2 antagonists (cimetidine and ranitidine).

At least three studies have demonstrated a 1.2 to 1.6 odds ration between Alzheimer's disease and prior surgery. However, each of the three studies was underpowered to reach statistical significance. The presumed mechanism is a uncontrolled oligomerization (micro aggregation) of normally present peptides or proteins. In 2008 a meeting of leading physicians and scientists met in Philadelphia, Pennsylvania with the purpose to study the potential relationship between anesthesia and the onset and progression of neurodegenerative disorders such as Alzheimer's disease. The consensus statement concluded that there exists sufficient evidence at multiple levels to warrant further investigations of neurodegeneration after anesthesia and surgery.

A landmark articlev[4] in the field of postoperative cognitive dysfunction was published in the journal Lancet in 1998 by the International Study of Postoperative Cognitive Dysfunction (ISPOCD) investigators. This study examined 1218 patients at least 60 years of age at 13 European hospitals from 8 countries that presented for major abdominal, non-cardiac thoracic, or orthopedic surgery under general anesthesia. Patients completed a battery of neuropsychological tests before surgery, and then 1 week and 3 months after surgery. Oxygen saturation was measured before surgery and then throughout the day and then the first 3 nights after surgery. Blood pressure was also measured every 3 minutes during surgery and for 15-30 minutes for the rest of the postoperative day and night. POCD was elicited in 25.8% of patients one week after surgery and in 9.9% of patients 3 months after surgery compared to a control group that did not have surgery and had an incidence of cognitive changes of 3.4% at 1 week and 2.8% at three months. Increasing age, duration of anesthesia, less formal schooling, a second operation, and postoperative respiratory infection were significant factors for POCD. The presence of hypoxemia and hypotension were not significant risk factors for POCD at any time point. Terri Monk[5] repeated this study, which was published in the journal of Anesthesiology in 2008. She found similar results to the ISPOCD investigators, however, she found that patients who exhibited POCD at hospital discharge and at three months post surgery had a statistically higher incidence of mortality (> 10%). She attributed this finding to the fact that cognitive decline may be an independent predictor of mortality due to patients not being adherent to medications or physical therapy regimens or to the fact that patients with POCD might not follow up with essential postoperative care.

Patients do suffer cognitive changes after surgery and anesthesia. The question is it because of the anesthetic per se or because of inflammatory changes induced by surgery that we see these changes. A study out of Chicago by Buvanendran[6] attempted to answer this question. This was a study of patients undergoing total hip arthroplasty under intrathecal analgesia. The authors of the study then measured inflammatory markers form the cerebrospinal fluid, blood and wound drainage. What they found was that CSF concentrations of prostaglandins and interleukins were significantly increased from baseline, indicating inflammatory changes brought about by the surgical procedure.

The field of neuropsychiatric testing for determination of POCD is complicated by the lack of an adequate definition of the disorder and a myriad of tests (greater than 50) that can be used to discern if changes indicative of POCD have occurred. The question becomes which test or battery of tests should be used, what cognitive domains should be studied (language, perceptual organization, executive function, learning, memory, psychomotor function, attention, concentration, and emotionality) and which battery of tests is most indicative of a change and how significant is the change from baseline. A study by Rasmussen, one of the original ISPOCD investigators, looked at this issue. He found that up to 40% of a control group not having surgery and anesthesia could have signs of cognitive dysfunction based on the battery of tests employed and what is regarded as significant change in those tests. Even in the best-designed studies some 3% of controls will exhibit signs of cognitive decline.

Often times we hyperventilate patients in the operating room. Hyperventilation will result in the patient being hypocapnic. This may have several potentially detrimental effects, such as decreased cerebral blood flow, decreased oxygen delivery because hemoglobin has a greater affinity for oxygen in an alkalotic environment, and hypocapnia may also lead to increased neuronal excitability. An early study out of Finland[7], examined the effects of carbon diox-

ide concentrations on recovery after general anesthesia. The study looked at 60 patients and divided the patients into three groups: hypercarbic ($PaCO_2$ at 54.9 mmHg), normocarbic, and hypocarbic (27.8 mmHg). The study found that patients that were allowed to become hypercarbic had quicker return of reaction time and a better sense of well being. The authors theorized that hypercarbia might be beneficial because of its central excitatory effects, as well as improved cardiac output and brain perfusion. They cautioned that hypercarbia might be detrimental in those with heart disease who might not be able to tolerate increased cardiac output and those patients with potential increases in intracranial pressure. A recent study from Anesthesiology[(8)] looking at an animal model of cerebral ischemia found that rats exposed to mild and moderate (80-100 mmHg) hypercapnia after an ischemic insult had better neurologic scores and fewer structural changes on histopathology examination. However, rats with severe hypercapnia had worsened cerebral edema. The authors speculated that hypercapnia though might increase intracranial pressure does improve tissue perfusion and oxygenation, and mild hypercapnia may have anti-inflammatory and antioxidant effects. These two studies should not change our practice yet but does provide interesting theoretical ideas that should lead to more research in this area.

Does regional anesthesia provide a benefit in reducing the burden of POCD? A by Heyer[(9)] looked at patients undergoing carotid endarterectomy under regional anesthesia with dexmedetomidine as a sedative agent. They compared these patients to patients undergoing coronary angiography and also a historical control group. The authors found that patients undergoing CEA under sedation had significantly worse cognitive function on postoperative day 1, which was worse than patients undergoing angiography. The incidence of 25% of worsened cognitive outcome was similar to a previous study by the authors of patients undergoing CEA under general anesthesia.

The classic article comparing the comparative effects of general versus regional anesthesia and the impact on POCD on outcome was published in JAMA in 1995 by Williams-Russo[(10)]. This well-designed study looked at 262 patients randomized to either general anesthesia or epidural anesthesia for a single surgical procedure: total knee arthroplasty. Neuropsychological tests were performed at baseline, at one month, and then at 6 months. 5% of patients in each group had a significant deterioration in cognitive function at 6 months; however, the choice of anesthetic did not affect the risk of whether or not a patient was to develop POCD. The authors hypothesized that the most likely mechanism of cerebral injury after surgery was cerebral ischemia, but did not examine in detail blood pressure changes in either group or any perioperative desaturation leading to the potential for POCD. The authors also did not control the amount of sedation for the patients in the epidural group; patients received midazolam and fentanyl at the discretion of the caregiver. As we all know the level of sedation obtained from the combination of these two drugs could be tantamount to a general anesthetic.

Christopher Wu out of Johns Hopkins University published a meta-analysis[(11)] of cognitive outcomes between general and regional anesthesia. He included 24 studies in his analysis with a total of 12,917 patients; 19 trials were randomized, controlled trials, and 4 were observational. One trial was a combination of the two methods. 23 out of 24 studies did not find a difference in outcome between regional and general anesthesia. A later meta-analysis by Bryson[(12)] reviewed the literature form 1995 to 2005 and graded each study using the Jadad scoring system (randomization, blinding, and accounting for withdrawal with a maximum score of 5, with a score of 3 or better considered a quality study). His analysis of 16 trials found only 3 with a Jadad with a score of 3 or better. Only one study of 60 patients found a greater cognitive decline after general anesthesia, but the trial did not employ sophisticated cognitive testing but rather relied on a bedside clinical assessment of the patient's mental status by either a family member or a clinician. He concluded «best available evidence indicates that the choice between regional and general anesthesia bears no statistically significant influence on the likelihood of postoperative cognitive dysfunction».

Intuitively it would make sense to believe that regional anesthesia would be superior to general anesthesia vis a vis cognitive changes but the reasons for there not being a difference may be because of several factors: neuraxial anesthesia is a brief unimodal intervention along the perioperative time period; many factors influence the results of neuropsychological tests; patient drop out may be a factor; almost all studies of regional anesthesia allowed sedation along with the regional technique; postoperative pain management was not well controlled; and finally, it may be the insult of surgery per se rather than the anesthetic that leads to POCD.

Unfortunately, few studies have tried to use multimodal postoperative analgesia to blunt the inflammatory response after surgery. Surgery itself produces a complex neuroendocrine, inflammatory and coagulation cascade response. Methods to blunt these changes may be more important than solely the choice of anesthetic. A retrospective study out of the Mayo Clinic[(13)] looked at a multimodal approach to postoperative pain management. The pathway included peripheral nerve blocks such as lumbar plexus or sciatic nerve block and non steroidal anti-inflammatory drugs in patients undergoing joint arthroplasty. The patients who had a continuous regional anesthetic postoperatively combined with

avoidance of opiate medications had a shorter hospital stay, earlier ambulation, improved ranged of motion, and lower perioperative pain scores. This occurred despite the fact that the study group had a large portion (69%) of patients having general anesthesia for the surgical procedure. While the study did not strictly examine neurocognitive outcomes via testing the fact that patients had improved markers of recovery may be the more important outcome.

Opiates may be a prime culprit in poor postoperative cognitive outcomes. Opiates are well known to cause respiratory depression and have the potential for addiction. But as importantly may disrupt sleep, lessen refreshing REM sleep and worsen pain by causing hyperalgesia and thus creating a vicious cycle of more opiates, poorer sleep, etc. Opiates affect sleep by decreasing adenosine levels in the pontine reticular formation and basal forebrain.

Are there methods or medications that we can employ to improve cognitive outcomes after surgery? One small study by Wang[14] titrated isoflurane using a BIS monitor. Patients were divided into a BIS group with a target of 50-60 versus a control group using standard practice. Hypertension was treated either with opiates or IV antihypertensive agents. The group that had the BIS monitor used 30% less cumulative isoflurane and had an earlier time to discharge from the PACU. However, no differences were found in several neuropsychological tests. However, the tests employed may have not been sensitive enough to determine if there was indeed a difference between the two groups. Another study in contradistinction by Farag[15] asked the question are we not giving enough anesthesia? The theory being that allowing the brain not to be completely quiescent allows portions of the brain to fire seeking synaptic connections and by not finding these connections these synapses entered into an apoptotic cascade of death. Farag randomized two groups to receive either a high BIS target of 50-60 versus another group with a low BIS of 30-40. He found that patients in the lower BIS group performed better on processing speed indices at 4-6 weeks postoperatively. Unfortunately, both of these two fascinating studies have not been repeated in a larger formal study.

Other modalities of anesthesia care may provide improved outcomes. These have included the use of cerebral oximetry, the avoidance of inhalational anesthetics and instead conduct anesthesia with propofol, dexmedetomidine, lidocaine, etc. Thee studies have been small but may give tantalizing proof to altering our anesthetic plan to help cognitive recoveries. However, a wonderful editorial by David Warner[16] out of the Mayo Clinic argued that general anesthetics are protective against acute brain injury. He argued that anesthetics are weak antagonists of glutamate at NMDA receptors, reduce oxidant stress, inhibit spontaneous depolarization in focal ischemic areas, favorably redistribute cerebral blood flow and reduce oxygen consumption in the brain. In essence why is general anesthesia protective in models of cerebral ischemia but not in the realm of POCD.

What is the long-term sequelae to POCD? A study by one of the original ISCOPD authors[17] did a long-term follow-up of patients from the original ISPOCD study. Some 336 patients greater than 60 were evaluated. 10.4% had a cognitive decline at an average of 532 days post surgery, however, only 0.9% had a cognitive declines measured at all time points (7 days, 3 months, and 1-2 years postop). This is reassuring in that though patients do exhibit cognitive changes after surgery and anesthesia these changes may not be permanent.

A recent study[18] looked at the risk of surgery and anesthesia and its long-term implications on the risk of development of Alzheimer's disease. This study out of Washington University in St Louis, Missouri followed 575 participants for up to 21 years. Patients were divided into three groups: one group underwent anesthesia and surgery; another group was admitted to the hospital sometime during the 21 year time span for a major medical illness but did not have surgery; and the third group had neither surgery nor was admitted to the hospital for a major medical illness. The author found that there was no increase in progression to dementia in any of the three groups. This study was unusual in that most studies in the field of POCD looked at patients with no preexisting cognitive dysfunction. There are a few criticisms of the study: it was a database study; dropout from each group cannot be determined from the study; the group that had surgery was younger than the group admitted to the hospital; and finally the study participants had a higher level of education than the general public and this may have contributed to the lack of a difference. Finally, this study looked at a significant cognitive decline, Alzheimer's, and did not examine lesser cognitive changes that could occur after surgery and anesthesia.

Postoperative cognitive dysfunction poses significant burdens to patients, their families, and society. The issue is whether it is the result of anesthesia or rather the stress and inflammatory response created by patients having surgery. An important question is there techniques or monitoring that can reduce the incidence of POCD? What we do know is that much more work needs to be done in this field as most clinical studies have not been of appropriate design or quality.

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