Does Regional Anesthesia Lead to Better Postoperative Cognitive Function in the Elderly Patient than General Anesthesia?

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In 1955 P.D. Bedford published in the journal *Lancet* a classic article on the issue of postoperative cognitive defects in the elderly after general anesthesia.[1] He described that out of 1193 patients who had undergone general anesthesia 410 patients (34%) had never been the same after their operation. He found that 18 patients had suffered such extreme dementia that each had become a "human vegetable." The article while thought provoking was of a retrospective nature of one individual's personal experience. There was no control group or any attempt to do a detailed psychometric testing.

With aging there is a reduction in neuronal density such that by the age of 80 there is a 30% loss of brain mass. The concentration of receptors of several neurotransmitters also decreases as we age. The number of serotonin receptors in the cortex decreases, there is a reduced level of acetylcholine in several areas of the brain; dopamine levels in the substantia nigra and neostriatum also decrease. Age-related diseases such as Alzheimer's and Parkinson's increase as well as the incidence of cerebral arteriosclerosis that might place the elderly brain at increased risk of postoperative cognitive dysfunction (POCD).

In the United States 20% of the population will be older than 65 by the year 2030, and 21% of individuals older than 60 will undergo a surgical procedure sometime in the remainder of their life. There are 234 million major surgeries per year worldwide in developed countries.[2] Depending on the country and its population of elderly some 20 to 35% of all surgeries will be on those older than 65. If one then assumes that at a minimum some 45 million elderly patients receive an anesthetic for their surgery yearly and the risk of demonstrable cognitive change after surgery is approximately 10% (meaning almost 5 million at risk individuals a year) one can see that this is a major health crisis and one that has not seen enough discussion or research into its causes and solutions.

There are a myriad of nonpharmacologic risks factors for POCD. These include patient-related factors such as increasing age; prior

cognitive impairment from depression or a low educational level; intraoperative factors such as cardiac surgery, release of inflammatory mediators, and longer duration of anesthesia; postoperative factors such as pain, respiratory complications, infections, and reoperations within one week; and two factors that have not borne out to be a cause of POCD: perioperative hypoxemia and hypotension.

Several classes of medications have been associated with cognitive decline. These include opiates such as meperidine, fentanyl, and morphine; sedative-hypnotics such as benzodiazepines and barbiturates; antihistamines including diphenhydramine and hydroxyzine; even the nonsteroidal drugs naproxen, ibuprofen, and indomethacin; and finally drugs that affect cholinergic transmission in the central nervous system such as anticholinergics comprised of atropine and scopalamine; antiparkinsonian agents benztropine and levodopa; the neuroleptics clozapine, thioridazine, and chlorpromazine; tricyclic antidepressants such as amitryptiline and imipramine; Class 1A antiarrhythmics including digoxin, beta-adrenergic antagonists; and finally H-2 receptor antagonists such as cimetidine and ranitidine.[3]

One of the most important studies in the field of POCD was the International Study of Postoperative Cognitive Dysfunction (ISCOPD1) study published in the journal Lancet in 1998.[4] This landmark multicenter and multinational study examined 1218 patients at least 60 years of age scheduled for non-cardiac surgery. Neuropsychological tests were performed before surgery, and then at one week and 3 months postoperatively. The patients also had continuous pulse oximetry and blood pressure monitoring for three nights after surgery. While the presence of hypotension and hypoxemia did not lead to an increased risk of cognitive decline the odds of having POCD increased with increasing age, duration of anesthesia longer than one hour, and an educational level less than high school in patients having cognitive decline one week after surgery. At three months after surgery the presence of old age and the use of benzodiazepines before surgery increased the risk of cognitive decline. The chance of POCD one week after surgery was 23% in those aged 60-69 and increased to 29% in those older than 70. At three months 7% of patients 60-69 had abnormal neuropsychometric testing and this was 14% in those older than 70.

There exists animal data that anesthetic drugs such as ketamine and GABA agonists trigger cell death by disrupting neuronal permeability, allowing leakage of mitochondrial cytochrome C, leading to an apoptotic cascade.[5] Other potential mechanisms of POCD or neurodegeneration include NMDA excitotoxicity, oxidant stress, and suppression of cholinergic signaling. At least three human studies demonstrate a 1.2 to 1.6 odds ratio between Alzheimer's disease and prior surgery, though due to being

underpowered the studies did not demonstrate statistical significance. One possible mechanism for neurodegenerative disorders is uncontrolled oligomerization of normally present proteins or peptides in the brain. Examples include Alzheimer's disease and β-amyloid peptides.[6]

The issue is whether we can reduce the risk of POCD in our patients by choosing an alternative anesthetic strategy such as neuraxial block in preference to general anesthesia. A classic study by Pam Williams-Russo tried to answer this question. This was a study of a single surgical procedure-total knee arthroplasty-that was published in JAMA in 1995. It involved 262 patients who receive neuropsychological testing at baseline, then at one week and at 6 months. Groups were divided into general anesthesia and epidural anesthesia. The average age of the patients was 60. The epidural group received fentanyl and midazolam for sedation during the case. There was no difference in groups in cognitive decline with 5% of each group suffering a decline. The two troubling issues with this study is one that the amount of sedation administered to the epidural group may have been tantamount to a general anesthetic and secondly the postoperative pain control was not studied.[7]

A metaanalysis by Wu[8] published in Regional Anesthesia and Pain Medicine in 2004 looked at 24 studies comparing cognitive function after either general or neuraxial anesthesia. 19 of the trials were randomized controlled studies and 4 were observational trials. 23 of the trials did not show any benefit to neuraxial blockade. The trials enrolled 12,917 patients in total. Wu speculated that the reason that neuraxial anesthesia did not lessen the cognitive burden is that a brief unimodal intervention, high patient drop out rate in the studies, and many other factors may influence results of neurocognitive tests beyond just the choice of anesthesia. Wu also argued that the routine use of intraoperative sedation might have skewed the results against a potential positive effect of regional anesthesia. The one study that did show a difference was by Sato out of Japan.[9] This looked at patients older than 80 who required surgery for femoral neck fracture. All patients received spinal tetracaine as their anesthetic. No preoperative or intraoperative sedation was administered. Diclofenac was used for postoperative pain control. While patients did experience a 15% decline in cognitive function based on the Abbreviated Mental Test (this decline is lower than one would have otherwise expected in this population) all patients had a return to their baseline cognition by discharge.

Multimodal analgesia may improve neuropsychological outcome after surgery. Severe pain occurs in 60% of patients having joint replacement surgery and multimodal analgesia employing peripheral nerve blocks and non-opiate pain relievers may provide superior analgesia, limitation of parenteral opiates on cognitive function, and lead to earlier

recovery. An interesting abstract by Jankowski[10] from the 2005 annual meeting of the American Society of Anesthesiologists looked at employing such a pathway. They found that the patients who had general anesthesia alone had higher cognitive defects than patients managed with continuous nerve blocks alone. Even patients who had a general anesthetic combined with a postoperative continuous nerve block did better cognitively than those managed conventionally.

If a patient refuses a regional anesthetic or cannot receive one for various medical reasons can general anesthesia be modified to potentially reduce the risk of POCD? An interesting study in a rat model found that propofol maintains spatial memory better, whereas isoflurane or nitrous oxide impaired the ability of aged rates to learn spatial memory tasks.[11] A study by Wang[12] found that in patients undergoing cardiac surgery (which has a high rate of cognitive decline) an infusion of lidocaine showed less of a deficit on neuropsychological tests. A study by Ma in animals found that Xenon had less of a decremental effect on cognitive function than traditional inhaled anesthetic agents.[13] One study in cardiac patients found that the use of preoperative statins reduced the risk of postoperative delirium by 46%. It was hypothesized by the authors that statins reduce circulating levels of cytokines and acute phase proteins and that statins work by reducing the level of these inflammatory agents.[14]

The risk of postoperative cognitive dysfunction in the elderly has been known for over 50 years and has received more attention in the last decade but still remains an enormous health burden to patients, their families, and to healthcare systems around the world. The role of general anesthesia as the sole reason for POCD is unclear and much work needs to be done to determine the best agents and techniques to reduce this burden.

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