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Cognition, Anesthesia, and Surgery

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Introduction

General anesthesia is a state of unconsciousness with the absence of pain sensation over the entire body, achieved through the administration of anesthetic drugs. It is used during certain medical and surgical procedures. The induction of unconsciousness raises the interesting question of whether this state is completely reversible, e.g. when the patient regains consciousness will all faculties return to their pre-existing state. As early as 1887 (the first demonstration of general anesthesia occurred in the 1840's), Savage wrote "I only point out that I have met with a series of cases of insanity in which the use of anaesthetics, in predisposed subjects, has been followed by insanity."¹ In his article he goes on to describe delirium and suggests that any cause that will give rise to delirium could result in progressive "weak mindedness" and subsequent dementia. To a large extent, that level of understanding has not evolved substantially; there is still a lack of clarity as to whether delirium results in persistent cognitive change. However, modern studies have provided significantly more information on cognitive aspects of anesthesia particularly as it relates to elderly patients. If, as described in this review, cognitive alterations following anesthesia and surgery do occur, the questions are whether these problems are the direct result of drug action, a result of specific physiology such as aging, a reaction to the surgery or some combination of these effects. These questions are important in that they could impact decisions regarding surgical care and choice of anesthetic regimens, and might direct clinicians toward means of prevention and/or treatment. In this review, we survey the current knowledge of cognitive function and aging as a background for a discussion of the primary concerns arising when providing anesthetic care for elderly patients.

Some definitions are important. Delirium, or acute confusional state, is a syndrome that presents as confusion and disorientation. Cognitive dysfunction, frequently called postoperative cognitive dysfunction (POCD) or long term cognitive impairment (LTCI or LCI), is most typically defined as deterioration on specific tests that are administered at two or more times. The times at which the tests are administered vary tremendously but the first test is typically administered before surgery. The content of the tests, from a neurocognitive perspective, and the means by which they are evaluated are highly variable, as will be described below. Dementia is a general term that describes a group of symptoms including judgment, language and motor skills that result from neuronal injury. From a practical

perspective, cognitive dysfunction is one component of dementia. Amongst the types of dementia are Alzheimer's disease, Lewy body disease, and vascular dementia.² In an attempt to define states and symptoms of individuals who are developing dementia, a number of pre-dementia constructs have been defined. The most common versions are called mild cognitive impairment (MCI).³ These states are intermediate between those cognitive changes expected with normal aging and those associated with dementia.

Cognitive Aging

There is a general sense that cognitive function declines with aging. Therefore the significant question is whether any change following anesthesia and surgery is causally related to that event or just represents a red herring, i.e the patient was going to have alterations anyway and just happened to have surgery.⁴ In understanding whether anesthesia and surgery have an impact on cognitive ability, it is worth some effort to understand the current thinking about cognitive change in the elderly and the limitations associated with testing even normal adults in the absence of surgery.

Salthouse has reviewed cognitive changes with aging, pointing out that while many, but not all, of the tests that are typically employed in the perioperative period do generally decrease with increasing age.^{5,6} There are multiple means of thinking about cognitive function. A very common format, proposed by Catell, is based on the idea of fluid versus crystallized abilities.⁷ In this formulation, fluid capacities, such as the ability to calculate or order things or remember new things are functions that decline progressively with age while crystallized intelligence are those things that accumulate with age; those things we might call wisdom. Perhaps more relevant to the type of evaluations that occur in the perioperative period, Figures 1 displays composite scores of abilities over chronological age while Figure 2 presents performance on specific tests over a range of chronological age. Both of these figures show that most measures decrease over time, although some (e.g. vocabulary knowledge in Fig 1) seem to improve with age. However, Ramsar and colleagues suggest that changing performance in older adults reflects memory search demands, which escalate as experience grows, i.e there is more in their brain to sort through.⁸ Thus the increased time is not really a slowing in function but a normal reaction to a larger set of files.

Our understanding of the underlying neurophysiology of aging is under development. It is apparent that, on average, brains tend to shrink with age.⁹ The atrophy appears due primarily to pruning of neurons and loss of white matter rather than loss of intact neurons. Advances in neurogenesis and neuroplasticity may provide new insights into how brains maintain neural function and react to neural damage, however there is little current information available to apply to this area of study.

Delirium

Delirium occurs in many patient populations including patients with medical illness and psychiatric illness.¹⁰ The focus of this review is on postoperative delirium. Postoperative delirium is clinically important. It is extremely distressing to both the patient and his or her family. In 2001, Franco reported that postoperative patients with delirium required an average of an additional 1.4 hospital days and incurred \$2,947 per patient in additional

charges.¹¹ Leslie and Inouye suggest that all cause delirium costs the health care system between \$143 billion and \$152 billion per year.¹² Postoperative delirium is of great interest to researchers as the patients are, for the most part, normal prior to surgery and therefore present an opportunity to examine before any insult that may cause delirium. From a research perspective it is important to screen for delirium prior to surgery, however in general practice assessing patients for delirium is not required during a preoperative assessment.

Emergence from the anesthetic state can be defined as the transition from unconsciousness to full wakefulness. During emergence, many patients develop agitation which is commonly called emergence delirium. This state occurs commonly in all age groups, particularly pediatric patients and generally resolves relatively quickly. Elderly patients may have emergence delirium. Radtke has studied emergence delirium in elderly patients and defined a state of hypoactive or inadequate emergence in which the return to full wakefulness is delayed.¹³ The nature and implications of inadequate emergence is still being determined. Delirium may occur upon emergence, soon after emergence in the PACU or at 24–72 hours after the end of surgery following a period of lucency and normal behavior. This delayed onset of delirium is referred to as postoperative delirium and has been the focus of most attention.

Although clearly a concept for many years, the current research on delirium has evolved from the definition published in the 3rd edition of the Diagnostic and Statistical Manual (DSM III), which was published in 1980. (see table 1). This was minorly altered in 1987 (DSM III-R) and provided the basis of the Confusion Assessment Method (CAM), which was published by Inouye and colleagues in 1990.¹⁴ Although there have been subsequent updates to the DSM, the CAM has not been substantially altered and remains the primary instrument for defining delirium. Other instruments for determining the presence or absence of delirium exist and still others may be utilized to assess the severity of delirium. The Memorial Delirium Assessment Scale was specifically designed to measure severity of delirium and can be combined with the CAM to provide a broader understanding of a patient's condition.¹⁵ The Delirium Rating Scale Revised 98 is another instrument that provides severity assessment.¹⁶

Delirium is a behavioral construct that is diagnosed by examination of the patient. The CAM was specifically designed so that non-psychiatrically trained (but trained in CAM) personnel could perform these assessments. The CAM provides a present/absent diagnosis of delirium. There is an extensive manual describing the use of the CAM (<http://www.hospitalelderlifeprogram.org/pdf/TheConfusionAssessmentMethod.pdf>). The CAM has been utilized in a variety of circumstances and has been modified for other environments. The CAM-ICU is a version that was modified for use in intubated patients.^{17,18} The CAM is a copy protected entity, so any use in specific program development or modification requires permission. For truly accurate diagnosis, it is important to appreciate that none of these instruments are completely self-explanatory. Proper assessment of delirium requires training and ongoing quality assurance.

Delirium is frequently divided into motoric subtypes.¹⁹ Hyperactive delirium describes those patients who are actively delirious, trying to get out of bed and acting out on their delirious thought patterns. Hypoactive delirium describes those patients who are quiet and stable in their environment (typically in bed) but whom fulfill the criteria for delirium using any of the available diagnostic instruments. Patients who display both of these patterns are called mixed pattern delirium. The motoric subtypes are not part of any of the delirium diagnostic instruments; the level of activity is not part of delirium assessment. The distribution of these subtypes has been reported as 30% hyperactive, 24% hypoactive and 46% mixed.²⁰ Interestingly, hypoactive delirium may be more associated with hallucinations and poor outcomes than hyperactive delirium.²¹ Recently, some investigators have described sub-syndromal delirium, describing patients who are close to but do not quite fulfill all criteria for delirium. The value of sub-syndromal delirium as a diagnostic entity is still under development.²²

The incidence of postoperative delirium varies primarily with the type of procedures. For general surgery, the incidence of delirium is generally found to range from 5–15%.²³ Patients experiencing hip fracture have a higher incidence, ranging from 16–62%, with an average rate of 35% across 1,823 patients included in 12 studies reviewed by Bitsch.²⁴ Delirium following cardiac surgery has reported to be approximately 50%,²⁵ while more recent reports have found an incidence more like general surgery.^{26,27} The literature on delirium in the ICU, both medical and surgical, indicates an extremely high incidence near 80%.²⁸

The cause of delirium remains unknown. Multiple theories have been proposed including general constructs of neural balance²⁹ and the suggestion that delirium is a severe form of sickness syndrome.³⁰ Specific factors that have been associated with delirium include alterations of cholinergic activity,³¹ inflammatory phenomenon including inflammation induced signaling in the central nervous system,³² alterations in the blood brain barrier,³³ excessive depth of anesthesia³⁴ or depth of sedation³⁵, a secondary phenomenon to anesthetic neurotoxicity,³⁶ use of a single dose of ketamine,³⁷ a result of disruption of sleep hygiene,³⁸ secondary to either pain or pain medications³⁹ or the result of a genetic predisposition.⁴⁰ With the exception of the work on depth of anesthesia and sedation, perhaps ketamine administration, and trying to balance pain with analgesia, this literature has failed to direct any specific effective therapy for delirium. Although there has been much interest in the potential for regional anesthesia to have a lower incidence of delirium, to date this has not been found.⁴¹ Two potentially confounding issues for all studies of regional versus general anesthesia are the difficulty in controlling sedation or level of sedation in the regional anesthesia groups and the issue of postanesthesia stress response following the end of regional anesthetics. Clearly, a better understanding of the pathophysiology of delirium would be valuable but must await further research.

Attempts to prevent delirium include programmatic approaches, pharmacologic approaches and efforts to manage anesthetic depth. Marcantonio randomized patients to either routine care or a specific geriatric consultation (similar to comprehensive geriatric assessment) and decreased the incidence of delirium from 50% to 32%.⁴² The Hospital Elder Life Program (HELP) is a complex intervention which includes nursing protocols to address risk factors

and orientation that has been shown to reduce rates of delirium and functional decline, 43,44 In a recent study in a medical unit of a community hospital, HELP decreased the incidence of delirium from 20% in the pre-intervention group to 12% in the intervention group.44 There was also a substantial change in length of stay and associated costs. The program is being modified for surgical units.43

A number of pharmacologic approaches to prevent delirium have been studied in a variety of populations. Significant delirium prevention effects are associated with haloperidol and second generation antipsychotic medication.45 There are also reports of fascia iliaca nerve block, perioperative gabapentin, melatonin, and a single dose of ketamine during anesthetic induction.45 In mechanically ventilated patients early studies suggest dexmedetomidine may be superior to other sedation strategies.46,47

The major concerns regarding delirium have to do with both the impact on the individual and the impact on the health care system. In hospital mortality for patients who present with delirium is reported between 4 and 17%.48–50 Longer term mortality from months to years is also high.51,52 Length of stay, both in intensive care units26 and hospitals48, increased complications53 and a higher rate of discharge to nursing homes54,55 are all associated with delirium. Patients who have been interviewed about their delirium frequently remember the incident and found it extremely distressing.

As opposed to various prophylactic regimens which have shown some success, the treatment of delirium remains inadequate. The general approach is to try to identify and eliminate precipitating factors, such as polypharmacy and dehydration. The standard of care for management of symptoms is haloperidol.56 A number of important issues are associated with this practice. First, haloperidol should be administered intravenously even though it is labeled for subcutaneous and intramuscular use. Intravenous haloperidol has been used successfully for decades in this fashion and is significantly more effective by this route. Second, the point of therapy is only to control symptoms, not to anesthetize the patient. Haloperidol has an extremely long half-life in the elderly, so doses in excess of a few milligrams will be associated with heavy sedation that can last for days. Finally, starting with low doses of 0.5 – 1.0 mg, the practitioner must wait 15–20 minutes between doses to assess the effectiveness of therapy before administering more drug.

Future directions for delirium research should hopefully include both investigations into the pathophysiology as well as further assessments of treatment modalities that have preliminary evidence of efficacy. This area of brain dysfunction would benefit from some consensus amongst anesthesiologists, surgeons and particularly geriatricians, psychiatrists and neurologists. When a patient develops delirium, the approach is likely to be distinctly different if the physician is from one of these three specialties. There is a need to distinguish early postoperative delirium from a prolonged recovery from anesthetic agents and to assess how delirium resolves or does not resolve. While it has been convenient to distinguish between delirium and POCD from a research perspective, there is a vital need to determine if there is really a distinction between the long term effects of patients recovering from delirium and POCD.

POCD

As noted in the introduction, alterations in cognitive function following major surgery have been reported since almost the beginning of modern surgery and anesthesia. Apart from delirium described above, two major forms of this disorder appear to exist in current thinking. One, described by Sauer et al as severe POCD is a circumstance in which catastrophic alterations follow surgery.⁵⁷ These types of alterations are so profound that no specific testing is needed to identify dysfunction. There is very little known about these cases; they appear primarily as anecdotes. These patients are rarely included in prospective studies and, had they been enrolled, would not have been able to complete the postoperative tests. Thus, there is no data on the incidence or prevalence of severe POCD. There is a popular sentiment (mostly on the internet these days) that these cases represent a rapid advancement of Alzheimer's disease. The evidence regarding the relationship of surgery, anesthesia and POCD to dementia are presented below.

Certainly more well characterized is the state referred to as POCD or long term cognitive impairment. POCD describes patients with significant, but not catastrophic, alteration in cognitive function. There is a lack of consensus regarding which tests should be used, when the tests should be administered and the degree of alteration that is clinically and physiologically significant.^{58,59} The majority of studies employ some version of memory tests including both immediate recall and delayed memory (e.g. 30 minutes) and evaluation of some level of executive function. The actual content of a testing battery, whether based on existing batteries, such as the Alzheimer Disease Research Center battery, or others remains open to much discussion. Many publications have been based on the battery originally used by the International Study of Postoperative Cognitive Function.^{60–65} Recently, the National Institute of Health has promoted the NIH Toolbox as a standard battery to be used across multiple disease states and age groups. To date, there are no published studies using the Toolbox in the perioperative period. No standard approach has been agreed upon although attempts to establish a consensus have been reported.⁶⁶

There is some support for the idea that all elderly patients should be screened for cognitive alterations prior to surgery.⁶⁷ Alternatives for such a screening tool include the MiniCog^{68–70} and the Mini Mental State Examination (MMSE).⁷¹ If the screening score suggests impairment, a more complete assessment would be required. Reports in which the only test of cognitive function is the MMSE are probably not adequate to truly assess function.

As one might expect, timing of testing can have an important impact on results. Preoperative testing should be done before the day of surgery as a patient is probably not capable of focusing on cognitive tests immediately prior to entering an operating room. A lower baseline test will minimize any real alteration. The timing of testing after surgery is controversial. There is, unfortunately, little data regarding cognitive recovery from anesthesia. Younger patients certainly may recover quite quickly from general anesthesia although there does seem to be a fair amount of variance (clinical impression of the author). In clinical studies, testing has been reported from the actual day of surgery, a few days to weeks after surgery and at multiple months after surgery. As will be noted below, POCD

seems to be time limited, so the timing of testing is an important issue and makes comparing reports somewhat difficult.

Perhaps the most controversial aspect of making a determination of POCD is the degree of change that is considered statistically or clinically significant. Multiple authors have criticized the high variability of this aspect.^{58,66} Amongst methods reviewed by Rudolph, the most common were percent decline, requiring >1 standard deviation change on two tests, factor analysis, individual test analysis and Z-score methodology in which a statistical measurement of a score's relationship is compared to the mean in a group of scores. Mahanna et. al. made the point that, depending upon the statistical definition, the number of patients in a single dataset that would be defined as POCD varied from 70% to 16%.⁶⁶ Exactly what would be considered clinically significant depends, to a certain extent, on the status of the individual. Following on Jette's construct of disability, the clinical relevance evolves in a social context.⁷² Thus, an accounting executive might find any decrease in executive function to be a major problem, while a fully retired individual may find it a minor issue.

The largest studies of POCD to date have utilized the ISPOCD battery. In the original study of 1218 patients in which the primary goal was to assess the relationship between hypotension, hypoxemia and cognitive change, 25.8 % of patients over 60 having general anesthesia had cognitive dysfunction at 1 week while 9.9% had cognitive function at 3 months.⁶⁰ Increasing age, education level (less education is more likely to have POCD), requiring a second operation, having a postoperative infection and postoperative respiratory complications were associated with early POCD. Only increasing age was associated with POCD at 3 months. Using the same battery on a wide age group of patients, Monk et. al.⁶⁵ found that at three months following surgery, 5.7% of young, 5.6% of middle-aged, and 12.7% elderly patients had POCD. An important finding from this study was that patients with POCD at hospital discharge were more likely to die in the first 3 months after surgery.

The duration of POCD is a significant issue. Overall, the majority of cases in patients that survive appear to resolve in 3–6 months.⁷³ Cases of long term cognitive impairment after prolonged ICU care are probably a different circumstance and efforts by the reader should be made to distinguish these cases from those involving elective and relatively uncomplicated surgery.⁷⁴ As noted below, while there is controversy, there appears to be little evidence that POCD evolves into dementia.

The fact that such cases resolve in 3–6 months is hardly a reason to dismiss POCD as an unimportant complication. As noted above, the impact of POCD, as with any type of disability, evolves in a social context.⁷² Individuals with high functioning job responsibilities may find it impossible to maintain employment. In the original ISPOCD cohort, patients with POCD were much more likely to leave the workforce and require social service support. It is known that patients having major surgery may take 3–6 months to achieve full recovery for activities of daily living.⁷⁵ This is also consistent with the time period of POCD. Patients with POCD have been found to have not only an increased risk of mortality but also a higher risk of leaving the labor market prematurely, and a greater dependency on social transfer payments.⁷⁶ While much remains to be learned, a

complication that persists for 3–6 months following surgery is very much in need of understanding with the hopes of altering this course.

The pathophysiology of POCD remains unclear. The primary recent candidates are exacerbations of inflammation or inflammatory signaling⁷⁷ and an interaction with the pathophysiology of Alzheimer's disease.⁷⁸ For a broader discussion, the reader is referred to the above references and recent reviews.^{79–82}

Dementia

As described above, dementia is a state of functional deterioration that includes many of the cognitive areas assessed for POCD. Dementia is a more complicated and complete state with multiple causes. Currently, Alzheimer's dementia represents that largest cohort of patients with dementing illness, but other forms of dementia are also common.⁸³ Patients with dementia that present to the OR rarely carry specific diagnoses, partially because definitive diagnosis of many dementias is only made at autopsy. Currently, there is no indication that any specific form of dementia would suggest a specific approach to surgery and anesthesia.

The primary concerns for the anesthesiologist are 1) whether anesthesia causes or accelerates dementia and 2) whether delirium and/or POCD are harbingers of dementia. Multiple retrospective studies have utilized registries of patients that are characterized for dementia to explore the that finding to exposure to anesthesia.⁸⁴ Apart from the general limitation of retrospective reviews, these studies generally lack a clear definition of surgical procedures or anesthetic care. Two recent studies of a Chinese database concluded that patients who had an exposure to anesthesia were more likely to develop dementia.^{85,86} An extensive evaluation of an Alzheimer's Disease Research Center database from Washington University came to the opposite conclusion, that surgery was no more likely than either medical illness or a control group consisting of a statistically created event to increase the trajectory of dementia.⁸⁷ A meta-analysis of many such studies, which does not include many of the more recent reports, concluded that the evidence did not support a relationship between exposure to surgery and anesthesia and the development of dementia.⁸⁴

There is relatively little in the way of literature describing whether POCD leads to dementia. An evaluation of the patients included in the Danish cohort of patients in the ISPOCD study followed through a Danish registry did not support the notion that patients who had been diagnosed with POCD were more likely to develop dementia than those who did not have POCD.⁸⁸

Conclusion

Alterations in cognition following surgery have been reported almost since invention of anesthesia. Postoperative delirium is a behavioral construct associated with increased morbidity, mortality and healthcare expenditures. While the pathophysiology remains unclear, a variety of approaches to prevent and treat delirium have moderate efficacy. POCD remains a research construct that requires further definition and a consensus regarding how to define and measure this problem. Disagreement regarding the importance of POCD has emerged primarily from research questioning its relationship to dementia, although issues

regarding measurement and the potential for postoperative cognitive improvement have been expressed. The relationship of anesthesia to dementia in general and Alzheimer's disease is particular remains unclear.

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Fig. 1. Means and standard errors for composite scores in five abilities as a function of age based on data from studies by Salthouse and colleagues (e.g., Salthouse, 2009a). Sample sizes ranges from 2369 to 41419.

Fig. 2.

Means and standard errors for scores on various neuropsychological tests based on data from studies by Salthouse and colleagues (e.g., Salthouse, Atkinson, & Berish, 2003; Salthouse, Fristoe, & Rhee, 1996; Salthouse & Mein, 1995; Salthouse, Pink, & Toker-Drob, 2008). Sample sizes ranged from 269 to 1455.

Table**DSM-III-R Criteria for Delirium (1987)**

Reduced ability to maintain attention to external stimuli (e.g., questions must be repeated because attention wanders) and to appropriately shift attention to new external stimuli (e.g., perseverates answer to a previous question).

Disorganized thinking, as indicated by rambling, irrelevant, or incoherent speech.

At least two of the following:

Reduced level of consciousness; e.g., difficulty keeping awake during examination;

Perceptual disturbances: misinterpretations, illusions, or hallucinations;

Disturbance of sleep-wake cycle with insomnia or daytime sleepiness;

Increased **or** decreased psychomotor activity;

Disorientation to time, place, or person;

Memory impairment

Clinical features develop over a short period of time (usually hours to days) and tend **to** fluctuate over the course of a day.

Either one of the following:

Evidence from the history, physical examination, or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance;

In the absence of such evidence, an etiological organic factor can be presumed if the disturbance cannot be accounted for by any non-organic mental disorder; e.g., manic episode accounting for agitation and sleep disturbance.