COGNITIVE OUTCOMES IN THE OLDER SURGICAL PATIENTS

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INTRODUCTION

Perioperative management of the geriatric surgical patients is becoming an increasingly important component of anesthetic practice in the 21st century. This phenomenon is due to the fact that people aged 65 years or older is the segment with the fastest growth in the population. It is estimated that by the year 2025, 20% of the U.S. population will be > 65 years of age (1). Currently, the elderly comprises one third of all operations being performed (2). Of those older than 65 years, one out of two will undergo an operation in their lifetime.

This changing demographics of the surgical patient population has tremendous impact for the practice of anesthesia. Whereas in the past decades, concern has focused on avoiding surgery for the elderly because of preoperative frailty resulting in increased risks undergoing major surgery. Recent advances in anesthetic practice and surgical techniques including minimally invasive surgical approaches have greatly improved perioperative morbidity and mortality and thus increasing the number of elderly patients presenting for surgery. The concern now is that because more sicker and older patients
are presenting for surgery, perioperative morbidity and mortality rates may be on the rise again. As a result, a renewed interest has arisen in identifying factors associated with adverse postoperative outcomes in order to develop strategies to improve the perioperative care and outcomes of geriatric surgical patients.

In two separate cohorts of older patients undergoing noncardiac surgery, we showed that the most common non-fatal complications after surgery involved the cardiac, neurological and pulmonary systems (3, 4). In this lecture, we will focus on the cognitive outcomes after surgery in the older surgical patients.

**POSTOPERATIVE DELIRIUM AND POSTOPERATIVE COGNITIVE DECLINE**

Delirium is an acute confusional state with alterations in attention and consciousness (5). In contrast, postoperative cognitive decline (POCD) refers to declines in cognitive functioning that can occur in the absence of delirium and are detected through neuropsychological testing. Delirium occurs in 14% to 50% of hospitalized medical patients, and its associated mortality rate is 10% to 65% (6, 7). After major noncardiac surgery, 10% to 60% of patients have delirium (8) (9), and 7% to 26% have POCD (10-13). Delirium can be superimposed on dementia or other neurologic disorders associated with global cognitive impairment. As a result, the course of delirium can vary considerably and depends on the resolution of the causative factors.

Broadly speaking, POCD refers to problems in thinking and memory after surgery. POCD is not recognized yet in the International Classification of Diseases and is not listed as a diagnosis in the Diagnostic and Statistical Manual. The term POCD is
used mostly in literature to represent a decline in a variety of neuropsychological
domains including memory, executive functioning, and speed of processing. POCD has
been defined in a consensus statement as “a spectrum of postoperative central nervous
system (CNS) dysfunction both acute and persistent … including brain death, stroke,
subtle neurologic signs and neuropsychological impairment” (14).

POCD should be distinguished from delirium or dementia. Delirium describes an
acute confusional state featuring disturbances in attention and decreased awareness of the
environment (5, 15). Delirium symptoms fluctuate during the course of the day, and the
patient often is disoriented. In addition, hallucinations and inappropriate communications
or behavior may be observed in the presence of delirium. In contrast, a typical patient
with POCD is oriented but exhibits significant declines from his or her own baseline level
of performance on one or more neuropsychological domains (16-19). After surgery,
changes in cognitive status may present in the form of a frank delirium or POCD, or both.
POCD differs from dementia, which describes a chronic, often insidious,
decline in cognitive function. Alzheimer’s disease remains the most common form of
dementia, but there is considerable overlap in neurodegenerative disease.

1. Postoperative delirium

A. Hospitalized Non-surgical Elders

Delirium is a serious problem for hospitalized geriatric patients. It may be caused
by an underlying medical illness, but often, the exact etiology is not identifiable (20).
The course of delirium can vary considerably and depends on resolution of the causative
factors. The development of delirium is thought to be a multifactorial process in which
there is a complex interrelationship between \textit{baseline patient vulnerability} and \textit{precipitating factors or insults} (21). In elderly persons who were hospitalized for non-surgical reasons, some of the \textit{vulnerability factors} identified have included advanced age, cognitive impairment or dementia, functional impairment, depression, pre-existent high number of and severity of comorbid conditions, chronic renal insufficiency, dehydration, malnutrition, and sensory impairment (22-29). On the other hand, \textit{precipitating factors} that have been identified in the non-surgical setting include sleep disorders, sensory deprivation or overload, and psychological stress such as that resulting from bereavement or relocation to an unfamiliar environment, the use of physical restraints, more than three medications added, use of bladder catheter, and any iatrogenic event (6, 21).

\textbf{B. Geriatric Surgical Patients}

In the older surgical patients, what are the potential baseline vulnerability risk factors that have been shown to increase the occurrence of adverse postoperative cognitive outcomes? The most important geriatric risk factors for postoperative delirium and cognitive decline reported by previous studies are summarized below:

\begin{table}[h]
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\hline
\textbf{Postoperative Cognitive Decline} & \textbf{Postoperative Delirium} \\
\hline
Increasing age (11, 30) & Increasing age (especially \textgreater{} 70 years) (31-34) \\
Prior cognitive impairment (30) & Prior cognitive impairment (31-35) \\
Depression (30) & Depression (27, 36, 37) \\
Low education level (not completed high school) (11, 30) & Poor functional status (31, 33, 34) \\
Heart failure on admission (35) & Abnormal blood pressure (35) \\
& Abnormal serum electrolytes, or glucose (33, 38) \\
& Self-reported alcohol abuse (33, 34, 39) \\
& Narcotic use prior to admission (34) \\
\hline
\end{tabular}
\caption{Geriatric risk factors of postoperative cognitive decline or delirium}
\end{table}
In the perioperative period, the *precipitating risk factors* for the development of postoperative delirium in older patients include an unfamiliar environment, the stress of surgery, and exposure to medications that have the potential for profound effects on the central nervous system (CNS). Drug effects can range from subtle changes in consciousness to frank delirium.

In surgical patients, successful interventions of postoperative delirium are limited, the most successful study was that by Marcantonio *et al.* (40). In this study, elderly patients admitted for emergency surgical repair of hip fracture were randomly assigned to an intervention (a “proactive geriatrics consultation”) or the usual care. Delirium occurred in 32% of the intervention patients and in 50% of the usual-care patients. Despite this reduction in delirium, the length of hospital stay did not differ significantly between the two groups. Other intervention such as prophylactic treatment with pharmacologic agents did not prevent the occurrence of delirium. For example, haloperidol did not prevent delirium occurrence but did reduce its severity and duration, and possible hospital stay (41). This result suggests that haloperidol was effective in the treatment of delirium when it occurs, but not preventing its occurrence. Therefore, although previous clinical trials have been effective to a certain degree in the interventions of postoperative delirium, intervention specifically aimed at reducing reversible precipitating factors has not been targeted.

In the surgical setting, limited data exist as to whether specific intraoperative management precipitates postoperative delirium. Several areas which are of interest to anesthesiologists include drugs, anesthetic techniques and management.
We recently identified pain as an independent predictor of postoperative delirium (42), therefore a potentially important and modifiable precipitating factor for adverse cognitive outcomes. After major surgery, in addition to chronic pain that may be present preoperatively, surgical patients experience pain that is typically most severe during the first few days after surgery. During this period, the incidence of delirium is also the highest. Despite the onset of delirium, patients do have periods of lucidity in which pain assessment is possible. In patients ≥65 years of age who underwent elective noncardiac surgery, the levels of pain before surgery and the increase in pain after surgery (as measured by the visual analog scale) were independent predictors of the development of postoperative delirium (42). Our results are corroborated by another study of older patients undergoing major elective noncardiac operations (43) which also showed that higher postoperative pain scores at rest were associated with an increased risk of delirium in the postoperative period. In addition, we showed that patients with postoperative delirium not only have higher pain levels but also received more intravenous opioids postoperatively than those without delirium (44). These results suggest that in addition to pain, the CNS effects of opioids may cause or further contribute to the development of postoperative delirium and cognitive decline. Therefore, pain management may be an area to target for intervention that may result in further improvement in cognitive outcomes for the geriatric surgical patients.

Although previous studies have demonstrated that certain drugs may be associated with postoperative delirium, (45) there has been no prospective randomized clinical trials to determine if the elimination of certain drugs used in the perioperative period will actually lead to a lowering of the incidence of delirium postoperatively. As a result, no
definitive guidelines can be provided at present regarding avoiding certain drugs in the perioperative period. However, a sensible guideline is that “polypharmacy” is best to be avoided in the elderly patients because delirium has been shown to be related to the number of medications prescribed in non-surgical patients. (21, 45)

Controversy persists as to whether any anesthetic technique (regional versus general) has an impact on postoperative delirium. Earlier studies suggested an association between general anesthesia and a higher incidence of cognitive dysfunction relative to epidural anesthesia (46, 47). However, recent studies concluded that there was no relationship between anesthetic techniques and the magnitude or pattern of postoperative cognitive dysfunction (11),(48),(49). The influence of intraoperative hypotension on postoperative cognitive dysfunction has been evaluated. In a prospective, randomized study of older adults (age > 50 years) undergoing total hip replacement, Williams-Russo et al. (50) demonstrated that patients who underwent epidural anesthesia and were rendered markedly hypotensive had similar incidence of postoperative cognitive dysfunction as those who were maintained in the normotensive state.

To date, no single anesthetic technique has been identified to be superior for the elderly surgical patients in minimizing postoperative delirium. Until more definitive clinical studies become available, minimizing the number of medications used, avoiding hypoxemia and extremes of hypocarbia or hypercarbia, and providing adequate postoperative pain control appear to be the best approach in minimizing the occurrence of postoperative delirium in geriatric surgical patients.

Finally, a recent study showed that longer duration of fluid fasting preoperatively was independently associated with postoperative delirium (51). Although dehydration has
been linked to impaired cognitive performance in both young and older subjects (52, 53), a study in older subjects who had bowel preparation induced dehydration showed no change in cognitive function compared with those who had no bowel preparation (54). Since the duration and magnitude of hydration are critical factors affecting cognitive function, future studies examining the role of dehydration and cognitive performance should consider if there is a critical level of water deficit affecting cognition.

2. Postoperative Cognitive Decline

Postoperative cognitive dysfunction or decline (POCD) is increasingly recognized as a common phenomenon after major surgery (11-13, 48). Because older age is a strong preoperative risk factor of POCD (11),(55 ), the incidence of POCD is expected to increase as the population of older surgical patients grows. Improving the measurement of POCD and identifying its etiology is clinically important, as recent studies have associated POCD with impairments in daily functioning (56), premature departure from the labor market (57), and dependency on government economic assistance after hospital discharge (57). 

In previous studies, cognitive function was measured beginning 1 day to as long as 5 years after surgery. POCD can be broadly divided into acute, intermediate and late or long-term changes based on information from previous studies. Specifically, acute POCD has been used to describe cognitive decline detected within one week after surgery, intermediate POCD for changes within 3 months, and long-term POCD for changes 1-2 years following surgery. However, the exact significance of detecting POCD at these various time points is unclear. The time interval at which a diagnosis of
POCD holds the greatest clinical significance has not been determined, nor have any studies invalidated the importance of conducting assessments at a specific time point. Early assessments of POCD likely capture a different phenomenon than what late assessments of POCD capture, and each are accompanied by a unique set of issues. Surgery-related factors may affect test performance in the immediate postoperative period, including acute pain (58-60), the use of drugs (61, 62), nausea, limited mobility, and fatigue. Thus, it has been argued that patients should not be evaluated for POCD until at least one week postoperatively (14, 18, 63). Recent evidence suggested this delay might be arbitrary, as negative outcomes are associated with POCD detected in the first week after surgery. POCD assessments that occur in the immediate postoperative period are important for elucidating the relationship between POCD and delirium. Because POCD and delirium both feature deficits in attention, whether they are related events on a continuum or distinct conditions remains unclear. Recently, Monk et al. found that patients who were delirious after major noncardiac surgery were also more likely to have POCD at hospital discharge (55). Since most cases of delirium occur in the early postoperative period, an improved understanding of the relationship between POCD and delirium will be derived from additional studies that perform neurocognitive testing and delirium assessment simultaneously within the first several days after surgery.

The exact pathophysiology of POCD remains undefined. Previous studies on POCD have focused on investigating the risk factors associated with early POCD. In terms of patient-related baseline factors, or sometimes called predisposing factors, increasing age and lower levels of education have been identified as the main ones in the early study by the International Study on Postoperative Dysfunction (ISPOCD) (11). In a
subsequent study by Johnson et al. (12) that included only a subset of the population reported in the initial study, the avoidance of alcohol intake was determined to be a predisposing factor for POCD. Patient’s preoperative cognitive status also has been shown to be associated with POCD (64).

In addition to predisposing risk factors, numerous potential precipitating risk factors for POCD have been investigated. The early ISPOCD study reported that the duration of anesthesia, a second operation, postoperative infections, and pulmonary complications (11) increase the risk of POCD. In cardiac surgery, the use of cardiopulmonary bypass has been implicated as one of the precipitating factors (65, 66). During cardiopulmonary bypass, cannulation of the aortic root may result in cerebral microemboli, which could lead to POCD (67). In addition, a profound systemic inflammatory response occurs with cardiopulmonary bypass, which may contribute to POCD (68). However, despite the earlier reports that POCD is prevalent after cardiac surgery (65, 66), studies in patients who underwent cardiac surgery without the use of cardiopulmonary bypass did not demonstrate a lower incidence of POCD, despite a smaller embolic load in the middle cerebral artery measured by Doppler in patients undergoing off-pump surgery (69, 70). Thus, it remains inconclusive how surgery type actually affects POCD. Similarly, whether the type of anesthesia affects POCD remains inconclusive. In experimental settings involving animals, general anesthetics produced neurotoxicity and subsequent cognitive impairment in young and aged animals, but whether these changes are reproducible in clinical studies has not been determined (71). Most previous studies compared the cognitive outcomes between general vs. regional anesthesia. Earlier studies suggested an association between general anesthesia and a
higher incidence of cognitive dysfunction relative to epidural anesthesia (46, 47).

However, recent studies concluded that there was no relationship between anesthetic techniques and the magnitude or pattern of postoperative cognitive dysfunction (11, 13, 48, 49).

If anesthesia type did not seem to affect POCD, what about the conduct of anesthesia? The influence of intraoperative hypotension on POCD has also been evaluated. In a prospective, randomized study of older adults (age > 50 years) undergoing total hip replacement, Williams-Russo et al. (50) demonstrated that patients who underwent epidural anesthesia and were rendered markedly hypotensive had similar incidence of postoperative cognitive dysfunction as those who were maintained in the normotensive state. Taken together, to date, no single anesthetic type or technique has been identified to be superior in minimizing POCD for older surgical patients.

Given that the type of surgery and anesthetic type and management do not appear to influence rates of POCD, our group has focused on events in the postoperative period that may influence POCD, given that patients experience substantial pain postoperatively and are administered many medications with central nervous system effects. In 225 patients ≥ 65 years of age undergoing noncardiac surgery, we measured POCD in the first two postoperative days (60). In patients without postoperative delirium, 13% of patients experienced POCD on day 1, 7% on day 2, and 15% had POCD on either day 1 or day 2 after the surgery. Multivariate regression analyses revealed that only postoperative analgesia was associated with the development of POCD. Compared to those receiving postoperative analgesia through a patient-controlled analgesia device that administered opioids intravenously, those who received postoperative analgesia orally were at
significantly lower risk for the development of POCD. Our results demonstrate that older patients undergoing noncardiac surgery who are not delirious can experience significant declines in cognitive functioning postoperatively. Those at least risk of experiencing POCD were those who received postoperative analgesia orally. Opioid analgesics administered orally may result in a lower blood level of the drug due to first-pass effect when compared to intravenously administered narcotics which may directly cross the blood brain barrier. Alternatively, the use of oral narcotics for postoperative analgesia may be a marker for a less painful state. However, this result remains significant even when adjusting for the level of pain.

The question of whether major surgery and anesthesia ultimately lead to long-term cognitive decline is controversial. In a population study, Dijkstra et al. (72) reported that the number of operations and the total duration of anesthesia were related to the number of subject health-related complaints but did not predict cognitive performance or memory complaints. Several other studies that included assessments more than 6 months after surgery similarly reported no decline in cognitive status from that measured before surgery (73-77). However, two recent studies that included patients who had undergone noncardiac surgery reported that acute POCD was associated with increased mortality after surgery (for one study, at one year; and for the second study, at 3 months) (55, 57). Also, in cardiac surgical patients, Newman et al. (78) provided data showing that cognitive function at discharge was a significant predictor of long-term cognitive function. In contrast, a recent study by Avidan et al., provide results to the contrary (79). Continuing research on POCD is necessary to hopefully also shed light about the pathophysiology of other neurodegenerative disease including Alzheimer’s disease.
References


