AANA Journal Course
Update for Nurse Anesthetists

Sorting Through the Confusion: Adverse Cognitive Change After Surgery in Adults

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Cognitive change after surgery has become a common topic of research. However, postoperative delirium, emergence delirium, and postoperative cognitive dysfunction are not always phenomenologically distinct. The difficulty in distinguishing between different types of cognitive change after surgery is further complicated by the variety of measurement techniques applied to emergence delirium and postoperative cognitive dysfunction. Confusing one type of cognitive change after surgery with another has adverse implications for research and clinical practice. Therefore, to be effective clinicians and educated consumers of research into cognitive change after surgery, nurse anesthetists must be aware of the differences and similarities in postoperative delirium, emergence delirium, and postoperative cognitive dysfunction. To address this need, this course compares the history, characteristics, and limitations of the existing definitions for postoperative delirium, emergence delirium, and postoperative cognitive dysfunction.

Keywords: Emergence delirium, postoperative cognitive dysfunction, postoperative delirium.

Objectives
At the conclusion of this educational activity, the reader should be able to:

1. Briefly describe the history of cognitive change after surgery.
2. Describe the current definitional categories applied to cognitive change after surgery, and describe how current categories of cognitive change after surgery are measured and discriminated in clinical practice and research.
3. Describe the approximate incidence, known risk factors, known adverse outcomes, and hypothesized etiologies of current categories of cognitive change after surgery.
4. Describe known strategies to prevent and manage cognitive change after surgery.
5. Describe the implications of the current definitions of cognitive change after surgery.

Introduction
During the past decade, professional and public concern has led to an explosion of research into adverse cognitive change after surgery. As of July 19, 2010, a search of MEDLINE using the keywords emergence delirium, post-operative delirium, or postoperative cognitive dysfunction yielded more than 2,000 articles. In addition to the sheer volume of publications, any attempt to understand this body of research and incorporate it into clinical practice is further hindered by the variety of definitions applied to adverse cognitive changes after surgery.

Emergence delirium, postoperative delirium, and postoperative cognitive dysfunction (POCD) are conditions of adverse cognitive change that are observed after anesthesia and surgery. These adverse cognitive changes develop, resolve, and persist over different periods after surgery, are associated with different risk factors, and have different prognostic significance. Despite these distinctions, these adverse cognitive states are sometimes treated in the literature as being interchangeable depending on the objective of a given study. In particular, the lack of distinction between emergence delirium and postoperative delirium and between postoperative delirium and POCD confounds interpretation of the literature.

There are 2 reasons why definitions are critical when assessing cognitive change after surgery. First, clinically misinterpreting adverse cognitive change as a benign, chronic, or untreatable phenomenon may lead a practitioner to miss a disorder with potentially treatable causes.

* AANA Journal Course No. 31 (Part 3): AANA Journal course will consist of 6 successive articles, each with objectives for the reader and sources for additional reading. At the conclusion of the 6-part series, a final examination will be published on the AANA website. Successful completion will yield the participant 6 CE credits (6 contact hours).
Second, a lack of definitional clarity in research may lead to underestimation or overestimation of the effects of a given treatment or risk exposure, making comparison between studies difficult. Therefore, the purpose of this course is to provide readers with an understanding of the origin of the concepts of emergence delirium, postoperative delirium, and POCD; how these adverse cognitive states are defined; and how they are measured in the adult population after surgery. Armed with this knowledge, clinicians will be better equipped to determine if research findings involving these concepts should be incorporated into their own practice.

**Brief History**

- **Postoperative Delirium.** Postoperative delirium is the prototype for adverse cognitive change after surgery. Hippocrates described confusion, agitation, or lethargy after illness and injury as a harbinger of death, and delirium has appeared in the medical literature as a primary disease and a sequela of physical illness or injury for 2 millennia. The term delirium is attributed to Celsus in the first century AD, and the Latin translation literally means, “to go out of the furrow.”

  The first written descriptions of delirium after surgery are attributed to Pare in the 16th century or Dupuytren in 1819, but the modern conceptualization of postoperative delirium dates to 1908. In that year, German psychiatrist Karl Bonhoeffer described a classification system for psychosis that included acute endogenous reaction psychosis, or abnormal behavior secondary to non-neurological injury. Delirium as the cognitive sequela of physiological stress or illness was formalized in the first edition of *Mental Disorders: Diagnostic and Statistical Manual*. In this context, postoperative delirium is simply delirium that occurs after exposure to the stress of surgery.

  • **Emergence Delirium.** Savage was the first author to speculate that postoperative delirium and emergence delirium were distinct phenomena. In an article presenting several cases of adverse cognitive change after surgery, he noted:

    In some of the cases referred to, the symptoms followed at once, and there seems little room for doubt as to the cause; but in others hours or even days passed before any very characteristic effect followed, and I own it seems hard to connect these conditions.

  Despite this early recognition that abnormal behavior following emergence from general anesthesia could manifest at various latencies, emergence delirium did not become a distinct topic of investigation until widespread adoption of the postanesthesia care unit (PACU) after World War II. The intense patient observation inherent in the PACU setting quickly led to descriptive studies of psychomotor agitation in the immediate postoperative period.

  • **Postoperative Cognitive Dysfunction.** Although Savage noted in 1897 that cognitive abnormality after surgery could be temporary or permanent, the first systematic description of POCD is typically attributed to Bedford. Bedford reviewed the records of more than 1,000 patients who had undergone surgery during the previous 5 years. Based on this retrospective investigation, he determined that 10% of the patients had some form of cognitive deterioration since their surgeries, including 1.5% who had frank dementia. In the late 1970s, concern about the cognitive sequelae of “on-pump” coronary artery bypass graft (CABG) surgery led to a renewed interest in POCD. The first large-scale study of POCD after noncardiac surgery was published in 1998, and POCD research after cardiac and noncardiac surgery has grown exponentially since that time.

**Definitions**

- **Postoperative Delirium.** Postoperative delirium is an acute change in cognition that most frequently occurs 24 to 72 hours after surgery. The most reproducible clinical criterion for delirium is a decreased ability to focus, sustain, or shift attention (Table) that cannot be explained by a preexisting or evolving disorder, such as dementia or psychosis. Other cognitive processes, including perception, memory, and language may also be disturbed. The severity of the disturbance tends to fluctuate during the course of the day with accompanying disruption of the sleep-wake cycle. Depending on the subtype of delirium, the patient’s level of arousal may range from agitated or hypervigilant (hyperactive subtype) to somnolent or lethargic (hypoactive subtype) or may even oscillate between the extremes (mixed subtype).

  • **Emergence Delirium.** Emergence delirium, as opposed to postoperative delirium, is characterized by psychomotor agitation ranging from frequent, nonpurposeful movement to overt physical aggressiveness that occurs immediately or shortly after emergence from anesthesia and is self-limited. The suggested amount of time agitation may persist after emergence and still be considered self-limited is highly variable, with some authors advocating that emergence delirium must resolve by PACU discharge and others suggesting emergence delirium may last from minutes to hours.

  • **Postoperative Cognitive Dysfunction.** Postoperative cognitive dysfunction is characterized by decline in cognitive functioning that manifests after surgery. At present, the only consensus statement defining POCD applies to cognitive change after cardiac surgery, but authors have suggested that POCD be evaluated as a mild neurocognitive disorder. If the criteria in the *Diagnostic and Statistical Manual*, 4th edition, for mild neurocognitive disorder are used, for POCD to be present, the patient must demonstrate new-onset impaired functioning that:

    (1) affects at least 2 cognitive processes (see Table), (2) has persisted for at least 2 weeks, (3) has been confirmed by some form of objective testing, (4) accompanies a
general medical condition or nervous system dysfunction, and (5) is not better explained by the presence of delirium, dementia, or amnestic disorder.15

Incidence, Risk Factors, and Adverse Outcomes

• Postoperative Delirium. The incidence of postoperative delirium depends on the age of the surgical population, the type of surgery, and the tool used to detect delirium. For example, when the Confusion Assessment Method (CAM)24 was used to detect postoperative delirium, the reported incidence was approximately 12% after elective noncardiac surgery in patients older than 50 years,25 48% after CABG surgery in patients older than 59 years,26 and 30% after surgical repair of hip fracture in patients older than 70 years.27 In addition to the type of surgery, increasing age, preexisting cognitive or functional impairment, preoperative depression, preoperative use of opiates, and previous episodes of delirium have been reported as risk factors for postoperative delirium.23,28 Postoperative delirium has been associated with multiple adverse outcomes, including increased length of hospital stay,29 more frequent complications,30 and greater morbidity and mortality.31 In patients 70 years or older, delirium has also been associated with worse cognitive and functional recovery after discharge and more frequent placement in a skilled nursing facility.32

• Emergence Delirium. Emergence delirium manifests in 4.7% to 21.3% of adults after general anesthesia.17,18,33 Consistently identified risk factors for emergence delirium in adults are preoperative administration of benzodiazepines and untreated postoperative pain.17,18,33 Emergence delirium is associated with multiple adverse outcomes, including self-extubation, unintended removal of lines and tubes, injury to patient and staff, and longer stays in the PACU.17,18,33 Unlike postoperative delirium, emergence delirium was not associated with greater postoperative mortality in a population of mixed ages.18

• Postoperative Cognitive Dysfunction. The incidence of POCD depends on the degree of surgical insult, the timing of repeated neuropsychological testing, and the criteria used to define “dysfunction.” To estimate the relative incidence of POCD across various surgical populations, studies must share criteria for defining dysfunction. Rasmussen et al34 recommended definitional criteria that were developed in the first International Study of Postoperative Dysfunction (ISPOCD1).12 and these criteria have been used to assess POCD in minor and major noncardiac and cardiac surgical populations. Therefore, 3 studies using ISPOCD1 definitional criteria were used to compare the relative prevalence of POCD in these diverse surgical populations.

Monk et al35 reported the incidence of POCD after major noncardiac surgery as 36.6% in young (18-39 years), 30.4% in middle-aged (40-59 years), and 41.4% in elderly (≥ 60 years) patients at hospital discharge. Three months after surgery, the prevalence had declined to 5.7%, 5.6%, and 12.7%, respectively. Canet et al36 reported the incidence of POCD after minor surgery in patients aged 60 years or older as 6.8% at 1 month and 6.6% at 3 months postoperatively. Liu et al37 reported the incidence of POCD after CABG surgery as 49.1% at 1 week and 11.2% at 3 months after surgery in a sample of subjects with a mean ± SD age of 60 ± 8 years. Therefore, the degree of surgical insult seems to be a factor in the development of POCD and is much more influential in the immediate postoperative period.

Monk et al35 identified the risk factors for POCD at 3 months after surgery as advancing age, low educational level, POCD at hospital discharge, and prior stroke without detectable residual impairment. Canet et al36 identified risk factors for POCD after minor surgery as advancing age and inpatient versus outpatient surgery. Liu et al37 identified advancing age and diabetes mellitus as risk factors for POCD at 3 months after CABG; however, they also found that performing CABG on-pump versus off-pump did not significantly influence the incidence of POCD. Postoperative cognitive dysfunc-
tion has been associated with early exit from the labor force, decreased quality of life, and greater long-term mortality after noncardiac and cardiac surgery.38,39

Etiology

- **Postoperative Delirium.** Postoperative delirium occurs when a physiologically vulnerable patient is exposed to environmental stressors.14 Although the exact etiology of postoperative delirium is unknown, the disorder is associated with hypercortisolemia,40 increased blood-brain barrier permeability, and neuronal inflammation.41 Electroencephalography and neuroimaging studies demonstrate a generalized disruption of normal cortical function during delirium, the underlying mechanism of which may be impaired cholinergic neurotransmission.42,43
- **Emergence Delirium.** The etiology of emergence delirium is unknown. One current hypothesis for the occurrence of emergence delirium is that brain regions recover at different rates from general anesthesia and that this differential recovery rate can result in disinhibition and disorientation immediately after surgery. When a disinhibited and disoriented patient is exposed to a noxious stimulus, he or she responds with psychomotor agitation.33
- **Postoperative Cognitive Dysfunction.** The etiology of POCD is also unknown. Early suggested causes such as intraoperative hypoxemia or hypotension and the use of volatile anesthetics that do not consistently demonstrated an association with POCD.12,44 Animal models of POCD have demonstrated increased β-amyloid deposition and/or phosphorylation of tau proteins in the central nervous system, similar to that seen in Alzheimer disease. Therefore, several authors have reasonably suggested that POCD represents an acceleration of Alzheimer disease–type pathology.45-47

Measuring Cognitive Change After Surgery

- **Postoperative Delirium.** A number of validated instruments for measuring postoperative delirium are available. These instruments can be roughly divided into screening tools that codify delirium as present or absent and scales that quantify delirium severity, with delirium considered to be present once a preestablished cutoff has been reached. The CAM is the most common and simplest screening instrument currently used in the United States.24 The CAM evaluates 4 criteria: (1) an acute change in behavior from baseline that fluctuates over time; (2) difficulty focusing attention; (3) disorganized thought processes; and (4) aberrant level of arousal, such as agitation, daytime somnolence, or nighttime insomnia. If the patient meets criteria 1 and 2 and either 3 or 4, delirium is most likely present.

Other screening instruments include the CAM-Intensive Care Unit,48 NEECHAM scale,49 the Delirium Symptom Interview,50 the Delirium Detection Score,51 and the Nursing Delirium Screening Scale.52 Validated scales for measuring delirium include the Delirium Rating Scale 1998 Revision,53 the Memorial Delirium Assessment Scale,54 and the Delirium-O-Meter.55

Despite the availability of validated screening tools and measurement scales, delirium frequently remains undiagnosed in clinical practice. In one study, a research team and hospital staff used the CAM-Intensive Care Unit to screen medical and surgical intensive care unit patients for delirium. Research staff noted a patient to be delirious on 89 of 425 bed-days, while hospital staff physicians and nurses correctly identified only 28% and 35% of these delirious bed-days, respectively.56
- **Emergence Delirium.** Studies of emergence delirium use arousal scales developed for the intensive care setting or qualitative criteria to measure emergence delirium. The Richmond Agitation and Sedation Scale17 and Riker Sedation-Agitation Scale19 have been used to measure emergence delirium. These numeric rating scales respectively quantify arousal along a 7- to 10-point continuum ranging from unresponsiveness to combativeness. Yu et al33 instead used qualitative criteria to categorize the severity and duration of agitation as absent, mild, moderate, or severe.
- **Postoperative Cognitive Dysfunction.** Although patient and family complaints of cognitive change after surgery are common, subjective appraisals of cognitive performance after surgery are more closely related to mood state and anxiety level than actual performance on neuropsychological tests.57,58 Therefore, neuropsychological testing is necessary to detect POCD. Varying permutations of more than 70 different neuropsychological instruments have been used in test panels to quantify POCD.13,39 Regardless of composition, these test panels should be administered by a trained professional preoperatively and repeated at least 1 month after noncardiac surgery and 3 months after cardiac surgery.20,21 A full review of these instruments is impossible within the scope of this article. However, a useful example of a relatively simple test panel for establishing POCD is the CNS [central nervous system] Dysfunction After Cardiac Surgery consensus statement.20,21

The recommended CNS Dysfunction After Cardiac Surgery test panel consists of the Trail Making Test Parts A and B (Trails A and B), the Rey Auditory Verbal Learning Test, and the Grooved Pegboard Test. The Trails A and B are pencil-and-paper tests of attention and perception consisting of 25 circles distributed randomly across a page.59 (pp371-374) Each circle contains a letter or number.
In the Trails A, the circles contain the numbers 1 to 25, and the task is to draw a line connecting the numbers in ascending order. In the more complex Trails B, the circles contain the numbers 1 to 13 or the letters K to L, and the task is to draw a line connecting the numbers and letters in alternating and ascending order; that is, the line is drawn from 1 to A, A to 2, and so on. The score for each is the time required to draw a line linking the circles in the correct order. The Rey Auditory Verbal Learning Test is a test of verbal learning ability in which a list of words is repetitively read to the subject; the score is the number of words the subject can repeat correctly from memory after a certain number of readings.59(pp422-429) The Grooved Pegboard Test measures motor processing and requires the subject to correctly orient and insert a set of pegs into a board as rapidly as possible; the score is the time required for this effect.

Pharmacologic manipulations to reduce the incidence of delirium have demonstrated mixed success. Pharmacologic prophylaxis with centrally acting cholinesterase inhibitors and neuroleptic agents has not been demonstrated to prevent delirium in large-scale randomized, controlled trials.64-66 Although prophylaxis with haloperidol has been demonstrated to reduce the duration of delirium,64 the reduction did not affect the risk of eventual mortality or dementia.33

In contrast, adjuvant drugs such as the α2-agonist dexmedetomidine or the γ-aminobutyric acid analog gabapentin have been associated with a reduced incidence of postoperative delirium.67,68 One possible explanation for this effect is that these agents replace or decrease the requirement for cholinergically active benzodiazepines and opiates.67,68

• Emergence Delirium. There are presently no evidence-based strategies to prevent or treat emergence delirium in adults. Anecdotal recommendations from studies of emergence delirium include avoiding preoperative benzodiazepines; ruling out potential physiological causes such as airway obstruction or hypoxemia; identifying and eliminating noxious stimuli such as urinary retention, bright lights, and environmental noise; treating pain; and removing tubes and catheters as early as possible. If these strategies are unsuccessful, a small amount of a rapid-acting sedative such as propofol or midazolam may be necessary to keep patients from injuring themselves or others.17,18,33

• Postoperative Cognitive Dysfunction. At present, there are no anesthetic practices that consistently reduce the incidence of POCD at 3 months after surgery. A recent meta-analysis of randomized controlled trials found a nonsignificant trend toward greater risk of POCD after noncardiac surgery when general versus regional or neuraxial anesthesia was used.69 Likewise, a meta-analysis of randomized controlled trials comparing off-pump with on-pump CABG found a lower risk of POCD at 1 and 3 months but not at 6 or 12 months after surgery.69 Therefore, broadly applicable, evidence-based practices to prevent POCD remain elusive for noncardiac and cardiac patients. However, such recommendations may emerge as additional studies are added to the literature. As animal models suggest that surgery triggers an

Prevention and Management

• Postoperative Delirium. In the absence of a known etiology for postoperative delirium, current management strategies focus on reducing environmental stressors that can precipitate postoperative delirium. Effective prevention strategies include aggressively seeking and treating underlying infection; ensuring proper nutrition, hydration, and early mobilization after surgery; providing structured sensory input; allowing adequate opportunity for sleep; and managing agitation with small amounts of neuroleptic agents. The use of anticholinergic drugs, including opiates and benzodiazepines, should be avoided if possible.42,61 If opiates must be used, the route of administration (ie, intravenous versus epidural) does not impact the incidence of postoperative delirium, but meperidine has been consistently associated with greater risk regardless of route of administration.62 A recent meta-analysis of randomized, controlled studies found no significant effect of general versus regional anesthesia on the incidence of postoperative delirium.53
A clinician’s options are likewise limited when POCD is suspected or detected. Based on the association of subjective cognitive complaints with depressive symptoms and anxiety, patients with cognitive complaints after surgery should be screened and treated for depression and anxiety and assessed for cognitive impairment. It is thus difficult to draw a hard and fast time limit dividing these two classes of cases.

This absence of a firm distinction persists. For example, Deiner and Silverstein distinguish between the two by describing emergence delirium as “correlated with general anesthesia, and providing the patient is guarded from harming themselves, resolves without sequelae,” and postoperative delirium as delirium “that occurs after a relatively normal emergence and that occurs at some interval after surgery and anaesthesia.” Other authors offer similar criteria when the 2 phenomena are contrasted. However, these criteria offer more questions than answers when conducting empirical investigations.

If emergence delirium is defined only as psychomotor agitation, which phenomenon is occurring when patients are hypoactive for an unexplainable period after anesthesia? To address this limitation, Radtke et al proposed the term inadequate emergence and measured the phenomenon simultaneously with emergence delirium. In that study, inadequate emergence occurred after 3.2% of anesthetics and shared the behavioral attributes of hypoactive delirium. If emergence delirium occurs only in the PACU and must end before discharge, which phenomenon is occurring when abnormal behavior persists after PACU discharge? By using the CAM in patients after repair of hip fracture, Sharma et al demonstrated a 36% incidence of postoperative delirium in the PACU. Sharma et al observed the patients for the next several days and concluded that 75% of the patients in whom delirium developed in the PACU also had delirium on subsequent postoperative days.

Distinguishing between inadequate emergence or emergence delirium and postoperative delirium is important; if they are confused, providers and researchers may be missing many cases of postoperative delirium by not screening patients during recovery from anesthesia. If present but unobserved, these cases detract from the power of delirium research to effectively measure its outcome of interest and represent missed opportunities for clinicians to detect and treat reversible causes of delirium.

A similar situation exists with postoperative delirium and POCD. Although perceived as a transient phenomenon by many providers, delirium can persist for some time after hospitalization and surgery. By using the Delirium Symptom Interview, Levkoff et al found that up to 82% of a combined sample of medical and surgical patients older than 65 years in whom delirium developed while they were hospitalized still had residual delirium symptoms 6 months after discharge, and 31% still met diagnostic criteria for delirium. Given the nature of the tasks used to screen for POCD, a subject with delirium would likely meet the criteria for POCD. However, few studies of POCD report screening subjects for delirium and the presence of subjects with delirium reduces the power of a study to detect POCD. In clinical practice, undetected delirium is a missed opportunity to treat potentially reversible causes. Mislabeling delirium as POCD is problematic because delirium has much worse prognostic significance than POCD.

Conclusion

In the absence of phenomenological distinction between emergence delirium and postoperative delirium and between postoperative delirium and POCD, how should clinicians approach patients demonstrating cognitive change after surgery? Given the potentially reversible nature and adverse prognostic significance of postoperative delirium, a patient demonstrating behavior change after surgery should be actively screened for the disorder. If the patient screens positive for postoperative delirium, reversible causes should be sought and treated. Only if...
postoperative delirium is excluded can a clinician assume that emergence delirium or POCD is present. This same principle should hold true when interpreting the generalizability of research; clinicians should interpret the clinical relevance of any given study in the light of how it acknowledges and handles the distinctions among postoperative delirium, emergence delirium, and POCD. Failing to address the distinctions in a study could result in incorrect conclusions about the adverse effects of a risk factor or the benefits of a treatment. If the goal of a study is to examine emergence delirium or POCD, the study should have a plan to detect, discriminate, and analytically account for subjects with postoperative delirium.

REFERENCES


