Prevention and Management of Postoperative Delirium

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Introduction

The subject of this article is perioperative delirium, particularly in the elderly surgical patient. Elderly patients, defined as those over 65 years of age, account for 43% of surgical patients in the United States today.[1] Although this number excludes obstetric operations it does include both healthy vibrant older individuals as well as chronically and critically ill patients, whose risk for delirium is typically significant.

Delirium: Definition and Significance

Delirium is an episode of acute confusion that may be precipitated by a medical illness, medication, and/or a change of environment. Delirium is characterized by disturbance of consciousness with reduced ability to focus, sustain, or shift attention; and a change in cognition or the development of a perceptual disturbance that is not better accounted for by a preexisting dementia. The confusional episode develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day [Diagnostic and Statistical Manual of Mental Disorders (DSM IV)]. Delirium is known to be a common problem for elderly patients during the perioperative period and particularly during care in an intensive care unit (ICU). Anesthesiologists may underestimate

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the potential consequences of an episode of delirium and how the anesthetic plan may contribute to the prevention or development of delirium. When evaluating a patient for anesthesia, much care is taken to ensure that patients do not have significant underlying diagnoses, which can complicate their postoperative course. Often the focus is on comorbid cardiopulmonary illness and associated testing that enables risk stratification. Optimal treatment of preoperative cardiopulmonary disease is emphasized to reduce the risk of, for example, a perioperative myocardial infarction. And yet, cognitive status—outside of alert versus stuporous—is often overlooked. Like a diminished creatinine clearance heralds renal dysfunction and failure, short term memory loss, impaired orientation, and/or attention are signs of a fragile neurologic dysfunction and increase the risk for perioperative delirium.[2]

For many anesthesiologists, delirium is not often a significant concern. Commonly when it comes to our attention it is with a patient suffering from emergence delirium in the operating room or postanesthesia care unit (PACU). Most often delirium is thought to be a disease of older patients, however, emergence delirium is common in all age groups. The following recounts a conversation between one 19-year-old patient and his PACU nurse on arrival:

Patient: Are we playing laser tag?
Nurse: No, you're in the hospital; you're just waking up from surgery.
Patient: Oh, I'm sorry; I thought you were talking about laser tag.
The patient then dosed off, and upon reawaking said:
Patient: Well, you're lucky, 'cause I'm really good at laser tag, I'll protect you.

Half of the patients with emergence delirium have significant or dangerous levels of agitation. Often these are patients who have a persistent endotracheal tube or a bladder catheter and perceive the need to urinate or are otherwise anxious. These patients are typically disoriented and confused but generally improve back to baseline with verbal reorientation and patience.[3] The natural history of delirium not directly associated with anesthetic medications is often much more protracted.

Delirium has 2 major components, an acute onset of altered or fluctuating mental status and significant inattention. In general, physicians are more familiar with hyperactive delirium which is a state of agitation, hyperarousal, and/or hyperalertness. Often this is an agitated patient talking or yelling, pulling at monitors and lines and displaying psychotic features. This form of delirium, although more commonly recognized and treated, actually has a lower incidence than the hypoactive subtype. Patients who are hypoactively delirious are withdrawn, display a flat affect, and are less responsive and/or lethargic.[4]

Although patients with hypoactive delirium tend not to be as difficult to manage, most of these individuals will report psychotic symptoms when they are interviewed either during the episode or following it. Hypoactive delirium is thought to remain undiagnosed in 66% to 84% of patients.[5] This is particularly problematic as hypoactive delirium and mixed delirium—which has features of both subtypes—have a poorer prognosis and worse long-term morbidity and mortality outcomes.

In summary, delirium is not a benign syndrome. It is associated with longer hospital stays and increased admissions to ICUs and postacute care facilities. A solitary episode of delirium can increase mortality up to 3-fold over 6 months.[6] Evidence also shows an association between delirium and early postoperative cognitive dysfunction, defined as cognitive deficits on postoperative day (POD) 7, and may play a role in late postoperative cognitive dysfunction.[7] In addition to the known long-term health consequences, a single episode of delirium can increase the cost of hospitalization for a patient from an average of $23,000 to an average of $42,000.[8] The belief that acute confusion developing during a hospitalization is an insignificant, self-limited clinical problem is clearly incorrect.

■ Patient Risk Factors for Delirium

The best treatment for delirium is prevention. Understanding which patient cohorts are at risk for developing perioperative delirium and the implications for medication and anesthetic choices in at-risk patients are critical precursors to the reduction of delirium incidence. Older adults have significantly more episodes of hospital acquired delirium when compared with younger cohorts. One caveat to this rule is the consideration of a patients "physiologic" age. A spry, otherwise healthy 80-year-old patient admitted for a cholecystectomy has a lower risk of delirium as compared with a 50 year old admitted for a below the knee amputation, with chronic diabetes, congestive heart failure, chronic obstructive pulmonary disease, coronary artery disease, and a history of recurrent hospitalizations. Comorbid illnesses increase the risk that a patient will have 1 or more periods of delirium. This is an additive phenomenon where increasing numbers of diagnoses increases the likelihood of delirium. Preexisting neurologic dysfunction, such as Alzheimer disease, can make it harder for the patients' brain to cope with additional stressors. Other physiologic changes and disease processes prevalent in the perioperative period that increase the risk for delirium include hypoxemia, electrolyte and fluid imbalance, infections and sepsis.[5]

It is important to review chronic prescription and over-the-counter medications when determining a patient's risk for delirium. On

admission to the hospital, most providers tend to continue outpatient medications; however, with respect to a patient's delirium risk, some medications may be dangerous to continue. For example, it is well known that medications such as diphenhydramine have anticholinergic activity, which can contribute to urinary retention and development of delirium. Withdrawal syndromes, either from prescription medications or from street drugs or alcohol often are implicated in the alteration of mental status. Development of delirium can also be precipitated by new medications given to patients in the hospital, particularly by anesthesiologists. One study showed lorazepam to be an independent risk factor (RF) for the development of delirium, though the odds ratio was just 1.2 [confidence interval (CI), 1.1-1.4].[9] Anesthetic agents, with the exception of ketamine, agonize the γ-aminobutyric acid (GABA) receptor and are known to cause delirium, more commonly the hypoactive form.[10] Propofol, used as an induction agent and for maintenance of anesthesia both in the operating room and in the ICU, has tended toward being an independent RF for delirium.[10] Meperidine, most commonly used for management of postanesthetic shivering has been shown in multiple studies to be an independent RF for postoperative delirium.[11] Anticholinergic medications which cross the blood brain barrier, such as atropine, can precipitate confusion. These agents are frequently used to counteract the side effects of acetylcholinesterase inhibitors, commonly used to antagonize the effects of neuromuscular blocking drugs. Glycopyrrolate is typically favored over atropine for its pharmacokinetic properties pertaining to onset and duration (similar to that of neostigmine, and more gradual than atropine) and the fact that it is a quaternary amine and so cannot cross the blood brain barrier to cause as many neurologic sequelae. If delirium does develop as a consequence of anticholinergic medications, it is commonly the hyperactive subtype.[10] The question then arises: is this common practice for minimization of muscarinic side effects of anticholinergics appropriate for patients at high risk for delirium?

Anesthesiologists have investigated the potential benefit of providing a regional anesthetic in appropriate cases, thus minimizing exposure to GABAnergic drugs. There is no conclusive evidence showing that a regional anesthetic leads to any less postoperative delirium than a general anesthetic.[12] However, it should be noted that in many of these studies the patients undergoing an operation with regional anesthesia received benzodiazepine premedication, often significant doses, which are known to cause delirium. It is likely that a purely regional anesthetic, or a regional anesthetic accompanied by minimal sedation with opiates or non-GABA agonists, would lead to fewer episodes of postoperative confusion and inattention.[13] This idea is supported by the fact that the risk of developing delirium is tightly correlated with the duration of a general anesthetic.[7]

Just as the presence of an endotracheal tube, Foley catheter and full bladder are often precipitants of emergence delirium; postoperative pain is commonly a trigger for this acute confusional state. It has been shown that the more severely a patient experiences pain at rest after an operation, the more frequently they develop confusion. Interestingly, the maximum pain felt in a 24 hour period and pain with movement were not correlated with delirium. The authors of 1 study suggested that rest pain was a cause of delirium since it was a persistent stressor and had a more constant impact on their day and sleep-wake cycle.[11] In the same study, researchers also attempted to see if opiates were related to delirium. They found that neither the drug (with the exception of meperidine) nor the total daily dose of opiates (measured in morphine equivalents) correlated with progression to delirium. They were unable to show any difference in rates of delirium for patients whose pain was managed with neuraxial techniques versus opiate administration.

It is useful to know not only what RFs a patient has for delirium, but how to interpret the sum of these in order to determine the probability of developing delirium. Several studies have attempted to clarify this issue. One of the simplest RF assessments involves evaluation of the presence or absence of 4 RFs: visual impairment, cognitive impairment, severe illness, and blood urea nitrogen/creatinine ratio >18. Having no RFs correlates with a 9% risk of development of delirium; 1 or 2 RFs corresponds to a 23% risk of delirium, and presence of 3 or 4 RFs is associated with an 83% chance of a patient having one or more episodes of delirium.[14] Of note, this particular study excluded previously demented patients in its analysis, suggesting that the demented patients' risk would be even higher than the quoted percentages. Other studies have presented conceptually similar risk scoring systems which are more complex, but show similar results.[15]

■ Diagnosis of Delirium

Society seems to have accepted that as people age they become more confused and frequently "demented." Delirium is often considered to be a part of this "normal aging process." This is not the case. Although it is normal for the elderly to experience a slowing of reaction times, or more difficulty in dynamic processing of information, it is not normal to have persistent memory and cognitive dysfunction. Only 5% of patients of age 65 and over suffer from a dementia.[12] In the past, the diagnosis of hospital-acquired delirium was often made during a psychiatric consultation using the DSM criteria. The required psychiatric consult required a 30 to 60 minutes evaluation.[16] A method for the early and rapid identification of delirium by all hospital professionals was needed. Simply noting that a patient is awake, alert, conscious and following commands is insufficient, as 40% of these patients still meet

criteria for the diagnosis of delirium. Fortunately, a quick and easily performed assessment was created based on the DSM IV criteria, entitled the Confusion Assessment Method (CAM). This is a series of 4 criteria, of which 3 must be met for the diagnosis of delirium to be made. The CAM assessment was then modified to the CAM-ICU. The changes were made so that mechanically ventilated patients could be assessed as well; questions (Fig. 1) can be answered by squeezing a hand and nodding "yes" or "no." The CAM-ICU is performed at the bedside by either nursing staff or physicians and takes approximately 2 to 3 minutes, making it very feasible for this to be performed several times per day so that fluctuations in mental status are accurately documented. The accuracy of a positive CAM-ICU test in predicting delirium is 98.4%.[16]

The majority of studies on postoperative delirium found that it generally developed early in the postoperative period. One shows that POD 2 is the most common time to develop delirium[10]; another concluded that all of the patients studied developed delirium before POD 3.[17]

■ Prevention of Delirium

The prevention of delirium is of the utmost importance, as "once an initial episode of delirium has occurred…intervention has no significant effect on the severity of delirium or on the likelihood of recurrence."[18] Importantly, the preventive approach to delirium can begin even before the day that the patient presents for an operation.

Preoperative

Increasingly, patients are being evaluated in preoperative anesthesiology clinics at least several days before the day of surgery. These visits function to ensure that patients are medically optimized and in the best possible condition for surgery. Although preoperative evaluations often

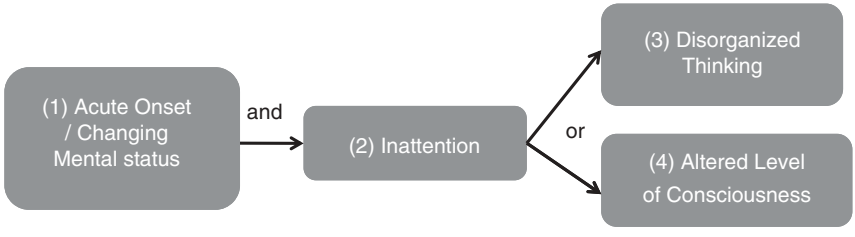

Figure 1. *Assessment of delirium by CAM-ICU tool. Positive for delirium when criteria (1) and (2) are met plus either (3) or (4). How to assess the above criteria: (1) Evaluate patient over time. (2) Ask patient to squeeze your hand each time the letter "A" is said, spell SAVE A HEART. Criteria filled if 3 or more are incorrect. (3) Ask the patient 4 questions: Will a stone float on water, Are there fish in the sea, Can you use a hammer to pound a nail, Does 1 pound weigh more than 2 pounds. Criteria filled if 2 or more are incorrect. (4) Assessment of RASS (Table 2).*

focus on assessment of cardiopulmonary risk and provision of therapies to minimize these risks, it is also feasible during these visits to assess the RFs for delirium and plan preventive measures for high risk patients. Several RFs for delirium, such as visual impairment, cognitive impairment, and severe illness can be identified when performing the history and physical. Depending upon the prediction model used, the only additional information needed to perform a risk calculation is the blood urea nitrogen/creatinine ratio.[13] For some of the other prediction models, additional necessary information may include serum albumin and the results of a Mini-Mental Status Examination and/or a Geriatric Depression Assessment scale.[14] These assessments generally add little time to the preoperative visit. Furthermore, as many anesthesia clinics are structured such that an attending physician does not conduct the entire interview (these are often facilitated by a resident physician or nurse practitioner) and does not interview all of the patients, this additional time would have little impact on physicians' ability to see patients throughout the day.

If a high risk patient is identified during the clinic visit, the anesthesiologist can discuss the implications of high risk status with the patient, family, and attending surgeon. Provided that the procedure is deemed necessary, the development of an operative and anesthetic plan which minimizes intraoperative time as well as exposure to benzodiazepines and other deliriogenic drugs could be formulated in advance of the surgery. In addition, the patient and family should be counseled with regard to what to expect postoperatively, and they should be encouraged to arrange family or private sitters to be with the patient throughout the hospitalization.

Postoperative

Nursing staff play a critical role in the prevention of postoperative delirium. Nurses are at the patients' bedside more frequently than any other hospital staff members and therefore have the greatest opportunity to reorient the patient to place, time, and situation. The simple intervention of talking with a patient and telling her where she is and why is commonly used by PACU and ICU nurses and is effective in preventing delirium. In addition, as delirium is often the result of other physiologic derangements, nurses can play a key role in process of identifying and correcting these etiologic abnormalities before the patient develops delirium. One component of this type of preemptive strategy that has proven to be successful is the utilization of in-hospital geriatric medicine consultations.[19] In 1 study, geriatricians were consulted either preoperatively or within 24 hours postoperatively. Geriatricians performed a thorough chart review, analyzing patients' medication regimens and current diagnoses, and verified that no diagnoses were missed. Particular

care was taken to ensure that patients were not receiving extraneous medications, that they had appropriate environmental cues (wearing their glasses, calendar in the room, etc), that bowel and bladder function were addressed, and that appropriate measures to prevent other postoperative problems such as myocardial infarction, atrial fibrillation, and pulmonary embolism were employed. This addition to the care team resulted in a delirium rate of only 32%, compared with 50% in the usual care group, corresponding to prevention of delirium in 1 patient for every 5.6 patients receiving the consultation.[20]

Interventions other than involvement of a consulting geriatrician have also been investigated. The focus of many of these approaches is aimed at reducing RFs for delirium. Importantly, patients at low risk and those at very high risk do not benefit as much from active intervention as do those in the intermediate risk category (1 or 2 of Inouyes' 4 RFs of poor vision, impaired cognition, severe illness, and dehydration). In this risk cohort, employment of the simple interventions in Table 1 was shown to reduce the incidence of delirium (9.9% in the intervention group versus 15% in the usual care group). A significant decrease was also demonstrated in both the total number of episodes of delirium (62 compared with 90) and in the patient-days of delirium (105 for the intervention group, 161 for standard care group). These benefits were most profound when a first episode was treated adequately. Treatment of recurrent episodes of delirium did not result in the same reduction in future episodes or patient-days of delirium.

When patients are mechanically ventilated in the ICU, the approach is different. In this setting, sedation is often required to ensure patient safety and patient-ventilator synchrony. Although it is ideal to keep most patients at a level of sedation from which they easily awake in response to voice, this is not always easily accomplished. Furthermore, because commonly used sedatives such as benzodiazepines are deliriogenic in dose-dependent fashion, it is important to use these drugs sparingly, if at all. The Richmond Agitation Sedation Scale (RASS; Table 2) is a particularly useful tool for the targeting of sedation. In the Surgical ICU at the University of Cincinnati, all sedation orders require an order for a goal level of sedation. Typically, RASS +1 to −1 is chosen as the sedation goal. However, in the rare event that patients require deeper levels of sedation for the purpose of safety, a deeper level of sedation (RASS −2 to −3) is chosen.[9] Since implementing a RASS-guided sedation protocol at our institution, the incidence of oversedation and use of benzodiazepines has diminished significantly.

■ Treatment of Delirium

If a patient does progress to delirium despite the utilization of all possible preventative measures, treatment must be initiated to minimize

Table 1. *Suggested Interventions to Prevent Delirium*

Risk Factor	Prevention Measure
Visual impairment	Utilization of glasses, large print books
Hearing impairment	Use of hearing aids or other amplifying devices, earwax removal as needed
Cognitive impairment	Continuous reorientation, writing the name on dry erase boards of nursing staff, respiratory technicians, etc
Dehydration	Early recognition, fluid replacement preferably oral when appropriate
Immobility	Getting the patient out of bed, to the chair, range of motion activities (ideally active, passive if that is not possible), minimization of physical restraints (including Foley catheters)
Sleep deprivation	Maintain sleep/wake cycle, keep unit quiet at night, easy visibility of windows, minimization of interruptions during the night for medications

Modified from *NEJM*. 1999;340:669–676.[18]

the duration and severity of the episode and to prevent further episodes. Optimization of all contributing medical problems, such as treatment of a urinary tract infection, is the best way to treat delirium.[21] After the precipitating medical problems are identified and treatment is begun, the management of the delirium by nonpharmacologic methods is the next-best approach. Reorienting a patient to place, time and situation is important, and the institution of practices aimed at maintaining day-night orientation is crucial. Encouraging the family to sit with the patient can be very helpful, reducing the need for restraints or sedative medications.

Table 2. *RASS Scale*

Score	Descriptor	Clinical Appearance
+4	Combative	Violent, a danger to themselves and others
+3	Very Agitated	Aggressive, pulling at catheters and monitors
+2	Agitated	Working against ventilator, nonpurposeful movement
+1	Restless	Anxious without aggressive behavior
0	Alert and Calm	
−1	Drowsy	Sustained awakening to voice >10 s
−2	Light Sedation	Awakens to voice <10 s
−3	Moderate Sedation	Movement or eye opening to voice
−4	Deep Sedation	Movement or eye opening to physical stimulation
−5	Unresponsive	

Modified from *Crit Care Nursing*. 2003;23:25–35.[4]
RASS indicates Richmond Agitation Sedation Scale.

It is important to stress that the mere presence of delirium is not an indication for the prescription of sedative or antipsychotic medication. When medications are used to treat agitated delirium, simply to quiet the patient or avoid the use of a sitter, they increase the risk of falls, injury, and loss of mobility. However, antipsychotic medications may still be necessary for symptoms such as delusions or hallucinations, or when conservative measures have failed to control patient behavior that is dangerous to themselves or others or interferes with essential medical treatment. When pharmacologic treatment is used to treat delirium symptoms, the goals should be clearly identified, documented, and regularly reassessed.

The majority of the surgical, anesthesia and critical care literature suggests haloperidol dosage in the range of 2.5 to 5 mg intravenously every 4 hours as needed for control of delirium symptoms. Although these doses may be required in the ICU, they are much higher than the doses used in geriatrics practice, where amounts as small as 0.25 mg to 0.5 mg orally are standard. If possible, lower doses should be used initially and titrated gradually to effect. One of the main side effects of haloperidol is the prolongation of QTc interval, which is associated with development of Torsades des Pointes. It is reasonable to assess the QTc on a daily basis, either on 12-lead electrocardiogram or on telemetry, in patients receiving significant amounts of haloperidol. An alternative plan for delirium management is needed if the QT interval is >500 ms. The second major side effect of typical antipsychotics, which may limit their use is extrapyramidal symptoms. This is less likely at lower doses under 2 mg/day, but quite common at higher doses. The atypical antipsychotics, such as olanzapine and risperidone are reasonable alternative choices for haloperidol and carry a smaller risk of development of extrapyramidal symptoms.[9] Medication side effects are common and often fairly pronounced in elderly patients. One strategy to minimize side effects is utilization of several different classes of medications at smaller doses. Geriatricians often will combine mood stabilizers, such as depakote or tegretol, with benzodiazepines and antipsychotics (either typical or atypical) to achieve the desired response: an awake, nonagitated patient who is free of psychotic symptoms.

Few researches have assessed whether delirium treatment should vary depending on the predominance of active or hypoactive symptoms. It is generally agreed that hyperactive, hypoactive and mixed delirium should all be treated similarly. Although it may seem counterintuitive to administer a sedating medication to a patient with hypoactive delirium, if psychosis is interfering with care or is frightening to the patient, somnolence or other symptoms of hypoactive delirium should not prevent treatment with antipsychotic medications.[10]

Evidence to support the use of other pharmacologic treatments for delirium is lacking. In an effort to avoid GABAnergic effects,

dexmedetomidine (DEX) seems a good alternative choice for sedation. At this time, DEX is approved for only short term sedation (<24 h). However, it is not uncommon for critically ill patients, particularly those in surgical and trauma ICUs, to require sedation for longer than 24 hours. Recent data from a small study of longer usage of DEX (mean usage 86 h with a range of 26-280 h) showed that there was no increase in the blood level of metabolites with usage of >24 hours versus <24 hours of drug administration.[22] Although more research is needed to confirm the safety of DEX for prolonged use, it holds the potential to significantly reduce the use of GABA agonizing drugs in both operating room and in the ICU.

■ ICU-wide Implementation of Delirium Prevention Strategies

All critically ill patients, regardless of age, are at an increased risk for development of delirium in the ICU environment. In patients with additional RFs, the risk of developing delirium is significantly increased. One approach to reducing the overall incidence of delirium is to institute preventative measures as standard of care for all patients in the ICU. All patients should be routinely oriented to time, place and situation, and have their sleep-wake cycles normalized to the extent possible. All patients should be ambulating or mobilized to chair as much as their diagnosis and care plan allow. In our ICU, recording of RASS and CAM-ICU scores is carried out every 8-hour shift. This routine screening for delirium is of particular help in identifying patients suffering from hypoactive delirium. Although by the time a patient is CAM positive he or she is already delirious and it is too late for prevention, early treatment through nonpharmacologic and pharmacologic means may have a significant impact on the progression of the patient's clinical course. It is important to remember that not all ICU agitation is delirium. Patients can be anxious and restless from undertreated pain as well. Opiates do not treat delirium and haloperidol does not treat pain. Although the evaluation of an agitated patient must attempt to identify the underlying cause, this search is often unsuccessful. In such circumstances, control of agitation is sometimes achieved only through pharmacologic trial and error, with small doses of different classes of drugs (opiates, benzodiazepines, antipsychotics) given intermittently, and the response to therapy used to guide further titration.

■ Conclusions

Delirium is a clinical diagnosis that must be made via direct patient evaluation. It is important to understand patient RFs for the development of postoperative delirium, and to understand the ameliorating or

exacerbating effects of the medications commonly used in perioperative medicine. Although delirium is best managed by prevention, ideally through a system of standardized interdisciplinary and multimodal intervention, anesthesiologists can contribute significantly to the reduction of delirium incidence by routinely incorporating risk assessment tools and best-evidence risk-reduction strategies into their daily practice.

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