Delirium and Cognitive Dysfunction in the Perioperative Period

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Perioperative cognitive changes are often overlooked until a patient presents with an agitated delirium several days after surgery. These acute changes in cognitive function, while sometimes dramatic, often are relegated to “emergence delirium” or “ICU psychosis” and are simply permitted to run their course. Delirium, however, is not a benign disease. Rather, it is associated with a significant increase in postoperative morbidity, disability, and death.\(^1,2\) Recently attention has focused on a broader set of disorders of postoperative cognitive dysfunction (POCD), which may represent a spectrum of organ system dysfunction of varying severity, duration, and reversibility.

Definitions

*Agitation*, which is simply excessive motor activity, is quite common in the postoperative period. It is a nonspecific symptom resulting from any type of internal discomfort including pain, anxiety, fear of death, etc. Agitation resulting from pain or anxiety is relatively easily treated with reassurance and the appropriate use of analgesics and benzodiazepines. Delirium, however, is more difficult to prevent, diagnose, and treat, and the clinical outcome of patients with delirium is much different.\(^3\)

*Anxiety* specifically describes an unpleasant alteration of mood and emotions that is not accompanied by cognitive dysfunction. The patient continues to think and comprehend normally. There appears to be no relationship between perioperative anxiety and the occurrence of delirium.\(^4,5\)

*Delirium*, like anxiety, is characterized by an unpleasant alteration of mood. Unlike anxiety, delirium is an acute confusional state accompanied by cognitive impairment. Accordingly, delirium has been described as “acute cognitive dysfunction” or “acute brain failure.” The distinction of cognitive impairment is critical to making the proper diagnosis and prescribing appropriate therapy. The DSM-IV-TR diagnostic criteria include: 1) a disturbance of consciousness with reduced ability to focus, sustain, or shift attention; 2) a change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing or evolving dementia; 3) development of the disturbance over a short period of time (hours to days) and a fluctuating course over the day.\(^6\) Clinical features of delirium are summarized in Table 1. Patients may be hyperactive and agitated, or hypoactive and lethargic. Hypoactive delirium may be difficult to appreciate, often remains undiagnosed, and may have a poorer long-term outcome than agitated delirium.\(^4\)

<table>
<thead>
<tr>
<th>Table 1. Clinical Features of Delirium</th>
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<tbody>
<tr>
<td>• Prodromal phase</td>
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<tr>
<td>• Fluctuating course with lucid intervals</td>
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<td>• Altered arousal and psychomotor abnormalities</td>
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<td>• Decreased attentiveness</td>
</tr>
<tr>
<td>• Disturbed sleep-wake cycle</td>
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<td>• Impaired memory</td>
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<td>• Disorganized thinking and speech</td>
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<tr>
<td>• Altered perceptions</td>
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<tr>
<td>• Disorientation</td>
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<td>• Dysgraphia</td>
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Etiology and Risk Factors

As many as one to two-thirds of older patients admitted to intensive care units will have an episode of delirium during their stay. The precise etiology is entirely unclear. Of course, organic causes of an altered mental status must always be considered and include drug and alcohol withdrawal, Wernicke's encephalopathy, hypertensive encephalopathy, hypoglycemia, hypoperfusion, hypoxemia, intracranial bleed, meningitis/encephalitis, and side effects of medications (all designated by the mnemonic WHHHHIMP).\(^7\) Some hypothesize that delirium results from vulnerability on the part of the patient (e.g., cognitive impairment, severe illness, visual impairment, etc.) and hospital-related insults (e.g., medications and procedures).\(^3\) Others suggest that acute brain dysfunction occurs secondary to a perioperative systemic inflammatory response, similar to other organ failures.\(^6,9-11\) Inouye and Charpentier developed a predictive model for the occurrence of delirium in hospitalized general medical patients greater than 70 years of age.\(^12\) Risk factors included the use of physical restraints, the presence of malnutrition, the addition of more than three medications over the last 24 hours, the use of a bladder catheter, and the occurrence of any iatrogenic event. A greater number of factors was associated with an increased incidence of new-onset delirium (0 factors, 4%; 1 to 2 factors, 20%; ≥ 3 factors 35%).

Subtle pre-existing attentional and cognitive deficits, decreased executive function, and depression are associated with an increased risk of postoperative delirium.\(^13-19\) Other pre-existing factors that have been correlated with the occurrence of perioperative delirium include: age 70 years or older; self-reported alcohol abuse; poor functional status; markedly abnormal preoperative serum sodium, potassium, or glucose levels; hypoalbuminemia; surgery for hip fracture; noncardiac thoracic surgery; and aortic aneurysm surgery.\(^20-25\) Overall, vascular surgical patients are about twice as likely as other elective surgical patients to experience delirium.\(^26\) Preoperative factors include prolonged operative time, large blood losses, and anemia.\(^6,18,25,27,28\) A recent prospective study of 563 cardiac surgery patients reported a 16% incidence of delirium. Independently associated with delirium were advanced age, preoperative cognitive impairment, major depression, anemia, atrial fibrillation, prolonged intubation and postoperative hypoxia.\(^29\)

Assessment

Many rating scales have been developed to communicate a patient’s level of agitation and/or delirium more easily. Among them, one of the most common scales, the “Ramsay scale,” simply rates the patient’s degree of arousal from anxious or agitated (level 1), to deeply sedated (levels 4 and 5), to anesthetized (level 6).\(^30\) Perhaps a more useful scale for assessment of agitation is the Richmond Agitation-Sedation Scale (Table 2), which rates a patient’s level of agitation or sedation on a 10-point scale, ranging from -5 (unarousable to vigorous stimulation) to +4 (physically combative).\(^31-33\)

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Description</th>
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<tr>
<td>+4</td>
<td>Combative</td>
<td>Combative, violent, immediate danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated</td>
<td>Pulls or removes tubes or catheters; aggressive</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
<td>Frequent nonpurposeful movement; dyssynchrony with ventilator</td>
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<tr>
<td>+1</td>
<td>Restless</td>
<td>Anxious, but movements not aggressive or vigorous</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
<td>Sustained awakening (&gt;10 sec) with eye contact to voice</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation</td>
<td>Briefly awakens (&lt;10 sec) with eye contract to voice</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation</td>
<td>Movement or eye opening to voice, but no eye contact</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation</td>
<td>No response to voice; responds to physical stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>Unarousable</td>
<td>No response to voice or physical stimulation</td>
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Delirium in postoperative and ICU patients commonly is assessed using the Confusion Assessment Method (CAM),\textsuperscript{34-36} which has been modified for ICU patients (CAM-ICU). The CAM-ICU briefly examines four key features of delirium: (1) acute onset or fluctuating course; (2) inattention; (3) disorganized thinking; and (4) altered level of consciousness. Diagnosis of delirium is made if the patient displays the first two features along with either disorganized thinking or altered level of consciousness. Testing with the CAM-ICU has been highly standardized, and the assessment is quick, repeatable, and reliable.\textsuperscript{37,38} A pediatric version of the scale has been recently validated.\textsuperscript{39}

**Therapy**

Postoperative delirium usually develops between postoperative days 2 to 7.\textsuperscript{40} This time-course correlates with the typical progression of postoperative systemic inflammatory response. One hypothesis for the etiology of delirium is that the postoperative increase in inflammatory, oxidative, and psychosocial stress stimulates the production of pro-inflammatory cytokines and the production of delirium-potentiating neurotoxins.\textsuperscript{6,41,42}

Clinically, however, delirium remains a diagnosis of exclusion. Identification and treatment of other causes of acute brain dysfunction, correction of electrolytes, and avoidance of benzodiazepines and other medications sometimes can be curative.

**Prevention**

Evidence for the efficacy of preventative measures for delirium is sparse, but conservative measures, such as prompt treatment of infections, maintenance of a normal sleep-wake cycle, avoidance of physical restraints, early mobilization, involvement of family members, and frequent reorientation have been suggested and appear reasonable on face value (Table 3).\textsuperscript{6,8,43} The presence of an endotracheal tube, urinary catheter or surgical drains, urinary retention, and pain are common triggers for acute confusion and agitation, especially in the post-anesthesia care unit (PACU), and the occurrence of delirium in the PACU appears predictive of continued postoperative delirium.\textsuperscript{44} Postoperative pain and increased pain severity have been correlated with the occurrence of delirium. In a study of hip fracture patients, cognitively intact patients with undertreated pain were nine times more likely to develop delirium than patients whose pain was adequately treated.\textsuperscript{45} Elderly patients who received oral opioid analgesics, compared with intravenous or neuraxial analgesia, had a decreased incidence of delirium.\textsuperscript{46} Minimization of tubes and drains and anticipatory treatment of pain are reasonable approaches to reducing the chance of delirium. A proactive geriatric consultation, or treatment within a specialized hospital program, may reduce delirium incidence and severity in elderly patients.\textsuperscript{8,47-51}

| Table 3. Risk Factors and Interventions for Delirium \textsuperscript{8} |
|---------------------------|---------------------------------------------------------------|
| Risk Factor               | Example of Intervention                                       |
| Cognitive impairment      | Frequent reorientation; provide stimulating activities       |
| Sleep deprivation         | Noise reduction strategies; schedule adjustments             |
| Immobility                | Early mobilization; ambulation; active range of motion;      |
|                           | minimize catheters and physical restraints                   |
| Visual impairment         | Provide glasses and adaptive equipment                        |
| Hearing impairment        | Provide hearing aids; special communication techniques       |
| Dehydration               | Encourage oral intake of fluids                              |

Few studies suggest any efficacy for prophylactic pharmacologic treatment. One study has suggested that preoperative administration of statins may reduce the risk of postoperative delirium following cardiac surgery,\textsuperscript{52} but others have reported that statin use is associated with increased risk.\textsuperscript{53} The use of ketamine during anesthetic
induction for cardiac surgery has also been reported to reduce the incidence of postoperative delirium compared to placebo-treated patients.  

Most anesthetic agents, with the exception of ketamine, antagonize GABA receptors and can produce confusion and delirium. Many common perioperative medications can contribute to the occurrence of delirium, including meperidine and anticholinergic medications such as diphenhydramine and atropine. With the exception of meperidine, neither opioid administration, nor the total dose administered, appears to correlate with the occurrence of delirium. Use of regional anesthetic techniques instead of general anesthesia does not appear to reduce the incidence of delirium, probably because the variable depth of accompanying sedation. In a study of elderly patients receiving a spinal anesthetic for hip fracture repair, a lighter level of propofol sedation (bispectral index > 80 compared with an index of 50) was associated with a 50% reduction in the incidence of delirium. A secondary analysis of 526 elderly patients undergoing hip surgery found no significant harm or benefit from general or regional anesthesia, or the use of benzodiazepines, narcotics or anticholinergic agents. Postoperatively, there is no evidence that pain management with neuraxial techniques is superior to management with opioids.

**Benzodiazepines**

Benzodiazepines are often used for the treatment of anxiety. Their duration of action in critically ill and elderly patients is unpredictable. While these drugs often are used to treat delirium and withdrawal, no adequately controlled trials support their use in the treatment of delirium unrelated to alcohol withdrawal. Elderly patients may become further disinhibited with the administration of benzodiazepines. Their use should be minimized in such patients and may be associated with an increased risk for delirium and prolongation of its duration in elderly patients.

**Haloperidol**

There is insufficient evidence to strongly recommend a particular pharmacologic treatment for delirium, but haloperidol often is used for this purpose and has been recommended in guidelines of the American Psychiatric Association (APA). Low-dose haloperidol may reduce the severity and duration of delirium, and the length of hospital stay in delirious elderly patients. Haloperidol is a butyrophenone with strong dopamine D2 receptor binding activity, which atypical antipsychotics lack. Although it is an alpha-1 adrenergic antagonist, it has few hypotensive side effects. It has little meaningful effect on ventilation. Extrapyramidal side effects are relatively uncommon in the critically ill patient, perhaps because of concurrent use of benzodiazepines or beta-blockers. Prolongation of the Q-T interval and serious ventricular arrhythmias, notably torsade-de-pointes, following haloperidol administration have been described in a “black box” warning by the Food and Drug Administration (FDA). Monitoring the Q-T interval of the electrocardiogram and correction of serum potassium and magnesium levels, if necessary, are advisable when high doses of haloperidol are used. APA guidelines suggest that a QTc interval greater than 450 msec or more than 25% over baseline may warrant discontinuation of the drug. Haloperidol also has been associated with neuroleptic malignant syndrome. The drug can decrease the threshold for seizures and should be used cautiously in patients with delirium tremens. Although not approved by the FDA, the intravenous route appears preferable in the critically ill patient, since absorption is assured. Side effects may be reduced with intravenous administration.

The starting dose for haloperidol is 0.5-1.0 mg, depending on level of agitation, age, and degree of illness. In general, a starting dose of 2 mg IV is reasonable for mild agitation; 5 mg for moderate; and 10 mg for severe agitation, with elderly patients receiving approximately one-third of this typical starting dose. Because the onset of action is about 11 minutes, allow at least 20 minutes between doses (longer in the elderly and critically ill). For continued agitation, double the previous dose. There is no specific upper limit. Supplemental anxiolytics and/or analgesics may be necessary. After the patient is calm for 24 hours, reduce the dose by 50% every 24 hours, and...
taper over 3-5 days. Usually only two to three doses per day are necessary since the serum 1/2-life is approximately 14 to 24 hours. Intravenous haloperidol is twice as potent as the oral form.\textsuperscript{77}

Other options

Pharmacologic options that may be useful for treatment of delirium include the atypical antipsychotics olanzapine, risperidone,\textsuperscript{78,79} and quetiapine.\textsuperscript{80-82} Prophylaxis with olanzapine has been reported to reduce the incidence of delirium, but not its duration or severity, following joint replacement.\textsuperscript{83} For treatment of delirium, the atypical antipsychotics appear to have similar efficacy as haloperidol, but additional studies will be necessary before such drugs can be strongly recommended. Short-term treatment with dexmedetomidine has been demonstrated to be effective for the treatment of delirium in several prospective studies.\textsuperscript{84-87} Cholinesterase inhibitors, such as physostigmine\textsuperscript{88} have been suggested for treatment, but a recent large study of the cholinesterase inhibitor rivastigmine did not demonstrate efficacy and the drug was associated with increased mortality.\textsuperscript{89} Interestingly, maintaining a body temperature $\leq 36^\circ\text{C}$ during total knee replacement under spinal anesthesia was reported to be associated with a lower incidence of cognitive dysfunction (delirium was not specifically assessed) following surgery.\textsuperscript{90}

Outcome

The occurrence of delirium is far from benign, and is associated with an increased risk of death and disability.\textsuperscript{91-95} In the postoperative period, the occurrence of delirium has been associated with prolonged ICU and hospital length of stay, greater use of sedatives and physical restraints, increased unintended decannulations and extubations, increased hospital costs, prolonged cognitive dysfunction, and higher mortality rates.\textsuperscript{20,96-100} Elderly patients who experienced delirium during their stay in a surgical ICU were more likely to be discharged to a place other than home, and have a greater functional decline than nondelirious patients.\textsuperscript{101,102} While the simple occurrence of postoperative delirium does not appear to be an independent predictor of mortality, \textsuperscript{103} persistence of delirium appears to be a predictor of increased 1-year mortality.\textsuperscript{104} One-quarter of delirious elderly patients die within 6 months.\textsuperscript{105}

The Spectrum of Postoperative Cognitive Dysfunction (POCD)

Delirium represents a profound manifestation of cognitive dysfunction. The current definition is binary (yes/no) and neglects differences in the severity and duration of brain dysfunction. Undoubtedly, there is a spectrum of organ dysfunction that falls short of a diagnosis of delirium, and can sometimes be diagnosed only by special testing. The definition of POCD is informal; it refers to any difficulty with memory, cognition, or attention following surgery and anesthesia. The incidence of POCD appears relatively common following cardiac and non-cardiac surgery, especially in the elderly. Its occurrence is associated with prolonged hospital stays, decreased likelihood of returning to the workforce, and increased mortality.\textsuperscript{106-108} Just as the etiology of delirium is unclear, so is the etiology of postoperative cognitive dysfunction and its potential relationship to anesthetic exposure. Other perioperative organ system dysfunctions, such as renal failure, have diverse causes. It is likely that there are multiple important causes of postoperative cerebral dysfunction. The hypothesis that anesthetic exposure may exacerbate neurodegenerative diseases such as Alzheimer disease, is receiving intense examination. Current studies, however, are inadequate to confirm or refute such a relationship. At best, the controversy remains in equipoise: we don’t have the scientific evidence that any particular anesthetic agent or technique, at clinically relevant doses and durations, causes or will prevent long-lasting cognitive dysfunction.\textsuperscript{109,110} In the absence of definitive recommendations, it seems reasonable to apply those recommendations found useful in reducing the incidence and severity of delirium, as discussed above, to an empiric effort to minimize the incidence and severity of postoperative cognitive dysfunction.
### References


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