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Postoperative Delirium in the Geriatric Patient

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SYNOPSIS

Postoperative delirium, a common complication in older surgical patients, is independently associated with increased morbidity and mortality. Patients over the age of 65 years receive greater than 1/3 of the over 40 million anesthetics delivered yearly in the United States. This number is expected to increase with the aging of the population. Thus, it is increasingly important that perioperative clinicians who care for geriatric patients have an understanding of the complex syndrome of postoperative delirium.

Keywords

Postoperative delirium; geriatric; risk factors; screening; management

INTRODUCTION

Postoperative delirium (POD) is a common complication in older surgical patients and is associated with significantly prolonged hospitalizations, cognitive impairment, functional decline, and increased 6–12 month mortality rate. [1–5] Postoperative delirium has a reported incidence from 10% to 70% depending on the criteria used for diagnosis, the population studied, and the type of surgical procedure. Higher incidences tend to be reported in the oldest, most medically-complex patients following vascular, cardiac, or hip fracture operations.[6–9] Skills essential for clinicians involved in the perioperative care of geriatric patient include the ability to 1) identify high-risk patients, 2) promptly diagnose POD, and 3) effectively manage patients with POD.

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DISCLOSURES

Conflicts of Interest:

Dr. Schenning: None

Dr. Deiner: None

RISK FACTORS

Postoperative delirium is a complex, geriatric syndrome that results from an interplay between a patient's baseline vulnerabilities (predisposing factors) and the "insults" that occur throughout the perioperative course (precipitating factors). [10] (Table 1) Though many of the predisposing risk factors are not amenable to change, identification of patients with these factors can allow caregivers to direct preventive efforts to at-risk patients (see "Management" below). Due to the heterogeneity of the populations studied, research methodologies, and the syndrome itself, the reported risk factors for postoperative delirium are varied. Predisposing risk factors frequently cited include age over 65 years, functional impairment, preexisting neuropsychiatric conditions, and the presence of multiple medical comorbidities. Specific comorbidities associated with the development of POD include heart failure, renal dysfunction, diabetes mellitus, and vascular disease. [11]

Together with knowledge of the predisposing factors, an understanding of the precipitating factors to which patients are exposed in the perioperative period can assist in directing perioperative care tailored to the individual patient. Though there is very little evidence implicating a particular anesthetic agent or technique, emerging evidence suggests that the depth of anesthesia might play a role (see "Current Controversies" below). Other factors related to an increased risk of postoperative delirium include increased surgical duration, complexity, and invasiveness. Postoperative factors implicated in the development of delirium include admission to an intensive care unit, prolonged intubation/mechanical ventilation, poor pain management, and disrupted sleep patterns.

DIAGNOSIS

Delirium is an acute confusional state with symptoms which wax and wane throughout the course of the illness. Because delirium is a complex syndrome with a variable clinical picture, clinicians must maintain a high index of suspicion to promptly detect postoperative delirium. Considering that delirium represents an acute or subacute change from baseline, it is important that each patient's baseline cognitive status is well documented. [12, 13] The diagnosis of delirium is based on history, physical examination, laboratory, and radiographic findings. Other neurocognitive disorders should be ruled out to confirm the diagnosis of delirium (Box 1).

Clinical features

On average, the onset of delirium begins 24 hours postoperatively, and resolves within 48 hours. [14] Delirium, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSMV), is a disturbance in attention, awareness, and cognition that develops over a short period of time and fluctuates in severity. [15] Clinically, delirium can take the form of hyperactive, hypoactive, or a mixed type that includes both hyperactive and hypoactive symptoms. Of these forms, the hypoactive subtype may be associated with the worst prognosis. [16, 17] Other symptoms associated with delirium are listed in Box 2.

Screening tools

There are several validated tools in use for the screening and diagnosis of delirium (Table 2). Several of these screening instruments, including the Confusion Assessment Method (CAM) [18] and the Delirium Symptom Interview (DSI), [19] were developed using criteria adapted from the DSM. Routine screening of at-risk patients using a validated screening tool facilitates early diagnosis, particularly in the hypoactive form of delirium which might otherwise go unrecognized. Despite the recent advances in validated tools, none of them is foolproof. It can be particularly challenging to diagnosis delirium in patients with preexisting cognitive impairment, dementia, or psychiatric conditions.

PATHOPHYSIOLOGY

The pathophysiology of postoperative delirium is not entirely known; however, there are many theories regarding the underlying processes behind the clinical syndrome. As described by Maldonado in his landmark review, potential mechanisms can be grouped into categories including neuroinflammation and oxidative stress. [24] These two areas likely interact to cause delirium by promoting neurotransmitter dysregulation and network disconnectivity causing an imbalance in the activation or inhibition of neural networks (in specific cholinergic and GABAergic systems). [25, 26] Below we describe the neuroinflammation and oxidative stress hypotheses in brief since these areas span a very large amount of literature.

Neuroinflammation

The peripheral neuroendocrine response to the stress of surgery and anesthesia leads to neuroinflammation. The immune and inflammatory response to stress activates the hypothalamicpituitary-adrenal (HPA) axis and induces the production of glucocorticoids. Glucocorticoids have a wide range of peripheral and central effects including the enhancement of neuroinflammation and ischemic injury. [27] The peripheral neuroendocrine response is propagated centrally via either the neural pathway (vagus nerve) activated by the HPA axis or the humoral pathway by peripheral mediators crossing the blood brain barrier. With respect to the humoral pathway, there is some evidence that peripheral mediators impact the brain at the choroid plexus and circumventricular organs leading to the production of proinflammatory cytokines in the brain. [28] Studies have explored peripheral inflammatory markers for delirium including C-reactive protein, tumor necrosis factor, and IL-6, -8, 10. [29–31] It is important to note that while these have been found to be significantly elevated in patients with delirium, they are not specific for delirium. [32, 33]

Neuroinflammation produces a syndrome of physiologic and behavioral changes termed “sickness behaviors” which are not specific to the postoperative period, and are common for many systemic illnesses. [34] Sickness behaviors, which are thought to be part of the adaptive response to injury, include depression, cognitive deficits, and social withdrawal. According to this theory, delirium is considered an exaggerated form of a sickness behavior.

Oxidative Stress

The oxidative stress hypothesis proposes that brain hypoperfusion induces local ischemia which triggers a chain of events. First, there is an increased production of reactive oxygen species. The increase in reactive oxygen species leads to excitotoxicity, apoptosis, and local inflammation. Because of melatonin's properties as a free radical scavenger, an antioxidant, and a regulator of circadian rhythm, its use in delirium prevention was explored. [35] However, a recent randomized double blind study of the administration of tryptophan, a precursor to melatonin, in older surgical patients found no difference in the incidence or duration of delirium. [36] Overall, the clinical evidence supporting the theory that global cerebral desaturation is a common cause of delirium is poor. A recent study compared the rate of postoperative delirium in patients undergoing cardiopulmonary bypass graft procedures with the Haga Brain Care Strategy to historical controls who did not receive the protocol. The Haga Brain Care Strategy included preoperative transcranial Doppler examinations and intraoperative cerebral oximetry. Cerebral desaturations that were >20% outside of the normal range resulted in intervention to restore oxygenation. The study found that patients who underwent surgery with the protocol had a 7.3% incidence of delirium versus a 13.3% incidence in the historical control which was statistically significant. [37] However, since patients undergoing general surgery rarely experience severe cerebral desaturation this strategy may not be widely generalizable. [38] One small study of geriatric abdominal surgery patients suggested that patients who developed delirium had lower preoperative regional oxygen saturation. [39] Overall, both the cardiac and noncardiac studies that have examined cerebral oximetry have either been small, retrospective, or a posthoc comparison of a parent study with a different endpoint. In the future, stronger evidence is needed to define whether cerebral hypoxia is a common cause of delirium in older surgery patients.

MANAGEMENT

Prevention, screening, and early treatment are the mainstays of postoperative delirium management. Most preventive strategies are nonpharmacologic as outlined in Box 3. In one randomized trial, a proactive geriatrics consultation reduced the incidence of postoperative delirium by over one-third following hip-fracture repair. [40] In this program, structured geriatrics consultations made recommendations regarding supplemental oxygen, fluids, electrolytes, nutrition, pain management, and early mobilization and physical rehabilitation. In an early landmark study, Inouye and colleagues employed a multicomponent intervention that decreased the incidence of delirium by 40% and the duration of delirium by 35%. [41] This strategy, which became known as the Hospital Elder Life Program (HELP), was directed toward managing the following 6 issues: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. [41] While the majority of strategies for delirium prevention are nonpharmacologic, the prophylactic use of ketamine or antipsychotics has shown some early success. These studies are further described under "Current Controversies" below.

After making the diagnosis of delirium, healthcare providers should attempt to identify and correct the underlying causes (Box 4). The use of pharmacologic strategies in managing

postoperative delirium has a role in the treatment of the underlying medical causes and management of symptoms. For example, medications are particularly helpful in addressing underlying causes of delirium such as pain [42] or sleep deprivation. The American Geriatrics Society released a delirium best practices statement this fall. [12] The panel spent a year performing a Cochrane-style review to identify rigorous performed studies of factors to prevent and treat delirium. According to these guidelines, the use of antipsychotics should be reserved for patients who are severely agitated and pose a risk to harm themselves or others. [12]

CURRENT CONTROVERSIES & FUTURE CONSIDERATIONS

In the Delirium Best Practices Statement, the American Geriatrics Society panel found that the only intraoperative intervention that had the quality of evidence required to make a recommendation for clinical care was anesthetic depth. [12] This does not mean that other intraoperative factors (drugs, hemodynamics, cerebral saturation) have no effect on delirium, but rather that more high quality studies are needed.

Based on a pilot study of depth of anesthesia in geriatric hip fracture patients, the Best Practices Statement suggests that anesthesiologists should avoid deep planes of anesthesia to prevent delirium. The guideline does mention that the risks of light anesthesia are not insignificant, and these include intraoperative awareness and sympathetic system activation. [12] Further evidence supporting this recommendation comes from a study of depth of sedation in patients who underwent hip fracture surgery under spinal anesthesia. [43] This was consistent with two larger trials where the rate of postoperative delirium was lower in patients who received intraoperative BIS monitoring vs. patients who did not. [44, 45] However, these two trials did not assign or randomize patients to a particular depth of anesthesia. It is worth mentioning that a study which randomizes hip fracture patients to light or heavy sedation is currently underway.

Use of Ketamine

A small randomized trial of a single bolus dose of ketamine or saline placebo after induction (0.5 mg/kg) showed impressive results. Patients who received ketamine had a 3% incidence of delirium compared to 31% of patients who received placebo. [46] The patients who received ketamine also had a significantly lower C-reactive protein level; therefore, the authors postulated that ketamine might have a salutary anti-inflammatory effect. Other mechanisms by which ketamine could attenuate the oxidative stress associated with surgery include inhibition of NMDA receptor activation and excitotoxic signaling, and reduction of neural apoptosis. [47] Currently, a multicenter trial called Prevention of Delirium and Complications Associated with Surgical Treatments (PODCAST) is underway to study the effects of a bolus dose of ketamine in a noncardiac surgical population on postoperative delirium and pain. [48]

Use of antipsychotics

The Best Practices Guidelines found insufficient evidence to recommend the use of antipsychotics to prevent delirium based the current contradictory literature and

"considerable" harm of antipsychotics. [12, 49–53] Currently there is an ongoing Dutch multicenter trial (Haloperidol Prophylaxis in Older Emergency Department Patients, HARPOON study) to determine efficacy and safety of haloperidol prophylaxis in at-risk patients. [54] Medical and surgical patients identified as high risk for delirium in the emergency department will be randomized to 1 mg haloperidol prophylaxis twice daily for seven days with delirium incidence as the primary endpoint, and secondary endpoints including delirium free days, length of stay, and mortality. Regarding the use of antipsychotics for the purpose of treating delirium the current guidelines recommend the "lowest effective dose" for the shortest duration, and only after nonpharmacologic interventions have failed.

Potential biomarkers

As mentioned above, postoperative delirium is a complex syndrome that is associated with varied phenotypes and is likely the result of a combination of neuroinflammatory and oxidative stress processes. As such, biomarker investigations have generally focused on inflammatory, noradrenergic, ischemic, and anticholinergic markers [55]. (Box 5) For example, postoperative norepinephrine levels were recently found to be much higher in postoperative patients who developed delirium [56]. Few studies have explored the genetic factors that predispose patients to postoperative delirium. While some have found the presence of the apolipoprotein E ε4 allele (APOE4) increases the risk of POD [57, 58], other studies found no association between APOE4 and delirium [59].

SUMMMARY

Postoperative delirium is a common complication plaguing geriatric surgical patients, and is independently associated with increased morbidity and mortality. Successful management of postoperative delirium requires an understanding of which patients are at the highest risk for developing postoperative delirium and a proactive approach to diagnosis and treatment.

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Box 1

Differential diagnosis of postoperative delirium

Emergence delirium

Postoperative cognitive dysfunction

Cerebrovascular Accident/Transient Ischemic Attack

Dementia

Depression or other psychiatric conditions

Box 2

Clinical features of postoperative delirium

Disturbance in attention, awareness, cognition, memory, concentration

Fluctuating severity of symptoms

Emotional lability

Agitation

Hallucinations or delusions

Disorganized thoughts or speech

Difficulty tracking conversations

Change in sleep/wake cycle

Change in level of arousal

Decreased appetite

Urinary/Bowel incontinence

Change in activity level

- Hyperactive
- Hypoactive
- Mixed

Box 3

Strategies for postoperative delirium prevention

Orient to setting

Increase mobility, physical therapy

Promote sleep hygiene

Proactive geriatrics consultation

Multicomponent interventions (i.e. Hospital Elder Life Program)

Appropriate medication management

- Control pain
- Avoid polypharmacy
- Decrease use of medications with psychoactive properties

Ensure access to glasses, contacts, hearing aids, dentures

Educate healthcare personnel

Box 4

Potential underlying causes of delirium

Infection

Sleep deprivation

Inadequate pain control

Sedating/psychoactive medications

Metabolic/electrolyte derangements

Alcohol/drug intoxication or withdrawal

Box 5

Candidate biomarkers for postoperative delirium

Inflammatory (Interleukins, microglial activity, C-reactive protein, ESR, HLA-DR, CD68)

Dopamine Receptors

Noradrenergic (Norepinephrine, cortisol)

Cerebral Damage (S-100β, neuron specific enolase)

Genetic (apolipoprotein E ε4)

Cholinergic (acetylcholinesterase)

Albumin levels

KEY POINTS

- Delirium is a common postoperative complication in the geriatric population
- Postoperative delirium is independently associated with increased morbidity and mortality
- Validated screening tools are useful for early detection
- Treatment is aimed at addressing underlying causes and managing symptoms

Table 1

Risk factors for postoperative delirium

Predisposing factors	**Precipitating factors**
Age (>65 years old)	Intraoperative
Neuropsychiatric conditions	• Blood loss/Blood transfusion
• Cognitive dysfunction	• Surgical duration
• Dementia	• Surgical urgency
• Depression	• Surgical complexity
• Alcohol abuse	• Invasiveness of procedure
• History of postoperative delirium	• Depth of anesthesia
• History of stroke	Postoperative
Use of psychotropic medications	• Admission to an intensive care unit (ICU)
Poor physical status	• Increased hospital/ICU length of stay
Medical comorbidities	• Increased duration of intubation/mechanical ventilation
• Heart failure	• Postoperative complications
• Kidney failure	– Infection, stroke
• Diabetes mellitus	• Use of physical restraints
• Atrial fibrillation	• Sleep disruption
• Anemia	• Pain
• Atherosclerosis	• Psychotropic medication use
• Tobacco use	

Table 2

Validated Delirium Screening Instruments

Tool	Sensitivity (%)	Specificity (%)	Criteria
Confusion Assessment Method (CAM) [18]	94–100	90–95	9 criteria from DSM-III-R: acute onset and fluctuating course, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, increased or decreased psychomotor activity, sleep-wake cycle disturbance
Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [20]	95–100	89–93	4 items: acute onset or fluctuating course, inattention, disorganized thinking, altered level of consciousness,
Delirium Symptom Interview (DSI) [19]	90	80	7 criteria from DSM-III: disorientation, consciousness, sleep/wake cycle, perceptual disturbance, speech, psychomotor activity, fluctuating behavior
Nursing Delirium Screening Scale (NuDESC) [21]	85.7	86.8	5 items: disorientation, behavior, communication, hallucinations, psychomotor retardation
Intensive Care Delirium Screening Checklist (ICDSC) [22]	99	64	8 items: altered level of consciousness, inattention, disorientation, psychosis, psychomotor agitation/retardation, inappropriate speech/mood, sleep/wake cycle, symptom fluctuation
NEECHAM Confusion Scale [23]	95	78	9 items in the following 3 domains: Processing, Behavior, Physiologic Control

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders