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Postoperative cognitive disorders

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Abstract

Purpose of review—The elderly are the fastest growing segment of the population and undergo 25–30% of all surgical procedures. Postoperative cognitive problems are common in older patients following major surgery. The socioeconomic implications of these cognitive disorders are profound; cognitive decline is associated with a loss of independence, a reduction in the quality of life, and death. This review will focus on the two most common cognitive problems following surgery: postoperative delirium and postoperative cognitive dysfunction (POCD).

Recent findings—For years, preoperative geriatric consultation/screening was the only intervention proven to decrease postoperative delirium. There are, however, several recent publications indicating that preoperative and postoperative pharmacological and medical (hydration, oxygenation) management can reduce postoperative delirium. Spinal anesthesia with minimal propofol sedation has been shown to decrease the incidence of postoperative delirium in hip-fracture patients. Likewise, dexmedetomidine sedation in mechanically ventilated patients in the ICU is associated with less postoperative delirium and shorter ventilator times. Preoperative levels of education and brain function (cognitive reserve) may predict patients at risk for postoperative cognitive problems. Reduced white matter integrity is reported to place patients at a higher risk for both postoperative delirium and POCD.

Summary—The etiology of postoperative cognitive problems is unknown, but there is emerging evidence that decreased preoperative cognitive function contributes to the development of postoperative delirium and POCD. There is growing concern that inhalation anesthetics may be neurotoxic to the aging brain, but there are no human data evaluating this hypothesis to date. Randomized controlled trials evaluating interventions to improve long-term cognitive outcomes in elderly patients are urgently needed.

Keywords

anesthesia; delirium; postoperative cognitive dysfunction; surgery

Introduction

Postoperative cognitive changes have been reported in elderly patients for over a century, and anesthesia has often been mentioned as a possible cause of this problem. In 1955, Bedford [1] published a retrospective review of 1193 elderly patients who had surgery under general anesthesia during a 5-year period. He found that cognitive problems occurred in

approximately 10% of older patients after surgery. Most of these patients experienced mild problems after surgery (inability to write a decent letter, concentrate, go shopping alone or read a book, increased forgetfulness after surgery, unable to attend to business), but were still able to function independently. Bedford also described 18 cases (1.5%) in which patients developed extreme dementia and remained confused until their death. He concluded that the cognitive problems were related to anesthetic agents and hypotension and that 'operations on elderly people should be confined to unequivocally necessary cases'.

Postoperative confusion and cognitive problems are more common in elderly (> 65 years) than younger patients [2] and can be categorized as postoperative delirium, postoperative cognitive dysfunction (POCD), and dementia. This review will focus on postoperative delirium and POCD following noncardiac surgery; dementia will not be discussed as it is a gradually progressive process that rarely occurs for the first time immediately after surgery.

Postoperative delirium

The Diagnostic and Statistical Manual of Medical Disorders (DSM), fourth edition, [3] describes delirium as a 'disturbance of consciousness that is accompanied by a change in cognition that cannot be better accounted for by a pre-existing or evolving dementia'. It is characterized by a reduced clarity of awareness of the environment, a fluctuating course (waxing and waning of orientation throughout the day), and an inability to focus, sustain, or shift attention. Although delirium is usually a temporary condition, it is independently associated with increased mortality, length of hospital stay, functional disability, placement in long-term care institutions, and hospitalization costs [4]. It is estimated that postoperative delirium occurs in at least 20% of the 12.5 million individuals aged 65 years or older who are hospitalized each year and increases the cost of hospitalization by \$2500 for each patient who develops this complication [5].

The presentation of postoperative delirium is variable and patients may exhibit hyperactive, hypoactive, or mixed hyper-hypoactive cognitive and motor states. Hyperactive patients show increased psychomotor activity, such as rapid speech, irritability, and restlessness and are often disruptive, time-consuming, and harmful to staff. They are, therefore, more readily identified and treated. Hypoactive patients, by contrast, typically show a calm appearance combined with inattention, decreased mobility, and have difficulty answering simple questions about orientation. Hypoactive delirium may be misdiagnosed as depression or fatigue and may be due to acute terminal illness [6].

Assessment of delirium

There are a number of rapid bedside assessment tools used to diagnose delirium in hospitalized patients. Of these, the confusion assessment method (CAM) [7] is the best known and most frequently used by clinicians. Based on the DSM criteria for delirium, the CAM assesses the following four features: acute onset and fluctuating course; inattention; disorganized thinking; and altered level of consciousness. The diagnosis of delirium requires the presence of first two features and either third or fourth [7]. The CAM-ICU [8] is a modification of the CAM that relies on more nonverbal responses and can be used for the assessment of delirium in critically ill or intubated patients. The CAM-ICU requires minimal training and takes approximately 2 min to administer. It has been shown to have an even higher sensitivity (93–100%) and specificity (98–100%) than the original CAM [8].

Current research on postoperative delirium

Delirium research has predominantly focused on the identification and treatment of risk factors prior to surgery. Factors that have been associated with an increased risk of postoperative delirium include advancing age, sensory deprivation (visual or hearing

impairment), sleep deprivation, social isolation, physical restraint, use of bladder catheter, iatrogenic adverse events, polypharmacy, use of psychoactive drugs, comorbidities, severe illness (especially infection, fracture, or stroke), cognitive impairment, temperature abnormality (fever or hypothermia), dehydration, malnutrition, and low serum albumin [9].

Numerous studies have demonstrated that perioperative geriatric consultation, early surgery, effective pain management, and staff education can successfully decrease the incidence and severity of postoperative delirium in hip-fracture patients [10–15]. In the majority of these studies, many of the patients had preoperative cognitive impairment. A recent study by Bjorkelund *et al.* [16^{*}] evaluated a multifactorial intervention for postoperative delirium in cognitively intact elderly patients admitted for hip-fracture surgery. The preoperative intervention consisted of the use of supplemental oxygen, SBP maintenance more than 90 mmHg, red blood cell transfusion for hemoglobin less than 10 g/dl, adequate pain relief, intravenous fluid supplementation, normothermia, and the avoidance of polypharmacy. Perioperative interventions included spinal anesthesia with propofol sedation and postoperative analgesia with paracetamol and opioid as needed. This multifactorial intervention resulted in a 35% reduction in the incidence of postoperative delirium in patients who were lucid at hospital admission.

Recent randomized controlled trials (RCTs) suggest that pain management and depth of general anesthesia are important modifiable factors for postoperative delirium after hip-fracture surgery. A Cochrane review [17] compared outcome differences in hip-fracture patients receiving general versus regional anesthesia. The authors concluded that regional anesthesia has a slight benefit over general anesthesia in reducing acute postoperative confusion for hip-fracture surgery, but could not find a difference for mortality or other outcomes. A more recent study by Marino *et al.* [18] found that regional anesthesia techniques reduced total hydromorphone consumption and postoperative delirium (disorientation to time and/or place) compared with patient-controlled analgesia alone after unilateral hip replacement. In the past, most studies comparing postoperative delirium after regional versus general anesthesia have failed to control for level of intraoperative sedation and postoperative pain management. However, a recent RCT demonstrated that spinal anesthesia with light propofol sedation [depth of anesthesia with bispectral index (BIS) 80] compared to spinal with deep sedation (which was really general anesthesia, BIS approximately 50) was associated with a 50% decrease in the incidence of postoperative delirium after hip-fracture surgery [19^{**}]. Although the results of this study are encouraging, it excluded patients with severe cognitive impairment and found that patients with better preoperative cognition were more likely to show a benefit from light levels of sedations.

Antipsychotics are widely used in the management of established delirium, but there are few studies that assess the efficacy of antipsychotics for the prevention of postoperative delirium. A RCT [20] randomizing 430 patients undergoing hip surgery to receive either haloperidol, 0.5 mg three times daily, or placebo did not find a reduction in the incidence of postoperative delirium with perioperative low-dose haloperidol; however, the treatment did decrease the duration and severity of postoperative delirium as well as the duration of hospital stay. All patients in this study received a geriatric consultation.

Delirium occurs in up to 80% of sedated ICU patients. A multinational study randomized 375 medical/surgical ICU patients to receive either dexmedetomidine or midazolam for sedation while mechanically ventilated in the ICU [21]. The investigators found that patients who were treated with dexmedetomidine experienced less delirium (54 versus 77%) than midazolam-treated patients. A recent review [22^{*}] found that the ‘ABCDE bundle’, an integrated and interdisciplinary approach to the management of mechanically ventilated patients, can reduce adverse complications such as delirium. In this acronym (ABCDE), the

‘ABC’ refers to awake and breathing coordination to liberate the patient from sedation and mechanical ventilation, the ‘D’ refers to the use of dexmedetomidine sedation rather than benzodiazepines or opioids, and the ‘E’ refers to early mobility and exercise.

Postoperative cognitive dysfunction

POCD is a subtle impairment of memory, concentration, and information processing that is distinct from delirium and dementia. Despite the fact that POCD is not a formal psychiatric diagnosis, the term is commonly used in the literature and is considered to be a mild neurocognitive disorder. The DSM-IV [3] states that a mild neurocognitive disorder can only be diagnosed if the cognitive disturbance does not meet the criteria for three other conditions (delirium, dementia, or amnesic disorder). It further specifies that the diagnosis of mild neurocognitive disorder must be corroborated by the results of neuropsychological testing showing that an individual has a new onset of deficits in at least two areas of cognitive functioning lasting for a period of at least 2 weeks. These diagnostic criteria make it impossible to accurately identify POCD during the hospital stay. Due to the subtle nature of POCD, it is often only the patient and/or partner who recognize the onset of this problem. The symptoms vary from mild memory loss to an inability to concentrate or process information. Price *et al.* [23] analyzed the severity of POCD in 77 patients at 3 months after noncardiac surgery and found that executive dysfunction (problems with processing speed and organization) and combined executive/memory impairment were associated with significant functional limitations, whereas patients with only memory decline did not exhibit functional impairment. POCD at 3 months after noncardiac surgery has also been associated with increased mortality for as long as 8 years after surgery [2,24].

Assessment of postoperative cognitive dysfunction

There are no formal criteria for the assessment and diagnosis of POCD. Methodological discrepancies between studies include variable test batteries, lack of control groups, significant loss of patients during follow-up, and inconsistent intervals between testing periods [25]. One publication reported that nine different diagnostic criteria were used in various studies to diagnose POCD and that the incidence of POCD varies widely depending on the statistical definition applied to cognitive data [26]. Consistent diagnostic criteria for POCD must be developed for meaningful research into this cognitive disorder to occur.

Current research on postoperative cognitive dysfunction

The first large prospective study describing postoperative cognitive decline following noncardiac surgery was published by a multinational research group in 1998 [27]. In this study, patients aged 60 years or older, who were undergoing major abdominal and orthopedic surgery, completed a battery of psychometric tests prior to surgery and at 1 week and 3 months after surgery. Cognitive dysfunction occurred in 25% of the patients at hospital discharge and 10% had measurable cognitive changes at 3 months after surgery. Advancing age was the only significant predictor for POCD at 3 months after surgery. Using the same study design, Monk *et al.* [2] evaluated adults of all ages undergoing major noncardiac surgery and diagnosed POCD in 30–40% of adult patients of all ages at hospital discharge. However, only the elderly (> 60 years) were at significant risk (13%) for POCD at 3 months after surgery. The independent risk factors for POCD at this time point were increasing age, lower educational level, a history of a previous cerebral vascular accident (CVA) with no residual impairment, and POCD at hospital discharge. These investigators also found that the occurrence of POCD was associated with an increased risk of death in the first year after surgery.

Over the past 30 years, there have been numerous investigations examining Bedford's original claim [1] that general anesthesia is responsible for postoperative cognitive problems. Two large prospective studies evaluated cognitive outcomes with regional versus general anesthesia after major surgery [28,29]. Both studies included a large participant pool and applied rigorous methodological approaches in order to assess cognitive outcomes for up to 6 months following surgery. Both studies clearly demonstrate that the type of anesthesia (general versus regional) did not impact long-term cognitive outcome. However, all of the patients receiving regional anesthesia also received intravenous opioids and sedatives during the surgical procedure; it is not known whether regional anesthesia with no additional intravenous agents would improve postoperative cognitive outcome. A recent study comparing coronary angiography with light sedation, total hip joint replacement surgery with general anesthesia, or coronary artery bypass graft (CAB) surgery under general anesthesia, found a 16-17% incidence of POCD at 3 months postsurgery in all three groups. These findings suggest that the POCD may be independent of the nature or type of surgical procedure and type of anesthesia [30**].

Potential mechanisms for postoperative cognitive disorders

The mechanisms responsible for postoperative cognitive decline after noncardiac surgery are unknown, but potential risk factors can be classified into patient, surgical, and anesthetic categories. It is likely that the cause of POCD in the elderly patient is multifactorial and may include the preoperative health status of the patient, the patient's preoperative level of cognition, perioperative events related to the surgery itself, and, possibly, neurotoxic effects of anesthetic agents.

Is inhalational anesthesia neurotoxic in elderly patients?

Inhaled general anesthetics, which pass readily into the brain, are used in the majority of major surgical procedures. For decades, it was assumed that inhaled anesthetics were nontoxic and that their effects were rapidly reversed at the end of the procedure. There is now concern, however, that inhaled anesthetics may be neurotoxic to the aging brain.

In 2004, Eckenhoff *et al.* [31] demonstrated that clinical concentrations of two inhaled anesthetics, halothane and isoflurane, enhanced the oligomerization and aggregation of amyloid peptides in cell cultures. These in-vitro data suggested that inhaled anesthetic exposure might increase pathologic changes normally seen in Alzheimer's disease, especially in high-risk populations like the elderly. Subsequent investigations have demonstrated that isoflurane anesthesia activates enzymes called caspases, which may also contribute to the formation of neurofibrillary tangles, a key pathological feature of Alzheimer's disease, and the production of beta amyloid, the key component of amyloid plaques [32]. These findings have led to concerns that inhaled anesthetics may alter the brain in some lasting way, possibly accelerate the course of Alzheimer's disease, and contribute to postoperative cognitive problems in predisposed individuals. Human studies have not linked anesthesia or surgery to postoperative cognitive problems and short-term cognitive outcomes are not improved with regional anesthesia (which does not include inhalational anesthetic agents) compared to general anesthesia [28,29,30**]. Additional RCTs are needed to determine whether inhaled anesthetics worsen long-term postoperative cognitive outcomes in older patients.

Does preoperative cognitive function affect postoperative cognitive outcomes?

Numerous studies have shown that preoperative cerebral infarct or cognitive impairment is a risk factor for postoperative cognitive problems [2,33,34,35**]. The concept of cerebral cognitive reserve is often cited to explain why individuals with a similar degree of cerebral

insult often have significant differences in the degree of cognitive symptoms. Satz [36] described a concept of brain reserve, which may help to explain vulnerability to postoperative cognitive problems: greater brain reserve serves as a protective factor, whereas less brain reserve serves as a vulnerability factor to a lesion or pathology (Fig. 1). These postulates can be applied to the topic of postoperative cognitive disorders. In the figure, patient A has greater reserve (which can be measured in a number of ways: education level, intelligence, brain size, white matter lesions, etc.) relative to patient B. Both patients experience a perioperative insult to the brain that results in a similarly sized 'lesion'. Patient A, however, because of cognitive reserve, does not demonstrate postoperative delirium or postoperative cognitive change and remains above the critical threshold for identifying a measurable change in functional outcome. Patient B with less preoperative cognitive reserve, by contrast, falls below this critical threshold and demonstrates significant changes in function which may manifest as postoperative delirium or POCD in the postoperative period.

Research formally investigating the role of reserve in the development of POCD suggests that patients with preoperative vascular risk factors may be at greater risk for POCD. Lund *et al.* [37] evaluated patients who had undergone an on-pump coronary artery bypass surgery and found that the severity of presurgical white matter abnormalities, a brain MRI variable associated with ischemia and small vessel vascular disease, predicted the frequency of postoperative cognitive impairment at 3 months postsurgery. Maekawa *et al.* [38] found that white matter lesions and cerebral infarctions on MRI scans were predictive of impaired cognition prior to elective cardiac surgery and placed these patients at a higher risk for postoperative neurological dysfunction. Similarly, preoperative white matter fractional anisotropy acquired via magnetic resonance diffusion methods has been associated with postoperative delirium [39].

Conclusion

The cause of postoperative cognitive problems has not been clearly elucidated because it is a heterogeneous and multifactorial disorder involving a complex interrelationship between a vulnerable patient with preoperative risk factors and numerous precipitating factors in the perioperative period. There is increasing evidence that impaired preoperative brain status (cognitive reserve) predicts patients at high risk for these problems. Future research should focus on interventions to prevent and treat postoperative cognitive problems in these high-risk patients.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 405–406).

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Key points

- Postoperative delirium can present as a hyperactive, hypoactive or mixed hyper-hypoactive state. Hypoactive delirium is underdiagnosed because the patients are calm and not disruptive.
- The CAM-ICU screening tool relies on nonverbal responses and is a simple, convenient tool for the diagnosis of delirium.
- Perioperative geriatric consultation in high-risk elderly patients has been shown to decrease the incidence of postoperative delirium.
- POCD is difficult to diagnose because there are no formal diagnostic criteria and the cognitive changes are usually subtle.
- Cell and animal studies suggest that volatile anesthetic agents may be neurotoxic to the aging brain, however, there are no human studies confirming these findings.
- There is growing evidence that impaired preoperative cognitive status places patients at high-risk for postoperative cognitive problems.

Figure 1. Brain reserve capacity and threshold concept