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Postoperative delirium and cognitive dysfunction

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Abstract

Postoperative delirium and cognitive dysfunction (POCD) are topics of special importance in the geriatric surgical population. They are separate entities, whose relationship has yet to be fully elucidated. Although not limited to geriatric patients, the incidence and impact of both are more profound in geriatric patients. Delirium has been shown to be associated with longer and more costly hospital course and higher likelihood of death within 6 months or postoperative institutionalization. POCD has been associated with increased mortality, risk of leaving the labour market prematurely, and dependency on social transfer payments. Here, we review their definitions and aetiology, and discuss treatment and prevention in elderly patients undergoing major non-cardiac surgery. Good basic care demands identification of at-risk patients, awareness of common perioperative aggravating factors, simple prevention interventions, recognition of the disease states, and basic treatments for patients with severe hyperactive manifestations.

Key words [age factors](#) ● [anaesthesia, geriatric](#) ● [brain](#) ● [complications](#)

Definitions

Delirium is well defined and is described in the *Diagnostic and Statistical Manual of Mental Disorders fourth edition* (DSM-IV-TR; www.dsmivtr.org/). The key characteristics are a change in mental status characterized by a reduced awareness of the environment and a disturbance in attention. This may be accompanied by other, more florid, perceptual symptoms (hallucinations) or cognitive symptoms including disorientation or temporary memory dysfunction. The patient may express hypoactive, hyperactive, or mixed psychomotor behaviours. Several tests have been developed and validated for use in diagnosis and grading of delirium. These include the Confusion Assessment Method (CAM), the Delirium Rating Scale Revised-98, and the Delirium Symptom Interview.^{9 21} A recent study from Japan found that the NEECHAM Confusion Scale and the Estimation of Physiologic Ability and Surgical Stress (E-PASS) are useful in diagnosis as well.¹⁷ Severity may vary, can be graded, and may have prognostic value.⁵² By definition, although the disorder develops acutely, the condition will wax and wane during the course of a day. These symptoms are not exclusive to delirium. Patients

who have baseline dementia, psychosis, or anxiety/depressive disorder may present diagnostic challenges.

There are many subtypes of delirium, including those attributable to an underlying medical condition (*delirium due to a general medical condition*), medications (*substance-induced delirium, substance intoxication delirium*), or withdrawal from medications (*substance withdrawal delirium*). Sometimes delirium may be multifactorial (*delirium due to multiple aetiologies*) or of unclear aetiology (*delirium not otherwise specified—NOS*). Emergence agitation or delirium might be thought of as a subset of *substance-induced* delirium. It has predominance in paediatric patients, has been correlated with general anaesthesia, and provided the patient is guarded from harming themselves, usually resolves without sequelae.²⁴ Emergence delirium in the paediatric population has been demonstrated to be associated with preoperative anxiety and responds to behavioural preparation and preoperative sedation.²⁵ For the purpose of this review, we are interested in delirium that occurs after a relatively normal emergence and that occurs at some interval after surgery and anaesthesia. This entity, which is more closely associated with older age, is referred to as postoperative (interval) delirium.

Postoperative delirium (POD) is not temporally related to emergence from anaesthesia. By definition, patients with POD do not have an identifiable aetiology, although there can be other contributing factors. These patients often emerge smoothly, and may be lucid in the post-anaesthesia care unit. However, after this initial lucid interval, the patients develop the classic fluctuating mental status, most commonly between postoperative days 1 and 3. Some postoperative patients may reside in the ICU; however, the term *ICU delirium* (previously known as *ICU psychosis*) may include both medical and surgical patients. POD can differ from delirium in medical patients because the admission characteristics of the two groups can be different. By definition, patients hospitalized for medical indications are either acutely ill or have exacerbations of chronic diseases. Most surgical operations are elective and patients have been managed to ensure optimal physical status before entering the hospital. Surgery and the associated anaesthetics and analgesics are generally absent in medical patients, but can contribute to POD. An important reason to distinguish POD from delirium seen in medical patients is the report by Brauer and colleagues,⁸ suggesting that patients with POD are more likely to result in initial complete recovery than other forms of delirium. However, POD is far from benign. In several recent 2 yr-plus cohort studies of elderly patients, hip fracture patients who develop POD are more likely to die, be diagnosed with dementia or mild cognitive impairment (MCI), and require institutionalization.^{6 26}

In contrast, postoperative cognitive dysfunction (POCD) is more difficult to define. Broadly, POCD refers to deterioration in cognition temporally associated with surgery. While the diagnosis of delirium requires a detection of symptoms, the diagnosis of POCD requires preoperative neuropsychological testing (baseline) and a determination that defines how much of a decline is called cognitive dysfunction. The spectrum of abilities referred to as cognition is diverse, including learning and memory, verbal abilities, perception, attention, executive functions, and abstract thinking. It is possible to have a decrement in one area without a deficit in another. Self-reporting of cognitive symptoms has been shown to correlate poorly with objective testing, so valid pre- and postoperative testing is essential to the diagnosis of POCD.²³ Many elderly patients have pre-existing MCI that has gone undiagnosed.

Unfortunately, there has not been a standard methodology used in the multiple studies within the POCD literature.³⁶ Selection of neuropsychological test instruments and the amount of change considered to be significant, timing of testing, and inclusion and exclusion criteria have all varied.³⁸ Furthermore, the batteries used, while relevant, have had floor effects and we have not incorporated batteries that are somewhat different from those used by dementia researchers. Hence, it is

difficult to define the presence and therefore incidence of POCD or to clearly understand the relationship between POCD and other dementing illnesses. Some commonly used testing instruments include the Logical Memory Test, the CERAD word list memory, the Boston Naming test, Category Fluency test, Digit Span Test, Trail making test, and Digit symbol substitution test. Interestingly, POCD test batteries tend to be a compilation of tests which have shown differences among subjects in previous studies of POCD. The domains that were most sensitive include verbal learning and working memory, episodic memory, processing speed, and set shifting.

The method of scoring the testing batteries and determining how much dysfunction is clinically significant remains an open subject. One method is the percentage change method, that is, $\frac{\text{postoperative score} - \text{preoperative score}}{\text{preoperative score}}$. Averaging across groups is discouraged, because while some patients will decline, others improve over time and this difference can be masked. Another method defines a number of standard deviations outside of which a score will be called a decline. However, this method is flawed for patients with low baseline scores (floor effect). By necessity, the absolute magnitude of the change required for significance will vary between studies, since the norm is determined from the preoperative baseline test scores. Finally, some studies have used per cent change (e.g. 20%) to define decline. The limitation of this method is that the baseline low scoring patients require a smaller change in their raw score to meet POCD criterion.

The timing of testing is important as well. It is possible that patients who undergo baseline testing on the morning of their procedure might not score and also patients tested days before, secondary, preprocedural anxiety. After operation, patients who are testing shortly after surgery can test worse than those who are tested weeks to months later possibly due to pain, residual drugs, and health status. However, long-term follow-up and testing is confounded by attrition, that is, patients who experience the greatest decline are the least likely to follow-up with their postoperative cognitive testing and drop out of the study. This may be a significant cause for underestimating the true incidence of POCD. Additionally, there can be significant variability between testing sessions due to learning and examiner bias.²⁹ Although variability in neuropsychological test data contributes to a low consistency between postoperative test sessions, the differences detected suggest that this does not fully explain the detection of cognitive dysfunction after major surgery.³⁹ It is clear that deterioration is not random variation between testing sessions.

The current literature is also diverse with respect to inclusion and exclusion criteria of patients with MCI. MCI is described as the prodromal state, a heterogeneous group of conditions including Alzheimer's dementia, cerebral vascular disease, and other dementia. Most of the major studies have excluded this group due to limitations of the test battery. This is true even though this group may be the most significant risk for POCD by virtue of having less cognitive reserve.⁴⁵ By not differentiating this patient population, it is possible that the incidence of cognitive decline has been 'washed out' by the larger sample.

Pathophysiology and aetiology

Delirium as a behavioural manifestation of cortical dysfunction is associated with characteristic signs. The EEG may show diffuse slowing of background activity. A wide variety of disturbances in neurotransmitter systems has been described. Serum anticholinergic activity has been associated with delirium and may be especially important, and also other mediators such as melatonin, norepinephrine, and lymphokines.^{19 48} Delirium has been hypothesized to occur as a result of the inflammatory response associated with the stress of surgery. Interestingly, elevated preoperative inflammatory markers including C-reactive protein, interleukin 6, and insulin growth factor 1 (IGF-1) have not been found to

be associated with the development of POD.^{27 42} However, postoperative chemokines have been found to be more elevated in patients who became delirious than in matched controls. This difference was non-significant by postoperative day 4, and other inflammatory cytokines were not found to be different in the two groups at any time point. This would point to a mechanism for delirium which might include initial leucocyte migration into the central nervous system (CNS) and potentially a breakdown of the blood-brain barrier.⁴²

Although the mechanism of delirium has not been elucidated, there has been significant description of associated patient risk factors. Some of these may be considered pre-existing, that is, existing vulnerabilities, and others precipitating, that is, noxious injuries. Age >70, pre-existing cognitive impairment, preoperative use of narcotics or benzodiazepines, previous history of POD, and self-reported health impairment from alcohol are all closely associated with the development of POD.²⁸ Other predisposing risk factors include vision impairment, severe illness, cognitive impairment, and serum urea nitrogen: creatinine ratio of 18 or greater.¹⁹ Vascular risk factors have also been strongly associated with development of delirium (tobacco use and vascular surgery), although it is unclear whether the increased risk is due to atherosclerotic burden or the surgical procedure itself.⁴⁰ Decreased cerebral perfusion as a risk factor for POD is supported by a recent study which associated low preoperative regional oxygen saturation as measured by a cerebral oximeter.³⁵ Low preoperative executive scores and depressive symptoms, as measured by the several different instruments, have been found to identify patients at risk of POD.^{15 46} POD is also associated with pre-existing attentional deficits in non-demented patients.³⁰ Precipitating factors include: the use of physical restraints, malnutrition, more than three medications added 24-48 h before the onset of delirium, the use of a urinary bladder catheter, and iatrogenic events, including electrolyte and fluid abnormalities.¹⁹ Specific perioperative risk factors include greater intraoperative blood loss, more postoperative transfusions, and postoperative haematocrit of <30%.³² Severe acute pain regardless of the method of analgesia (opioid type, method, and dose) is associated with POD.¹³ Although it is tempting to speculate the mechanism from these observations, association may not infer causality. Certain types of injury, particularly hip fractures, and serious illness requiring intensive care are also associated with a high incidence of delirium.

Aetiology of postoperative cognitive decline is also unclear. Several mechanisms have been postulated. These include perioperative hypoxaemia and ischaemia. However, these variables as measured by pulse oximetry and arterial pressure were not found to be significant by the ISPOCD group.³⁴ This surprising result may become somewhat more comprehensible in future studies involving cerebral oximetry. Although there have been laboratory studies which suggest that general anaesthetic agents have toxic effects on the CNS, this effect is less evident in clinical studies. Interestingly, choice of anaesthesia (general vs regional) has not been found to be significant.^{10 11 50 51} However, major surgery does appear to be a principle culprit, whereas general anaesthesia and ambulatory surgery are not.³⁴ Increased inflammatory activity may play a role in early POCD. Elevated C-reactive protein is associated with impaired mental status in elderly hip fracture patients.⁵

Similar to POD literature, more has been described regarding risk factors and associations for POCD than the mechanism itself. Advancing age has been found as a risk factor for POCD, although minor declines have been described in younger patients as well.²² Preoperative cognitive and physical impairment and cognitive impairment during hospitalization correlate with poorer postoperative outcomes at 2 and 12 months.¹⁶ However, the epsilon-4 allele of the ApoE gene, which is strongly associated with the development of Alzheimer's disease, is not associated with the development of POCD.¹ POD has also been associated with early postoperative dysfunction (at 7 days); however, the association with long-

term cognitive function is less clear. [41](#) [49](#) There may indeed be an association between POD and POCD, but the relationship has yet to be elucidated. The ISPOCD1 study did not find that the patients who developed delirium were the same patients who developed POCD. Most studies have focused on either POD or POCD; in the future, studies designed to evaluate this patient population for both and examine their association may enhance our understanding of this issue. Perioperative patient risk factors and perioperative triggers associated with POD and POCD are summarized in Tables [1](#) and [2](#), respectively.

View this table: In this window In a new window	Table 1 Preoperative risk factors
View this table: In this window In a new window	Table 2 Delirium: perioperative triggers

Incidence

The incidence of POD between studies ranges from 5% to 15%.^{[4](#)} Within certain high-risk groups such as hip fracture patients, the range is 16–62% with an average of 35%.^{[7](#)} POCD is more complicated to describe, as the true incidence can be masked by attrition of the worst cases. Additionally, POCD can improve with time, so incidence must be described at a particular interval after surgery. Currently, it seems the incidence of initial deterioration in older patients is high (25% at 2–10 days) with gradual resolution (10% at 3 months, 5% at 6 months, and 1% at 1 yr).^{[2](#)} At 1 yr, the cognitive decline is indistinguishable from matched controls. However, no study has accounted for the aforementioned attrition.

Treatment and prevention

POD is preventable in some patients, and delirium prevention/intervention programmes have met with some success. A proactive geriatric consult alone has been shown to significantly decrease the incidence of POD.^{[31](#)} Successful intervention programmes include the Hospital Elder Life Program. This programme focused on protocol-driven management of six risk factors for delirium: visual and hearing impairment, cognitive impairment, sleep deprivation, immobility, and dehydration. The study patients had significant reduction in the number and duration of episodes of delirium.^{[20](#)} Specific interventions include prominent presentation of orienting information, for example, date, time, name of hospital personnel, cognitive stimulation activities, exercise, feeding and fluid assistance, and non-pharmacological sleep aids (e.g. relaxing music and massage). Attempts at pharmacological prophylaxis have met with mixed results. Although we have excluded cardiac surgery patients from our discussion, it is interesting to note that a single dose of ketamine (0.5 mg kg⁻¹) given upon induction was associated with lower serum levels of C-reactive protein and lower incidence of delirium in this population. Authors postulate that ketamine's neuroprotective effects including prevention of excitotoxic injury and apoptosis and its suppression of CNS inflammatory response might be responsible.^{[18](#)} It should be noted that a single dose of ketamine has been reported to have a profound, 2 week impact on patients with refractory depression.^{[37](#)} Another study of cardiac surgery patients targeted the reduced cholinergic transmission associated with delirium with rivastigmine, a cholinesterase inhibitor. This study did not find that prophylaxis was associated with a decreased incidence of delirium, although the study found an overall lower rate of delirium than expected and was therefore underpowered for their primary outcome. A study of haloperidol prophylaxis in combination with non-pharmacological delirium prevention strategies had similar methodological difficulties, and showed no difference in the incidence of delirium. However, patients who received delirium prophylaxis with

haloperidol did have a significant reduction in delirium severity and duration with an associated decrease in hospital length of stay.⁴³

Treatment of POD has remained constant—identification of underlying medical issues, optimization of environment and pain control, and pharmacological treatment for refractory cases. It is important to stress that pharmacological treatment is not first line. However, it may be necessary when agitation puts the patient and caregivers at risk of harm or prevents normal postoperative care. The drug of choice remains haloperidol. It is an antipsychotic D2 dopamine receptor antagonist and is administered at a dose of 0.5–1 mg i.v. every 10–15 min until the behaviour is controlled. I.M. dosing is possible as well, but much less desirable. The dosage is 2–10 mg and interval for titration is 60–90 min. Careful titration is important to avoid oversedation and prolonged effects secondary to its long (up to 72 h) half-life. Newer antipsychotics have been shown to be effective in acute agitation when administered as i.m. injections, but have not been tested in medical and surgical patients.³ Physical restraints are undesirable except in the most severe cases and then only as a temporary measure while pharmacological and other interventions have failed. Treatment of POD is summarized in Table 3.

View this table: » In this window » In a new window	Table 3 Treatment of POD
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Prevention and treatment of postoperative cognitive decline is still undefined. It is unclear whether delirium prevention strategies affect long-term cognitive outcomes.

Future directions

High-quality perioperative care for elderly patients is a social and financial necessity. One of the fastest growing segments of the population is individuals over 65.¹² Delirium is immediately costly, by increasing hospital length of stay and more insidiously by its association with mortality and cognitive decline.¹⁴ POCD can remove individuals prematurely from the workforce or require previously independent individuals to seek help with activities of daily living or assisted care facilities.⁴⁷ Identification of at-risk individuals is possible, given the available literature. The creation of ‘centres of excellence’ where process measures are implemented and risk-adjusted outcomes explored might allow us to identify strategies to optimize care.³³ There is already evidence that this is possible and helpful.²⁰ However, there are not enough geriatricians to relegate the perioperative care of the elderly to specialists. Caring for perioperative geriatric patients by necessity must be a multidisciplinary effort.³³

The Cochrane review on delirium prevention in hospitalized elderly patients found that there is a paucity of high-quality research on delirium prevention. Reasons include the difficulties with detection and conducting research in these frail and debilitated patients, and the confounding factors of medical problems, pre-existing cognitive deficits, and attrition which we have mentioned previously.⁴⁴ An ideal study would focus on long- and short-term outcomes including mortality and physical and cognitive/psychological morbidity.

POCD, while established as a diagnostic entity, requires more research to understand its aetiology. This may facilitate future studies regarding treatment and prevention. At a minimum, larger studies using a standard definition and meticulous follow-up may enhance our understanding of this perioperative phenomenon. An agreement of what tests and degree of change defines a clinically significant cognitive deficit would facilitate comparison across studies examining either its incidence or the efficacy of an intervention. With respect to mechanistic understanding of POCD, new modalities such as cerebral oximetry and detection of serum markers of inflammation show promise.

Conclusion

As members of society and practitioners of perioperative medicine, we are invested in the future of excellence in geriatric care. In the clinical arena, more awareness and deliberate care plans are necessary to implement those interventions which are already known to decrease or ameliorate the incidence of POD. Education of care teams regarding these strategies for prevention is of the utmost importance. Geriatrician involvement where possible is helpful, but the essence of good basic care is identification of the at-risk individual, awareness of common perioperative aggravating factors, simple prevention interventions, recognition of the disease state when it occurs, and basic treatments for patients with severe hyperactive manifestations. Ongoing studies of clinical cohorts with and without MCI before operation may help us understand the risks of cognitive dysfunction after non-cardiac surgery. Future research may help us understand underlying biochemical or physical insults which may lead us to better directed prophylactic treatment.

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