Postoperative Cognitive Disorders: Postoperative Delirium and Postoperative Cognitive Dysfunction

Samuel Fitzpatrick[1], Kristine Owen[2]

[1]Anaesthetic Registrar, Fiona Stanley Hospital, Western Australia
[2]Anaesthetic Consultant, Fiona Stanley Hospital, Western Australia

Edited by: Alex Konstantatos, Anaesthetic Consultant, Alfred Hospital Victoria, Australia

†Corresponding author e-mail: s.fitz02@gmail.com

Published 7 August 2018

KEY POINTS

- Postoperative delirium is a common and potentially preventable cause of morbidity. It can manifest as hypoactive, hyperactive, or mixed subtypes.
- Postoperative delirium increases length of stay, reduces quality of life, and increases dependency for basic activities of daily living.
- Risk factors associated with delirium include age, complex comorbidities, previous cognitive impairment, sleep disruption, and type of surgery.
- Preoperative prediction and early perioperative recognition of high-risk patients allow for rapid diagnosis and treatment, which may reduce duration of delirium. There has been emerging evidence regarding preventative anaesthetic strategies for operative delirium including depth of anaesthesia monitoring and specific anaesthetic drugs.
- Postoperative cognitive dysfunction is a separate condition that refers to a decline in cognitive function following surgery as measured by neuropsychological testing. There has been significant recent work to redefine this condition to align with geriatric research.

INTRODUCTION

The frequency of elderly patients presenting for emergency and elective surgery continues to increase.

Increasing age has been implicated in the development of delirium and postoperative cognitive dysfunction; therefore, understanding of these conditions is important for delivering safe perioperative care in an aging population. Delirium has been associated with increased length of stay and increased morbidity, including falls, pressure area injuries, and increased functional dependency.[1] Early intervention is crucial to minimise the sequelae of delirium.

This tutorial will discuss the clinical features, incidence, diagnosis, presentation, prevention, and treatment of delirium and also cover risk factors and proposed aetiologies for postoperative cognitive dysfunction.

An online test is available for self-directed Continuous Medical Education (CME). It is estimated to take 1 hour to complete. Please record time spent and report this to your accrediting body if you wish to claim CME points. A certificate will be awarded upon passing the test. Please refer to the accreditation policy here.

TAKE ONLINE TEST

1. Change in level of arousal: drowsiness or decreased arousal* or increased arousal with hypervigilance
2. Delayed awakening from anaesthesia
3. Abrupt change in cognitive function (worsening confusion over hours or days), including problems with attention, difficulty concentrating, new memory problems, new disorientation
4. Difficulty tracking conversations and following instructions
5. Thinking and speech that is more disorganized, difficult to follow, slow,* or rapid
6. Quick-changing emotions, easy irritability, tearfulness, uncharacteristic refusals to engage with postoperative care
7. Expression of new paranoid thoughts or delusions (ie, fixed false beliefs)
8. New perceptual disturbances (eg illusions, hallucinations)
9. Motor changes such as slowed or decreased movements,* purposeless fidgeting or restlessness, new difficulties in maintaining posture such as sitting or standing*
10. Sleep/wake cycle changes such as sleeping during the day* and/or awake and active at night
11. Decreased appetite*
12. New incontinence of urine or stool*
13. Fluctuating symptoms and/or level of arousal over the course of minutes to hours

Table 1. Symptoms Associated With Delirium. *Hypoactive symptoms. Reprinted from the American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. Postoperative delirium in older adults: best practice statement from the American Geriatric society. *J Am Coll Surg*. 2015;220:136-148, with permission from Elsevier.

POSTOPERATIVE DELIRIUM

Clinical Features and Incidence

Delirium is a neuroinflammatory condition characterised by inattention and a fluctuating conscious level. Postoperative delirium can occur up to 30 days postprocedure. Delirium is common in hospitalized patients, with an incidence ranging from 14% on the general medical wards to 82% in the intensive care unit. Surgeries strongly associated with delirium include vascular, orthopaedic, and cardiac surgery, with the condition occurring in up to 50% of the patients postoperatively.[1]

Delirium can be diagnosed clinically using the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-V). The DSM-V describes the key components of delirium as being a change in the level of consciousness or disturbances in attention that develop over a short period of time. These changes usually fluctuate throughout the day and can be associated with additional cognitive disturbances, which may include memory deficit or disorientation.[2]

Delirium can be further categorised into hypoactive, hyperactive, and mixed subtypes. Of delirious patients, 71% have the hypoactive subtype.[3] Hyperactive patients are often agitated, aggressive, and combative. Hypoactive patients can have anhedonia and decreased alertness. The hypoactive subtype of delirium can be particularly difficult to diagnose, leading to missed treatment opportunities. See Table 1.

Screening at-risk individuals can increase the diagnosis of the hypoactive subtype of delirium, allowing for early intervention. Early intervention has the potential to reduce the duration and complications of postoperative delirium.[1] For a screening tool to be useful clinically, it should be validated for the intended population and be useable by nonspecialists. Examples of validated screening tools for the diagnosis of delirium on the medical ward are the 3D CAM and 4AT tools.[4,5] At our institution, we use the 4AT, which involves 4 tests including an assessment of alertness, 2 brief cognitive screening tests, and an assessment of the acuity of the observed changes in mental state. The 3D CAM is a bedside test based on the confusion assessment method algorithm. The CAM-ICU has been validated for the intensive care setting.[6]

Causes and Risk factors

A multifactorial model of delirium has been described in which patients with varying underlying susceptibility or vulnerability to delirium are exposed to 1 or more precipitating factors, which can then lead to the development of delirium (Figure 1).[1,2]

Patients from nursing homes with preexisting cognitive impairment are at high risk of developing delirium. These patients may develop delirium after a relatively minor insult, such as a urinary tract infection. On the other hand, patients with a low vulnerability to delirium may require a major insult, such as overwhelming sepsis before developing delirium.

There is emerging evidence regarding the neuroinflammatory aetiology of delirium. The theory suggests that subclinical inflammatory states prime the nervous system by activating neuronal tissue including microglia and astrocytes. When exposed to noxious stimuli, these primed neuronal tissues release a cascade of inflammatory cytokines and mediators, resulting in neuronal injury, which may include damage to the blood-brain barrier.[7] This damage to the blood-brain barrier and production of inflammatory mediators can culminate in postoperative delirium.

Risk factors, including precipitating and predisposing factors, are shown in Table 2.

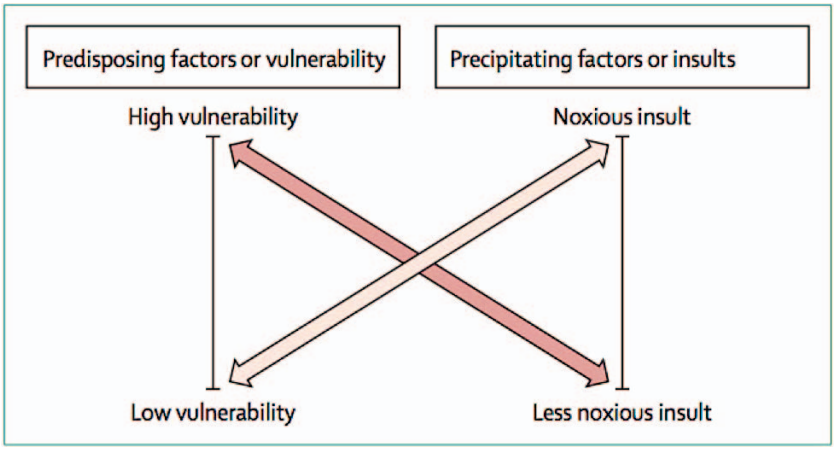

Figure 1. Multifactorial model of delirium. Reprinted from Inouye S, Westendorp R, Saczynski J. Delirium in elderly people. *Lancet*. 2015;383:911-922, with permission from Elsevier.

Predisposing Factors	Precipitating Factors
Age	Sleep disruption
Cognitive impairment	Emergency surgery
Complex comorbidities	Significant intraoperative blood loss
	Poorly controlled pain

Table 2. Risk Factors for Delirium

Prevention and Treatment

Identification of at-risk patients and targeted prevention may reduce the incidence and severity of delirium. The American Geriatric Society describes steps for this preemptive intervention in terms of behavioural and nonpharmacological treatment priorities. These are focused on minimising the impact of the precipitating factors that can lead to delirium.[8]

- Acute medical issues should be treated promptly.
- Reorientation strategies should be employed, and family members should be involved if available.
- Mobility should be encouraged where appropriate, and strict bed rest should be avoided.
- Medication management is an important aspect of delirium treatment and should include the avoidance or reduction of benzodiazepines and anticholinergics.
- Nutrition and fluid therapy should be optimised.

Institutions that have implemented these multicomponent strategies using interdisciplinary teams have been able to demonstrate significant reduction in the incidences of delirium (perioperative cognitive protection; see Table 3).

1. Sensory enhancement (ensuring glasses, hearing aids, or listening amplifiers)
2. Mobility enhancement (ambulating at least twice per day if possible)
3. Cognitive orientation and therapeutic activities (tailored to the individual)
4. Pain control with scheduled acetaminophen if appropriate
5. Cognitive stimulation (if possible, tailored to the individual's interests and mental status)
6. Simple communication standards and approaches to prevent the escalation of behaviours
7. Nutritional and fluid repletion enhancement
8. Sleep enhancement (daytime sleep hygiene, relaxation, nonpharmacological sleep protocol, and nighttime routine)
9. Medication review and appropriate medication management
10. Daily rounding by an interdisciplinary team to reinforce the interventions

Table 3. Behavioural and Nonpharmacological Strategies for Prevention of Delirium. Reprinted from the American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. Postoperative delirium in older adults: best practice statement from the American Geriatric Society. *J Am Coll Surg*. 2015;220:136-148, with permission from Elsevier.

Anaesthesia Technique

Anaesthesia has been implicated in the pathogenesis of delirium.

It is unclear whether choice of anaesthetic agent plays a significant role in the development of delirium. This includes choosing between general anaesthesia, conscious sedation, and regional anaesthesia. The European Society of Anaesthesiology found there was insufficient evidence to make a recommendation regarding the choice of anaesthetic agent used intraoperatively.[9]

Evidence suggests that the use of bispectral index (BIS)–guided anaesthetic care is associated with a reduced incidence of postoperative delirium.[10] BIS is derived from analysis of a patient's electroencephalogram with values between 0 and 100. The BIS monitor is used to guide titration of anaesthetic drugs. A target value of between 40 and 60 for general anaesthesia is considered ideal, thereby avoiding excessively deep anaesthesia. Two randomised controlled trials demonstrated that in the group randomised to BIS-guided care (between 40-60), there was a reduction in either propofol or volatile agent administered and the incidence of postoperative delirium as compared with routine care.[10, 11] This suggests that avoiding excessive depth of anaesthesia is an important preventative strategy for the management of delirium. The exact mechanism linking the depth of anaesthesia to postoperative delirium remains unclear.

Benzodiazepines have been implicated in the development of delirium, with exposure to midazolam identified as a risk factor for delirium in postsurgical and intensive care patients.[12] The routine use of benzodiazepine premedication should be discouraged, except in cases in which there is preexisting anxiety and benzodiazepine or alcohol withdrawal.

Ketamine, an N-methyl-D-aspartate antagonist with psychoactive properties, showed promising benefit for reduction in delirium when given prophylactically in a small trial in cardiac surgery, but this has not been supported by larger randomised control trials. Subanaesthetic doses of ketamine have been demonstrated to reduce postoperative markers of inflammation, pain, and opioid consumption as well as having an antidepressant effect. A large, multicentre trial that randomised patients to either 0.5 mg/kg, 1.0 mg/kg, or normal saline did not demonstrate a statistically significant difference in delirium, but there were higher rates of hallucinations and nightmares reported with each increased dose of ketamine.[13]

Dexmedetomidine, an α-2 agonist, has been demonstrated to reduce the incidence of delirium in patients older than 65 years after noncardiac surgery when given prophylactically (0.1 μg/kg/h) to patients admitted to the intensive care unit.[14]

Avoiding prolonged fasting and maintenance of hydration are important interventions that can reduce postoperative delirium.[9]

As mentioned previously (Tables 2 and 3), adequate pain control using a multimodal regimen is an important preventative strategy for delirium.

It is unclear whether neuraxial anaesthesia compared with general anaesthesia reduces the development of delirium. A recent trial in the neck of femur fracture surgery patients was unable to demonstrate a difference between patients who received spinal compared with general anaesthesia.[15]

POSTOPERATIVE COGNITIVE DYSFUNCTION

Cognitive decline increases with age. Cognitive impairment also occurs in patients in the postoperative period and is the subject of much contemporary research.

Postoperative cognitive dysfunction (POCD) refers to a deterioration in cognition temporally associated with surgery as quantified by neuropsychological tests. Ideally, these tests should be performed prior to surgery to aid as a point of reference. POCD does not yet correspond to a specific clinical diagnosis.[16]

In the geriatric literature, the term *mild cognitive impairment* (amnestic subtype) is used by the National Institute of Aging and Alzheimer's Disease and describes the interim period between normal cognition and dementia.[17] The DSM-V manual refers to mild cognitive impairment as a mild neurocognitive disorder, with dementia being a major neurocognitive disorder.[2] These terms are used for patients in the community and are not used in relation to perioperative impairment. The new consensus definition in the context of anaesthesia and surgery is due to be published shortly in the *British Journal of Anaesthesia*.[18]

Regardless of the evolving nature of the nomenclature used to describe this condition, postoperative cognitive dysfunction is associated with adverse outcomes, including reduced quality of life and increased mortality.[16,19,20]

The incidence of POCD among patients older than 65 years is approximately 25.8% at 1 week and 9.9% at 3 months following surgery.[21]

Aetiology and Risk Factors for POCD

Consistently identified risk factors for POCD include increasing age and preexisting cognitive impairment. Lower education levels have also been identified as a risk factor.[16,21]

Anaesthesia is assumed to be a completely reversible process; however, there has been emerging animal data linking exposure to anaesthetic agents and persisting neurodegenerative changes. The clinical significance of these findings in humans should be regarded with caution until confirmed by same-species data.

There are multiple theories for the aetiology of POCD that have not been validated by clinical trials at this point, including intraoperative hypoxemia, hypotension, and thrombus or emboli.[16]

There has been no difference in the incidence of POCD in patients undergoing regional compared with general anaesthesia.[16,22] One hypothesis to explain this involves neuronal changes due to noxious stimuli associated with surgery rather than an anaesthetic drug effect.[23]

Evaluations of genetic factors have identified apoprotein E as a potential mediator in those at risk of developing POCD. Apolipoprotein E is involved in the recovery from central nervous system injury, and the presence of the E4 allele is implicated in the development of POCD.[16]

SUMMARY

Delirium is a neuroinflammatory condition that is characterised by inattention and fluctuating conscious level. Delirium is a major cause of preventable morbidity and mortality. Early screening and diagnosis has been demonstrated to reduce the severity and duration of delirium.

Key anaesthetic strategies for the prevention of delirium include avoiding or minimizing the dose of high-risk medications, including benzodiazepines and anticholinergics, and minimizing fluid fasting time. There is suggestive evidence supporting the use of depth-of-anaesthesia monitoring. The current evidence does not support the use of specific anaesthetic drugs or modality of anaesthesia; however, there is suggestive evidence regarding the role of dexmedetomidine.

Postoperative cognitive dysfunction refers to a deterioration in cognition temporally associated with surgery as quantified by neuropsychological tests. The nomenclature and classification of this condition is continuing to evolve, and there has been significant work to align the geriatric and anaesthetic literature regarding this condition. Age, preexisting cognitive impairment, lower education level, and genetic susceptibility have been identified as risk factors for POCD. There is insufficient evidence to recommend specific anaesthetic techniques for the prevention of this condition.

REFERENCES

1. Inouye S, Westendorp R, Saczynski J. Delirium in elderly people. *Lancet*. 2015;383:911-922.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
3. Robinson T, Eiseman B. Postoperative delirium in the elderly: diagnosis and management. *Clin Interv Aging*. 2008:3;351-355.
4. Bellelli G, Morandi A, Davis D, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. *Age Ageing*. 2014:44;496-502.
5. Marcantonio E, Ngo L, O'Conner M. 3-D CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium. *Ann Intern Med*. 2014;161(8):554-561.
6. Ely EW, Margolin R, Francis J. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med*. 2001;29(7):1370-1379.
7. Cerejeira J, Firmino H, Vaz-Serra A. The neuroinflammatory hypothesis of delirium. *Acta Neuropathol*. 2010;119:737-754.
8. American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. Postoperative delirium in older adults: best practice statement from the American Geriatric Society. *J Am Coll Surg*. 2015;220:136-148.
9. Aldecoa C, Bettelli G, Bilotta F. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. *Eur J Anaesthesiol*. 2017;34:192-214.
10. Radke F, Franck M, Lendner J, et al. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. *Br J Anaesth*. 2013;110:98-115.
11. Chan M, Cheng B, Lee T. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol*. 2013;25:33-42.
12. Pandharipande P, Cotton B, Shintani A. Prevalence and risk factors for development of delirium in surgical and trauma intensive care patients. *J Trauma*. 2008;65:34-41.
13. Avidan MS. Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. *Lancet*. 2017;390:267-275.

14. Su X, Meng Zhoo-ting, Zin-hai WU, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2016;388:1893-1902.
15. Llango S, Pulle R, Bell J, et al. General versus spinal anaesthesia and postoperative delirium in an orthogeriatric population. *Australasian J Ageing*. 2015;35:42-47.
16. Miller R, ed. Cognitive dysfunction and other long-term complications of surgery and anaesthesia. In: *Miller's Anesthesia*. 8th ed. London, UK: Elsevier; 2015:Ch 99.
17. Albert MS, DeKosky ST, Dickinson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:270-279.
18. Everad L, Eckenhoff R; on behalf of the International Perioperative Cognition Nomenclature Working Group. Perioperative cognitive disorders. Response to: Postoperative delirium portends descent to dementia. *Br J Anaesth*. 2017;119:1241.
19. Monk T, Weldon B, Garvan C. Predictors of cognitive dysfunction after major non-cardiac surgery. *Anesthesiology*. 2008;108:18-30.
20. Steinmetz J, Christensen K, Lund T. Long-term consequences of postoperative cognitive dysfunction. *Anesthesiology*. 2009;110:548-555.
21. Moller J, Cluitmans P, Rasmussen L. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. *Lancet*. 1998;351:857.
22. Evered L, Scott D, Silbert B, et al. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anaesth Analg*. 2011;112:1179-1185.
23. Riedel B, Brown K, Silbert B. Cerebral protection: inflammation, endothelial dysfunction, and postoperative cognitive dysfunction. *Curr Opin Anaesthesiol*. 2014;27:89-97.