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# Cognitive function after anaesthesia in the elderly

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Despite advances in peri operative care, a significant percentage of elderly patients experience transient post operative delirium and/or long-term post-operative cognitive dysfunction (POCD). This chapter reviews the aetiology, clinical features, preventive strategies and treatment of these syndromes. Pre-operative, intra-operative, and post-operative risk factors for delirium and POCD following cardiac and non-cardiac surgery are discussed. It is most likely that the aetiology of delirium and POCD is multifactorial and may include factors such as age, decreased pre-operative cognitive function, general health status and, possibly, intra-operative events. Currently there is no single therapy that can be recommended for treating post-operative cognitive deterioration. Primary prevention of delirium and POCD is probably the most effective treatment strategy. Several large clinical trials show the effectiveness of multicomponent intervention protocols that are designed to target well-documented risk factors in order to reduce the incidence of post-operative delirium and, possibly, POCD in the elderly.

**Key words:** post-operative complications; delirium; dementia; anaesthesia; geriatric; cognitive function recovery; post-operative.

Advances in surgical techniques and in anaesthetic care have resulted in a substantial reduction in peri operative mortality and morbidity in the elderly. Patients with multiple medical problems are now able to undergo complex surgical procedures relatively late in life. Central nervous system (CNS) dysfunction, however, has increasingly been recognized as a complication after cardiac and non-cardiac surgery in the elderly.[1–3]

Post-operative cognitive deterioration can be classified into two main categories: post-operative delirium and mild neurocognitive disorder (commonly referred to in the literature as post-operative cognitive dysfunction (POCD)).[4] Post-operative delirium is

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a well-recognized clinical entity associated with increased morbidity and mortality, delayed functional recovery and prolonged hospital stay in the elderly. The characteristic features include impaired cognition, fluctuating levels of consciousness, and abnormalities in memory and perception.[5] Delirium is an extremely costly disorder, both to the patient in terms of morbidity and mortality and to the medical facility. Medicare expenditure associated with the diagnosis and treatment of this complication exceeds $4 billion per year (1994 dollars).[6]

POCD is a condition characterized by impairment of memory, concentration, language comprehension, and social integration.[7] This syndrome may be detected days to weeks after surgery and may remain as a permanent disorder. Socioeconomic implications of POCD are profound; they include loss of independence, extra nursing care and a high rate of discharge to long-term care. This review summarizes recent advances in our understanding of post-operative cognitive derangement, potential risk factors, management, and areas for further research.

## POST-OPERATIVE DELIRIUM

### Clinical features

Delirium is characterized chiefly by changes in consciousness and cognition over a brief period of time. Cognitive abnormalities include disorientation, language difficulties, or impairment in learning and memory. Emotional disturbances can be prominent, with intermittent and labile symptoms of anxiety, fear, irritability, anger and depression. Post-operative delirium often has a fluctuating course.

Simple bedside tests of cognitive function are useful for recognizing and following the changes in mental status. These tests assess orientation, short-term memory, language, perception and, to some degree, motor function. The Mini-Mental Status Exam is brief, easy to conduct, and can be used for serial testing.[8] It was not designed, however, to differentiate between delirium and dementia. Other commonly used tests for assessing post-operative mental status include the Abbreviated Mental Test[9] and the Confusion Assessment Method (CAM).[10] The CAM criteria provide a standardized rating of delirium that has been validated against geropsychiatric diagnosis and has high interobserver reliability. It is the most commonly used instrument for diagnosing delirium in hospitalized patients.

There is wide variation in the reported incidence of delirium, ranging from 0 to 73.5%.[11] Several factors such as age, type of surgery, diagnostic criteria and pre-operative medical status, as well as pre-operative cognitive status, may account for this disparity. The type of delirium most commonly encountered after surgery has been termed interval delirium; it usually occurs between the second and seventh post-operative days.

Emergence delirium refers to transient restlessness in the immediate post-operative period. It can occur in any age group. The occurrence rate of interval delirium in the elderly general surgery group was found to be about 10%.[12] Elderly patients undergoing major orthopaedic surgery (e.g. joint replacement, hip fracture) are at highest risk, with the incidence ranging from 24 to 50%.[13,14] The incidence of delirium after cardiac surgery in 16 prospective studies varied from 3 to 47%.[15]

**Table 1.** Mechanisms of brain injury.

| |
|---|
| Metabolic encephalopathy |
| Electrolyte disturbances (e.g. hyponatraemia, dehydration) |
| Hypoglycaemia |
| Hyperglycaemia |
| Renal dysfunction |
| Endocrine dysfunction (e.g. hypothyroidism) |
| Hypothermia |
| Hyperthermia |
| Hepatic dysfunction |
| Neurological injury |
| Hypoxia |
| Low cerebral perfusion pressure |
| Embolic or thrombotic stroke |
| Cerebral oedema |
| Hypertensive encephalopathy |
| Infection (e.g. encephalitis, meningitis) |
| Seizure |
| Toxic or prolonged drug action |

## Causes of CNS dysfunction after surgery

Little is known about the pathophysiological mechanisms of delirium. Pathogenetic factors are speculative and are based largely on animal research and post-mortem studies. The causes of global CNS dysfunction can be broadly divided into metabolic encephalopathy and neurological injury.

CNS functioning depends upon an adequate delivery of oxygen and nutrients, the effective removal of waste products, and an appropriate neurochemical milieu. Any drug-induced or somatic disturbance (e.g. hypoxia, hypoglycaemia) that interferes with the supply or use of a substrate for metabolism may cause global dysfunction. One hypothesis suggests that reduced cerebral oxidative metabolism may lead to abnormalities in various neurotransmitter systems.[16] Cerebral acetylcholine synthesis is particularly sensitive to hypoxia. Central cholinergic pathways are implicated in regulation of memory processing and alertness.[17]

Surgical trauma leads to many stress-related neuroendocrine disturbances such as a decreased level of active thyroid hormone, an increased level of cortisol, and release of cytokines. Changes in hormone levels may alter amino acid and neurotransmitter concentrations in the brain and thereby provoke delirium.[18]

Neurological injury may occur as a result of cerebral infarction secondary to embolic or thrombotic vascular occlusion or diffuse loss of neuronal tissue without overt infarction. Metabolic encephalopathy may lead to permanent brain damage as well. Somatic disturbances and risk factors for neurological injury implicated in the development of brain dysfunction are listed in Table 1.

## Risk factors for developing post-operative delirium

Multiple aetiological factors for post-operative delirium have been described, and it is likely that the pathogenesis is multifactorial[3,9,11,12,19–22] (Table 2). Severe illness

**Table 2.** The risk factors predisposing to the development of delirium.

| |
|---|
| Increasing age (especially > 75 years) |
| Psychosis |
| Personality disorder |
| Poor medical status |
| Parkinson's disease |
| Psychiatric illness |
| Dementia |
| Depression |
| Personality disorder |
| Nutritional deficiency (e.g. thiamine) |
| Alcohol and benzodiazepine withdrawal |
| Traumatic injury |
| Concussion |
| Subdural haematoma |
| Drugs with anticholinergic properties |

(ASA > II) and diminished cognitive and physical functioning pre-operatively are associated with post-operative delirium.[11,12] Clinical indicators of poor medical status include markedly abnormal electrolyte concentrations, especially sodium[19,20]; history of dementia, depression and cerebrovascular diseases[11,20,21]; and, possibly, a low level of albumin.[22] Advanced age, although poorly defined, is also a consistent independent predictor of post-operative delirium.[11,12,23] A history of alcohol abuse as well as the use of psychoactive medications (e.g. benzodiazepines) are other frequently mentioned predictive factors.[12,23]

## Perioperative factors contributing to post-operative delirium

Table 3 lists perioperative factors that may precipitate the development of post-operative delirium. An impaired cerebral oxygen supply may lead to transient or irreversible changes that may manifest as cognitive dysfunction. Oxygen delivery to the brain depends on cerebral blood flow (CBF) and oxygen content in arterial blood. Thus, perioperative hypotension, reduced blood haemoglobin level, or arterial hypoxaemia may lead to post-operative delirium. Despite its theoretical plausibility, there is no conclusive evidence of a cause and effect relationship between moderate perioperative hypoxaemia or hypotension and delirium. Although some studies demonstrated the association between perioperative hypoxia and cognitive dysfunction[24,25], larger trials have failed to show a connection between modest hypoxaemia and post-operative complications.[26,27] It appears, however, that intra-operative blood loss, the number of post-operative blood transfusions, and low post-operative haematocrit (30%) are associated with delirium.[28] In addition to hypoxaemia, various metabolic disturbances (i.e. hyponatraemia, hypocarbia, dehydration), as well as sepsis,

**Table 3.** Perioperative factors associated with post-operative delirium.

| |
|---|
| Medications and drug combinations |
| Drugs with central anticholinergic action |
| Anti-convulsants |
| Anti-inflammatory agents |
| Inhalational anaesthetics |
| Impaired cerebral oxygen supply |
| Hypotension |
| Hypoxaemia |
| Anaemia |
| Metabolic abnormalities |
| Electrolyte imbalance |
| Hypoglacaemia |
| Hypovolaemia |
| Endocrine disease |
| Infection/fever |
| Medical complications/ICU environment |

may cause delirium. Several large studies found no difference between general and regional anaesthesia in the incidence of delirium.[29,30]

Post-operative confusion is well documented after cardiopulmonary bypass.[31,32] Temporary depression of CBF and focal occlusion of cerebral vessels by microemboli of air and other debris are major factors implicated in the development of neurological impairment.[31,33] CBF is autoregulated between a mean arterial pressures (MAP) of 50 and 150 mmHg. Below and above this range CBF becomes pressure-passive—that is, the lower the MAP, the lower the CBF, and vice versa. The autoregulatory range is subject to large inter-individual and regional variation, however; prolonged episodes of focal changes detected by electroencephalogram were predictive of the development of post-operative delirium. Increasing the perfusion pressure when EEG changes were noted resulted in a lower incidence of cognitive dysfunction.[34] Microemboli have been documented in the cerebral vasculature of patients undergoing cardiovascular bypass. Arterial filtration reduces the incidence of both cerebral microembolization and cognitive dysfunction.[35]

The normal ageing process is characterized by a physiological reduction in organ function and altered pharmacokinetics and pharmacodynamics. Some of the major physiological changes that occur with ageing in the elderly include: (1) decrease in lean body mass, (2) decrease in total body water and (3) increase in body fat. In addition, elderly patients may suffer from chronic diseases. The extent of physiological deterioration is variable. The result of these changes is an increased variability in the dose–response relationship. A clinical result of this increased variability is an increased incidence of adverse drug reactions as well as poor predictability of the response. It is accurate to say that most perioperative drugs may have lingering CNS effects and produce post-operative cognitive impairment in some patients.

Anticholinergic drugs (i.e. atropine, scopolamine) are classic pharmacological causes of post-operative delirium.[36] Agents that are not anticholinergic but which block

muscarinic sites (e.g. antihistamines, some vasoactive drugs) are also implicated as precipitating factors of post-operative delirium.[17]

Elderly patients are more sensitive to the CNS effects of barbiturates, inhalational anaesthetics, benzodiazepines and opioids.[37] Although several reports have suggested a direct link between the residual amount of anaesthetic drugs and post-operative delirium, most of the studies have not been adjusted for confounding risk factors.[3,9,38] Among narcotic agents, meperidine is the most deliriogenic opioid.[9,38] Exposure to long-acting benzodiazepines had a stronger association with delirium than did exposure to shorter-acting agents.[38] Post-operative delirium could also be a manifestation of benzodiazepine withdrawal.[3,9] The use of newer, shorter-acting anaesthetic and analgesic drugs may contribute to less post-operative cognitive impairment and confusion in the elderly.[39,40]

## Treatment of post-operative delirium

Therapeutic measures to manage post-operative delirium are shown in Table 4. The treatment of post-operative delirium is primarily the recognition and management of underlying causes. Sedation of a patient with unrecognized illness (e.g. sepsis, uraemia, myocardial infarction) may lead to disaster. Initial diagnostic tests to rule out the organic cause of delirium include serum glucose and electrolyte levels, arterial blood gas analysis, chest X-ray, haematocrit and blood cultures. As dehydration and malnutrition are common causes of delirium in the hospitalized elderly, clinical evaluation should include assessment of fluid balance and nutritional status.[41]

Supportive therapy (i.e. adequate ventilation and oxygenation, haemodynamic support) must be administered from the start to ensure an optimal environment for recovery. Control of post-operative pain is important as there is an association between higher pain levels and the development of delirium.[42]

**Table 4.** Prevention and treatment of post-operative delirium.

| |
|---|
| Prevention |
| Evaluation and treatment of medical problems |
| Detailed history of concurrent medications |
| History of drugs or alcohol abuse |
| Adequate cerebral oxygen supply |
| Avoid anticholinergic drugs |
| Maintain electrolyte balance |
| Avoid dehydration |
| Multicomponent geriatric intervention programme |
| Management |
| Investigate and treat underlying cause |
| Treat pain |
| Pharmacological treatment |
| Haloperidol |
| Benzodiazepines for alcohol and benzodiazepine withdrawal |
| Supportive measures |

Pharmacological treatment is indicated if the patient is endangering himself or herself. Where sedation is needed, neuroleptic medications (e.g. haloperidol, chlorpromazine) are usually preferred to benzodiazepines. Although droperidol is less anticholinergic than other sedatives, and may produce rapid tranquilization, its use should be restricted in view of the recent warning by the Food and Drug Administration (FDA) of an association between droperidol and fatal cardiac arrhythmias.[43] Benzodiazepines are useful in the treatment of alcohol or benzodiazepine withdrawal. Physostigmine can be used to reverse the central action of anticholinergics as well as hypnotic drugs.[44]

### Prevention

Prevention of delirium is probably the most effective strategy for reducing its incidence. The principles of prophylaxis are listed in Table 4. Several studies have indicated that the multicomponent interventions resulted in significant reduction in the incidence and duration of delirium in the elderly.[45,46] Intervention protocols include frequent orientation, cognitive stimulation, noise-reduction strategies for sleep enhancement, early mobilization, as well as early volume repletion for dehydration. Eyeglasses and hearing aids should be worn when required to reduce sensory deficits.

Patients with co-morbidity and ASA physical status $>$ 2 have a higher incidence of post-operative delirium.[19] Optimizing the medical condition prior to surgery may thus decrease post-operative confusion. Antidepressant treatment for chronically depressed patients should be continued perioperatively.[47] Although the role of perioperative hypoxaemia and hypotension in the development of post-operative mental dysfunction is controversial, it is reasonable to maintain good oxygenation, normal blood pressure, and normal electrolyte levels. Anaesthetic drugs should be carefully titrated. Use of the Bispectral Index (BIS) monitor may decrease the utilization of anaesthetics and contribute to faster emergence of elderly patients.[48]

Post-operative preventive measures should be directed toward the early recognition and treatment of medical and surgical complications. Better control of post-operative pain may reduce the development of post-operative delirium as there is an association between higher pain levels and the development of delirium.[49]

Polypharmacy appears to play an important role in post-operative delirium and should be minimized.[50]

## POST-OPERATIVE COGNITIVE DYSFUNCTION

### Clinical features

The North American Diagnostic and Statistic Manual of Mental Disorders, Fourth Edition (DSM-IV) does not reference POCD directly.[51] According to Rasmussen, POCD, as a Mild Neurocognitive Disorder, is one of *the cognitive disorders not otherwise specified*. Specifically, for research and effective clinical management, the presence of cognitive dysfunction must be detectable in several functional domains listed in Table 5.[4]

The reported incidence of POCD varies. In 1955, Bedford observed minor dementia in a majority of older patients. Extreme symptoms in 18 patients led him to conclude that 'operations on elderly patients should be confined to unequivocally necessary cases'.[52] In a later study, Simpson and colleagues refuted the notion that anaesthesia and elective surgery themselves promoted a significant deterioration in the quality of life of

**Table 5.** Diagnostic criteria for POCD.

| |
|---|
| Memory impairment as identified by a reduced ability to learn or recall information |
| Disturbance in executive functioning (i.e. planning, organizing, sequencing, abstracting) |
| Disturbance in attention or speed of information processing impairment in perceptual-motor abilities |
| Impairment in language (e.g. comprehension, word finding) |

the elderly.[53] Their subject groups received a general anaesthetic, a local anaesthetic or no surgery/anaesthetic. They utilized standardized testing. A psychologist tested individuals demonstrating highest risks. The investigation demonstrated that any significant change in the subjects was readily attributable to other causes.[2,53]

POCD is seen in 20–60% of patients several months after cardiac surgery. The incidence is higher at discharge, 50–80%.[54–58] Following non-cardiac surgery on patients older than 60 years, 25% demonstrated dysfunction 1 week after surgery. This number fell to 10% 3 months later. A non-surgical, non-anaesthetized, similarly aged control group's neurocognitive abilities deteriorated by only 3%.[27]

## Diagnosis

Early studies attempting to document the presence of POCD failed to detect any dysfunction beyond a short period of time after general surgical procedures.[53,59–62] Methods of detection and diagnosis remain unreliable because neuropsychological tests with low sensitivity may not detect functional impairment. Low sensitivity also results in the inability to study differences among types of anaesthetics, and among time points after surgery in the same patient. A practice effect also diminishes the effectiveness of tests in research and clinical practice.[1]

## Risk factors/perioperative factors/pathophysiology

We know very little about the risk factors for POCD. Most researchers must include in the design of their studies a means for discovering these risks retrospectively. A typical study establishes groups based on age, operative complications, second operation, duration of anaesthesia, level of education and pre-operative medications, as well as perioperative hypotension and hypoxia.[2,27,63] Elderly patients with multiple health problems are at the highest risk for neurological and neurocognitive complications. Table 6 lists possible contributing features.

The largest trial examining the relationship between regional or general anaesthesia and POCD determined with more than 99% statistical power that 5% of the patients showed long-term, clinically detectable dysfunction. This study of elderly patients undergoing elective total knee replacement surgery found that neither cognitive outcome nor major cardiovascular complications varied with the anaesthetic approach.[29]

All pre-operative medications have the potential for producing lingering post-operative effects on cognition and psychomotor dysfunction. The literature contains numerous examples of persisting CNS dysfunction. The use of benzodiazepines, dopamine antagonists, alpha-2 agonists, alpha-1 antagonists, phenytoin, or

**Table 6.** Factors possibly associated with POCD.

| |
|---|
| Pre-operative medication |
| Hypothermia |
| Hypotension |
| Hypoxia |
| Catecholamines |
| Anticholinergics |
| Alpha stat versus pH stat strategies |
| Atheroemboli/cerebral hypoperfusion |
| Glycaemic control |
| Carotid endarterectomy |
| Cardiopulmonary bypass |

phenobarbital within 28 days of a stroke was implicated in the development of poor cognitive dysfunction.[64]

## Specific surgical procedures

A significant quantity of data describes and documents POCD after cardiac surgery.[4] Methodological problems such as undersized study populations, unreliable self-reporting, high drop-out rates, and practice characteristics are responsible for the inconsistent evidence of long-term deterioration after anaesthesia and non-cardiac surgery.[1,65]

In a recent paper investigating post-operative hyperthermia, the authors described a relationship between peak post-operative temperature after cardiac surgery and long-term neurocognitive decline. They were unable to demonstrate a direct effect of temperature on POCD. Alternatively, they propose that hyperthermia may uncover previous pathology or an otherwise susceptible patient.[66]

Another study examined cognitive outcome after off-pump versus on-pump coronary artery bypass graft surgery. This randomized controlled trial studied cognitive outcome at 3 and 12 months after surgery. Patients' cognitive functioning was higher after first time off-pump coronary artery bypass graft surgery at 3 months. However, the improvement was not significant after 12 months when compared to on-pump patients.[67]

An investigation of general and regional CBF and cognitive function after coronary surgery looked at 15 coronary surgical patients pre-operatively and at discharge. Pre-operative global CBF was significantly lower in the surgical patients than in age-matched healthy controls, and decreased after surgery. There were no differences in regional CBF. Neuropsychological scores and global or regional CBF were not related. This analysis demonstrated a significant, uniform post-operative drop in CBF unrelated to POCD.[68]

Management of pH during cardiopulmonary bypass affects cognitive outcome. Brain hyperperfusion occurs while maintaining pH-stat protocols. The associated vasodilatation may lead to an increase in cerebrovascular emboli.[4]

One centre performed prospective testing on 112 symptomatic and asymptomatic elective carotid endarterectomy patients to evaluate post-operative neuropsychometric

function. Nearly 80% of these patients had one or more lower test scores in the immediate post-operative period. On the other hand, approximately 60% of these patients scored better on one or more of the tests. These results may be related to the nature of the disease process and the subsequent restoration of CBF. Improved CBF may result in improved test scores. However, cerebral ischaemia and/or cerebrovascular emboli during the surgery may explain decreases in performance.[69] The conflicting results may also be related to the inadequacy of the tests themselves.

Post-operative dysfunction after non-cardiac surgery occurs in the elderly without relationship to hypoxia and hypotension.[27] A large multinational, multicentre investigation, examining POCD in middle-aged subjects undergoing non-cardiac surgery found an unexpected increase in incidence associated with epidural anaesthesia, possibly related to local anaesthetic infusions.[70] They also observed an increased incidence of POCD after major elective, non-cardiac surgery at 1 week and at 3 months, but a return to control levels after 3 months.

### Prevention/therapeutic intervention

There is no evidence that POCD, once diagnosed, can be successfully treated. Therapy is aimed at early recognition, early initiation of safety measures and supportive care, and education of family members.[1] Early recognition may prevent cognitively impaired individuals from prematurely returning to work, operating a motor vehicle, or participating in an activity that may potentially increase the patient's risk of injury. Interventions may be instituted early to prevent late cognitive functional decline.[54]

## SUMMARY

Review of the currently available data reveals that post-operative CNS dysfunction is a common, costly, and potentially devastating complication in the elderly. The syndrome of post-operative cognitive deterioration can be classified into two main categories: delirium, which may last for a few days to a few weeks, and POCD, which can be detected days to weeks after surgery and which may last for an indefinite period of time. Pre-operative medical condition, cognitive status, psychological factors, and age may predispose a patient to delirium. The precipitating factors may include polypharmacy, metabolic disturbances, impaired cerebral oxygen supply and cardiopulmonary bypass. Primary prevention is more effective than intervention after delirium develops. Multicomponent interventions that target well-documented risk factors for neurocognitive complications can help in preventing the development of post-operative delirium.

Several recent studies confirm unequivocally that surgery and perioperative interventions cause POCD. The incidence of cognitive dysfunction is independent of the anaesthetic technique, is higher after cardiac than non-cardiac surgery, and increases with age. Other risk factors implicated in the development of the POCD include low base-line cognitive functioning, microemboli and hypoperfusion during bypass (cardiac surgery), post-operative infection, and diminished left ventricular ejection function. The pathophysiology of POCD is poorly understood and there is no clear strategy for preventing this complication at the present time.

**Practice points**

- CNS dysfunction is a common and serious post-operative complication, resulting in increased morbidity and health care expense
- post-operative delirium is characterized by an acute disruption of attention and cognition. Early recognition and treatment of underlying causes are essential
- cautious use of multiple medications, restraints, or indwelling bladder catheters, as well as adequate pain control, may reduce the incidence of post-operative delirium
- multicomponent interventions tailored to the patient's risk factors lead to the most clinically relevant and potentially effective strategy for reducing the incidence of post-operative delirium
- the incidence of POCD is not affected by the type of anaesthesia
- neuroleptics are the drugs of choice for symptom control in patients with post-operative delirium

**Research agenda**

- neurochemical research identifying the role of cholinergic and gabaminergic systems in the CNS is necessary to elucidate the pathopysiological mechanisms of POCD dysfunction
- the pharmacology and the effect of reduced use of perioperative medications should be examined
- further studies are required to identify the association between perioperative factors and post-operative cognitive impairment
- the economic impact of various strategies designed to reduce the incidence of post-operative CNS dysfunction should be evaluated
- the diagnostic criteria for post-operative CNS dysfunction, as well as study design and execution, should be standardized to improve communication and compare the results obtained by various groups

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