# An Overview on Postoperative Cognitive Dysfunction; Pathophysiology, Risk Factors, Prevention and Treatment

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## ABSTRACT

Postoperative cognitive dysfunction (POCD) is an event that alarms medical personnel owing to its adverse effects, including heightened morbidity and mortality rates, prolonged recovery times, and increased lengths of hospital stay and healthcare expenditure. The populations at high risk are elderly, critical patients, or complicated cases that need prolonged surgery in which the hemodynamics are not stable. Although guidelines have been established to facilitate the early diagnosis of POCD, its prevention is recommended for good patient outcomes. A preoperative assessment is a prerequisite for patient optimization before surgery. Intraoperative, enhanced-recovery protocols have been widely adopted to promote recovery following surgery. Frequent, postoperative assessments of patients' vital signs and cognitive functions are required for early POCD detection. Patients diagnosed with POCD need regular follow-up, and proper patient counselling is paramount.

**Keywords:** Diagnostic and Statistical Manual of Mental Disorders (DSM-5); Enhanced Recovery After Surgery (ERAS); Montreal Cognitive Assessment Scale (MoCA); Neurocognitive disorder, Postoperative cognitive dysfunction (POCD) (Siriraj Med J 2022; 74: 705-713)

## INTRODUCTION

Postoperative cognitive dysfunction (POCD) is a condition that can occur during the postoperative or postanesthetic periods.[1] Previous study reported that upon discharge, 41.4% of patients aged over 60 years developed POCD and, notably, up to 12.7% of those patients were detected with POCD at 3 months.[1] Morbidity of the patients with POCD at 3 months and 1 year after surgery was 25.8% and 10%, respectively.[2] The etiologies can be categorized into (1) patient factors: age > 60 years old, low education level, American Society of Anesthesiologists (ASA) physical status ≥ 3, and comorbidities, for example, cerebrovascular disease, anemia (preoperative hemoglobin ≤ 11 g/dl), preexisting cognitive dysfunction, poor functional capacity, severe illness, postoperative respiratory complications and postoperative infection (2) surgical factors: complex and complicated surgeries or complications during surgery, type of surgery and time of surgery ≥ 4 hours and (3) anesthetic factors: intraoperative use of benzodiazepines and Isoflurane volatile anesthetic agent, intraoperative hypotension and oxygen desaturation during anesthetic induction.[3-7] POCD contributes to declined general health, longer length of hospitalization, longer length

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of postsurgical recovery, and an increase in 1-year post-surgical mortality rate.[8,9] The prevention of POCD requires cooperation between medical specialties throughout the preoperative, perioperative and postoperative periods.[9] The best strategy for combatting POCD is to prevent before it occurs. It is paramount that medical personnel have a thorough understanding about POCD so that they are capable of planning how to prevent POCD and also to enhance patients' postoperative recovery and quality of life.

This review discusses and summarizes the details of POCD by using evidence-based medicine covering POCD definitions, clinical symptoms, diagnosis, pathophysiology, risk factors, prevention, treatment, and prognosis.

## Definition

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has yet to issue a formal definition of POCD. However, the International Society of Postoperative Cognitive Dysfunction (ISPOCD) defines it as a condition that can develop when ≥ 1 abnormality in a discrete area of mental state such as memory, consciousness or attention is discovered, which can occur anytime from immediate postoperative period to 6 months later. Usually, the onset of impaired memory and intellectual disability ranges from weeks to months postoperatively while recovery is within days to weeks.[1,10] POCD can be diagnosed by comparing the differences in the results of baseline preoperative and postoperative psychometric testing.[9]

In 2018, the new consensus among international medical doctors and scientists was published in the British Journal of Anesthesia.[11] The clearer definition of POCD was introduced to facilitate research and education endeavors: (1) delayed neurocognitive recovery (within 30 days postoperatively) and (2) postoperative neurocognitive disorder (between 30 days and 12 months postoperatively). POCD can be differentiated from other diseases, such as delirium or dementia, as outlined in Table 1.[1,12-14]

## Pathophysiology

Although the pathophysiology of POCD is still not elucidated, it is, by evidence-based, associated with neuroinflammation, disruption of blood-brain barrier (BBB) integrity, neurosynaptic damage, mitochondrial dysfunction and oxidative stress.[15-19] Other mechanisms including hyperventilation, hypotension or cerebral microemboli were also proposed to involve POCD.[10] Surgical stimuli induce the expression of the inflammatory mediator, high mobility group box-1 (HMGB1), which interacts with the pattern recognition receptor (PRR) on macrophages causing downstream activation of innate immunity. Also, the S100 calcium-binding protein A12 (S100A12) level increases after the operation and thus resulting in intracephalic signal transduction and inflammation.[20] Upon surgical stimulation, intracellular RNA released from the damaged tissue is detected by the immune cells therefore inflammatory process is initiated. Proinflammatory cytokines from macrophages including tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6)

**TABLE 1.** Differential diagnoses of postoperative cognitive dysfunction.

| Parameters | Delirium | POCD | Dementia |
|---|---|---|---|
| Onset | Within 3 days | Within a few months | Months to years |
| Duration | Days to weeks | Weeks to months | Months till death |
| Attention | Decreased | Decreased | Decreased |
| Consciousness | Altered | Normal | Normal |
| Symptoms | Fluctuation within the day; alteration of consciousness; can be hypoactive or hyperactive | Memory decline or cognitive decline | Memory decline; executive function decline; changes in behavior and abilities Increased risk of functional decline |
| Activities of daily living | Increased risk of functional decline | No risk of functional decline | |

**Abbreviation:** POCD, Postoperative cognitive dysfunction

and IL-1β are upregulated in the blood circulation.[21-24] These cytokines can breach through the BBB via vagus nerve or paraventricular areas of the BBB leading to activation of cerebrovascular endothelial cells which will produce secondary messenger to secrete more proinflammatory cytokines.[25] An increase in brain-specific inflammatory markers such as serum S100 calcium-binding protein B (S100B) and neuron-specific enolase (NSE) after surgery also supports that brain inflammation could lead to POCD.[10,12,26,27] Albeit playing smaller role than surgery, anesthesia is involved in the pathophysiology of POCD. Past study demonstrated that isoflurane caused apoptosis in human neuronal cell lines and mouse brain potentially through the accumulation of amyloid β peptide. Randomized controlled studies also reported higher incidence of POCD and level of proinflammatory markers in groups anesthetized under volatile anesthesia implying that volatile might involve in POCD mechanism.[28,29]

## Risk factors

The risk factors of POCD can be divided into patient, surgical, and anesthetic factors.

### 1. Patient factors

#### *Old age*[1,30]

Age is a major factor of POCD especially in the elderly aged > 60 years old. Studies have shown that older age has various effects on the brain, for instance, decreased brain volume, decreased BBB density, decreased neurogenesis, reduced cognitive reserve, increased brain inflammation, and increased brain-vessel degeneration. The medial temporal lobe atrophy as well as the white matter hyperintensity as seen by magnetic resonance imaging (MRI) in the elderly were well correlated with clinical cognitive decline.[31]

#### *Low level of education*[9,32]

Many higher-educated people are prone to engage in greater levels of complex thinking, leading to heightened usage of the brain neural network. This extra utilization may result in the prevention of brain decay due to a corresponding increase in the cognitive reserve and improvements to the efficiency of neuronal replacement. Education levels may therefore be employed to indicate cognitive reserves as each additional year of study has been demonstrated to result in around a 10% reduction in the incidence of POCD.

#### *Preexisting cerebrovascular disease*[1,33]

The patients with preexisting cerebral infarction were reported to be 18.2% at risk of POCD compare with 4.9% in the control group. Therefore, cerebrovascular disease was considered the potential non-modifiable risk factors of POCD.

#### *Preexisting Systemic Lupus Erythematosus (SLE)*[34]

A correlation between cognitive impairment and underlying SLE had been reported previously. However, the incidence of cognitive dysfunction was not dependent on SLE duration, activity or evidence of preexisting neuropsychiatric involvement.

#### *Presence of insulin resistance*[35]

Preexisting insulin resistance was independently associated with the incidence of POCD. It has been shown that insulin resistance reflects metabolic disease which is related to neuropathological process regarding aging and cognitive function. A reduction in insulin receptor on the BBB according to insulin resistance results in decreased insulin transport into the brain causing POCD and Alzheimer's disease.

#### *Genetics*[36]

The Human Apolipoprotein E (ApoE) gene is located on chromosome 19. E4 allele of the APOE gene is evidenced to account for Alzheimer's disease, cognitive dysfunction and atherosclerosis. To date there are no studies confirming the effect of sex difference on POCD. However, men who are the carriers of *APOE4* alleles were reported to have higher risk of POCD than women with *APOE4*.

#### *Alcoholism*[37]

The elderly with history of alcohol abuse could pose a higher risk for POCD especially in the domains related to visuospatial and executive functions.

### 2. Surgical factors[1,6,38]

Complicated and prolonged surgeries > 4 hours, complications during the peri- or postoperative periods, and procedures needing multiple surgeries are all risk factors which could result in POCD. Cardiac surgery with the application of cardiopulmonary bypass pump (CPB) is a predisposing factor to POCD. Prolonged arterial cross clamping time in cardiac surgery plays an important role in POCD according to poor cerebral hypoperfusion.

### 3. Anesthetic factors

Factors such as a prolonged anesthetic period causing disequilibrium of fluids and electrolytes, acute blood loss, oxygen desaturation, and peri- or postoperative

anesthetic complications account for POCD. Studies have also demonstrated that various anesthetic agents can affect POCD; for example, midazolam may lead to memory impairment than propofol or remifentanil.[39] Medications affecting the cholinergic system can increase the POCD risk. On the other hand, previous studies have found that the perioperative usage of dexmedetomidine may result in a lower POCD risk by reducing the levels of IL-6 and S100B.[40-42] Intraoperative use of volatile anesthesia especially isoflurane and sevoflurane had been reported to influence higher risk of POCD when compared with intravenous propofol.[29]

**Assessment**

Assessment of POCD is not straightforward. Variations among assessors, different POCD definitions or diagnostic tools used, the timing of evaluation, emotion, degree of pain, medication profile, and environmental setting are common factors contributing to different assessment results. 43 Many studies have assessed POCD by observing changes in patients' neuropsychological signs. The Mini-Mental State Examination (MMSE) assesses orientation (time and place), memory (immediate and short-term), calculation, language (naming, repetition, listening, reading comprehension, and writing), visuospatial awareness, concentration, and attention while the Montreal Cognitive Assessment tool (MoCA) focuses on visuospatial and executive function (alternate trail-making test, copy the cube, and clock drawing), language ability, attention and calculation, delayed recall, and abstract thinking.[44] These tools are the most common clinical screening tests for POCD. However, they are not suitable for cognitive follow-up evaluation.[45] Other test batteries that are designed to evaluate cognitive status include various neuropsychological tests (NPT) which determine specified cognitive domains such as Digit span test, Trail Making Test, Groove Pegboard Test, etc.

Several screening tests for POCD with comparable sensitivity and specificity at differentiating mild cognitive impairment (MCI) from dementia are Addenbrooke's Cognitive Exam (ACE-III), Quick Mild Cognitive Impairment Screening (Qmci), Saint Louis University Mental Status (SLUMS), Mini-cog, Rowland Universal Dementia Assessment Scale (RUDAS) and Abbreviate Mental Test (AMT) (Table 2).[3,46-55]

The new consensus for POCD diagnosis recommends applying the diagnostic criteria for a neurocognitive disorder from DSM-5.[11] Neurocognitive assessment relies on a subjective test (based on the responses of the patient or close relatives), an objective test (standardized NPT) as well as an assessment of the patient's ability to perform the activities of daily living (ADL). This new approach provides a more accurate POCD diagnosis compared with the previous recommendation where only an objective test was considered. Recent publication reported the use of the Thai version of RUDAS to screen for POCD at postoperative day 5-9 through real-time video stream over mobile phone internet connection. Even though the test consumed longer time, almost 30 minutes per each patient, than usual face-to-face evaluation, this method encouraged the use of telemedicine in geriatric patients especially who were not well complied with clinical follow-up.[56]

**Prevention**

There are currently 2 main strategies for POCD prevention:[1,9]

1. Patient factors

Comprehensive geriatric assessment and preoperative assessment to stratify and optimize risks before proceeding to operations are recommended during the preoperative period.

2. Surgical and anesthetic factors

The Enhanced Recovery after Surgery (ERAS) protocol has been reported to improve postoperative recovery and to reduce rate of postoperative hospitalization and morbidity. The general principles of ERAS involve limited fluid intake, preference of laparoscopic surgery, appropriate anesthetic agent administration, adequate pain medications, early feeding, and early mobilization. The ERAS protocol covers the preoperative, intraoperative, and postoperative states, as outlined below.[3,42,57-64]

a. Preoperative state

- Controlling patients' underlying diseases, optimizing the risk factors, and providing preoperative counselling and prehabilitation.
- Recognizing the risks contributing to worsening outcomes such as major surgery, immobilization, and prolonged hospitalization.
- Encouraging social and moderate physical activities to improve cognitive function.
- Implementation of prehabilitation program at 6-8 weeks preoperatively which involves processes designed to improve the preoperative functional status of the patients by:

- Adequate and appropriate exercise including breathing exercises or resistance training.
- Supplementary dietary intake to improve malnutrition.
- Giving education and advice especially to elderly patients.
- Treatment of comorbidities e.g., atrial fibrillation which could relate to POCD.

b. Immediate preoperative state

**TABLE 2.** Neuropsychological tests for the assessment of postoperative cognitive dysfunction.

| Parameters | MMSE | MoCA | ACE-III | Qmci |
|---|---|---|---|---|
| Total score | 30 | 30 | 100 | 100 |
| Cut off Score for MCI | < 24 | < 26 | < 82–88 | < 62 |
| Average time to complete | 10 min | 15 min | 16 min | 5 min |
| Sensitivity (%) | 79.8% | 90 | 84–93 | 90 |
| Specificity (%) | 81.3% | 87 | 100 | 87 |
| Advantages | - Less time consuming<br>- Easy to use | - High sensitivity<br>- Can identify MCI and cognitive dysfunction in Alzheimer's and Parkinson's diseases | - Can differentiate MCI from early dementia<br>- Provides scores for different cognitive domains with correlation to NPT | - Less time consuming<br>- High sensitivity<br>- Useful test to detect MCI and dementia |
| Disadvantages | - Low sensitivity and not suitable to screen for MCI | - Designed for MCI rather than dementia | - Cannot differentiate dementia subtypes | - Maybe inaccurate when used in certain subgroups e.g., post stroke patients |
| **Parameters** | **SLUMS** | **Mini-cog** | **RUDAS** | **AMT** |
| Total score | 30 | 5 | 100 | 10 |
| Cut off Score for MCI | < 27 | < 4 | < 25 | < 9 |
| Average time to complete | 7 min | 3 min | 10 min | 3-5 min |
| Sensitivity (%) | 98 | 85.7 | 76.2 | 91.5 |
| Specificity (%) | 98 | 79.4 | 75 | 82.4 |
| Advantages | - High sensitivity and specificity | - Less time consuming<br>- Can be used in primary care setting | - Can differentiate MCI from dementia and normal cognition | - Less time consuming<br>- Can be used as first line screening in acute setting |
| Disadvantages | - May be affected in patients with ≤ 6 years of education and non-white ethnicity<br>- New tool, not widely used | - Cannot be used in patients with visual impairment or difficulty to hold the pen/pencil | - May be affected in patients with ≤ 6 years of education | - Normal AMT may not exclude MCI therefore it cannot be used as a rule-out test |

**Abbreviations:** ACE-III, Addenbrooke's Cognitive Examination III; AMT, Abbreviated Mental Test; MCI, Mild cognitive impairment; MOCA, The Montreal Cognitive Assessment tool; NPT, Neuropsychological test; Qmci, The Quick Mild Cognitive Impairment; RUDAS, Rowland Universal Dementia Assessment Scale; SLUMPS, Saint Louis University Mental Status

- Reducing the fasting time is beneficial since prolonged starvation stimulates stress and anxiety. Maintaining patients in an euvolemic state is recommended.
- Oral carbohydrate preloading is suggested to stimulate the neuroendocrine response to stress.
- Thromboprophylaxis is recommended for all patients either by intermittent pneumatic compression devices, compression stockings or encouraging early mobilization. The risk of bleeding needs to be evaluated before anticoagulant administration.
- Antibiotic prophylaxis should be given 60 minutes before skin incisions.

c. Intraoperative state
- Preanesthetic sedatives and anxiolytics are not routinely administered.
  Short-acting opioids are recommended.
- Sevoflurane, desflurane, intravenous thiopental, and propofol infusions are recommended to reduce risks for POCD.
- Monitoring of anesthetic depth and cerebral oxygenation during surgery.
- Anesthetic agents with small molecular structures, isoflurane and desflurane, could create amyloid β-oligomerization which involve POCD. A large molecular agent like propofol, if administered with smaller molecular agents, could also result in amyloid β-oligomerization production.
- Avoidance of prolonged nitric oxide usage.
- Laparoscopic surgeries are recommended, given the decreased levels of bowel distention and lower incidences of postoperative nausea and vomiting.
- Low tidal volume ventilation (5–7 mL/kg) and real-time hemodynamic monitoring via an esophageal doppler are recommended.
- A high level of oxygen can increase blood flow to the anastomotic site, lessen the risk of delayed wound healing, and lower the incidences of postoperative nausea and vomiting.
- Epidural analgesia is recommended for open surgical procedures.
- Avoidance of drains or nasogastric tubes as they hinder early mobilization.
- Administration of a local anesthetic around the wound helps reduce pain and urinary retention.
- Fluids overloading should be avoided according to poor intestinal anastomosis, prolonged bowel ileus, and systemic edema.
- Balanced salt solutions are recommended because saline overload leads to metabolic acidosis and hyperchloremia.
- Hypotension from central neuraxial blockade and general anesthesia should be resolved by vasoconstrictors rather than fluid resuscitation.
- Keeping normothermia as hypothermia may result in increased metabolic demand, altered drug metabolism, and impaired immunity and coagulation.

d. Postoperative state
- Opioids should be used rationally. Paracetamol and NSAIDs are encouraged for pain control.
- Epidural anesthesia should be given continuously.
- Oral fluids should be given 2 hours after surgery, and intravenous fluids should be administered cautiously to reduce anastomotic dehiscence and infection.
- Maintenance of blood glucose between 180–200 mg/dl.
- Early mobilization is encouraged. Nasogastric tubes, abdominal drains, opioids, and epidural catheters should therefore not be used from the second day onwards unless necessary.
- The patients should be settled in a calm environment and properly advised before their discharge.

**Treatment**

POCD treatment is usually based on 2 major principles:[1,10]

1. POCD can be mimicked by POCD-like conditions (e.g., myocardial infarction, septic shock, medication or toxic-substance abuse, electrolyte imbalance, a hypo- or hyperglycemic state, endocrine or liver dysfunction, and neurological deficits). Hypoglycemia can be treated with an intravenous glucose solution. Thiamine is the proper treatment if Wernicke encephalopathy is suspected.

2. The general principles of surgical patient care can be adapted for POCD patients. Some essential methods include the provision of adequate ventilation and oxygenation, hemodynamic support, or adequate postoperative pain control. Pain control is critical and consequently requires sufficient patient counselling. Monitoring of vital signs, electrolytes, and the cardiovascular and pulmonary functions is suggested for enhanced recovery. When POCD is resolved, patients may recall fragments of memories during their POCD episodes which may create stress. It is therefore necessary that medical personnel give appropriate advice and counselling.

## CONCLUSION

POCD is a condition that warrants early detection and treatment. The best measure to is to prevent it before the resulting cognitive dysfunction develops. Proper pre-, intra- and postoperative patient care should be considered to reduce the risks of POCD. Preoperative assessments are necessary to identify patients at risk and to optimize patients' condition for particular surgical procedures. According to the ERAS protocol, hemodynamic stabilization, adequate fluid administration, avoidance of excessive anesthetic agents, and appropriate management of hypotension or hypothermia are measures for POCD risk reduction. Adequate postoperative pain control, breathing exercise, and early mobilization are essential to prevent POCD and improve patients' outcomes. Additionally, appropriate environmental settings and frequent postoperative POCD assessments are encouraged. Once POCD develops, patients should be treated promptly, scheduled for regular follow-ups, and given proper counselling.

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