**Postoperative Cognitive Dysfunction**

*Can we prevent it?*

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**Types of postoperative cognitive dysfunction**

- **Emergence delirium** - Immediate postop confusion, restlessness. Affects all ages, but prominent in elderly, emergency surgery
- **Interval delirium** - POD 2-7; fluctuating impairment of cognition, memory, emotional lability
- **Characteristic postoperative cognitive dysfunction** - Lasts 3 months to years

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**Postoperative Delirium**

- Brief, fluctuating
- Impaired cognition
- Fluctuating levels of consciousness
- Altered psychomotor activity (pulling out IVs, etc.)
- Emotional lability (crying, anger)

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**Synonyms of POCD**

- Postoperative psychosis
- Mild neurocognitive disorder
- Acute confusional state
- Mental dysfunction
- Acute brain syndrome

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**History of POCD**

- Postoperative psychosis
  - Historical term. Various forms of cognitive disorder recognized since 1819
- **Bedford** - Retrospective review of > 4,200 elderly patients
  - (Bedford PD Adverse cerebral effects of anaesthesia on old people. *Lancet* 1955;2:259-63.)
History of POCD


Sequelae of Postoperative Cognitive Dysfunction

- Increased morbidity
- Prolonged hospitalization
- Necessitates long-term care
- Loss of functional ability
- Cost!

Sequelae of Postoperative Cognitive Dysfunction

- Patients with POCD at hospital discharge were more likely to die in the first 3 months after surgery (P = 0.02).
- Patients who had POCD at both hospital discharge and 3 months after surgery were more likely to die in the first year after surgery (P = 0.02).

Incidence of Cognitive Dysfunction

- Age is a prominent risk factor.
- Affects 10% overall elderly surgical patients
- Can occur in any age group; delirium (immediate post-op) more common in young.
- Incidence highest in days-weeks postop. (50-80%)
- Declines to 5-60% at 3 months
- After six months may also be due to depression or awareness of age related changes. Dijkstra JB et al Br J Anaesth 1999;82(6))

Sequelae

- 720 patients enrolled in multicenter studies of POCD 1995-2000
- Cognitive function assessed before, 1 week and 30 days after non-cardiac surgery
- patients with POCD at 3 months showed higher rates of mortality and lower rates of return to function
- Steinmetz, Jacob; Christensen, Karl Bang; Lund, Thomas; Lohse, Nicolai; Rasmussen, Lars S. the ISPOCD Group Anesthesiology 2009;110(3):548-555.
Risk Factors

- The independent risk factors for POCD at 3 months after surgery were:
  - increasing age
  - lower educational level
  - history of previous cerebral vascular accident with no residual impairment
  - POCD at hospital discharge.


Age as a major risk factor

- Advanced age is a consistent, independent predictor
  - Decreased lean body mass
  - Decrease total body water
  - Increase in body fat
  - Thus, increase in dose-response variability.

Theory on Aging

Older patients are at a functional cliff, and if they have a major stress, such as loss of cognitive function after surgery, some of them will functionally decline. This decline is associated with increased mortality, loss of independence and further declines in health and independence.

Incidence of Cognitive Dysfunction

- 25-50% following ortho procedures
- 30% following cardiac surgery post-op, 7% after 5 days.
- Low incidence with minimally-invasive procedures (~1-3% with Cataract ext.)
- Meta-analysis of 80 studies showed incidence as high as 75%

Characteristics of POCD

- Temporal association with surgery
- Fluctuating symptoms
- Impairment of
  - Memory
  - Learning
  - Sensory and language processing
  - Concentration
  - Social integration
  - Sleep-wake cycle
Characteristics of POCD

- Hallucinations
- Delusions
- Motor dysfunction - tremor
- Lability of mood, anger, depression
- Diagnosis is difficult!

Pathophysiology Hypotheses

1. Metabolic encephalopathy
2. Neurological injury

Metabolic encephalopathy

- Hypoxia
  - Ach synthesis sensitive to hypoxia (would alter memory, alertness, motor function)
- Hypoglycemia
- Hypothermia
- Surgical trauma (factors may alter amino acids and neurotransmitters)
  - Decreases thyroid hormone
  - Increases cortisol
  - Releases cytokines

Neurological Injury

- Cerebral infarction
- Fat or air embolism
- Thrombus

Standardized Understanding is Elusive

- Mahanna et al. applied different criteria to same sample
- Found rates of POCD to vary 20% - 70%

**International Study of POCD**

- 1218 patients over 60 yoa
- Tested pre-op, 1 week, and 3 months after major non-cardiac surgery

<table>
<thead>
<tr>
<th></th>
<th>1 week</th>
<th>3 months</th>
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<tbody>
<tr>
<td>Surgery</td>
<td>25.8%</td>
<td>9.9%</td>
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<tr>
<td>Control</td>
<td>3.4</td>
<td>2.8</td>
</tr>
<tr>
<td><em>p</em> value</td>
<td>0.0001</td>
<td>0.0037</td>
</tr>
</tbody>
</table>


**International Study of POCD**

- Risk factors:
  - Age
  - Duration of anesthesia
  - Lower education
  - Second operation
  - Postoperative infections
  - Respiratory complications


**International Study of POCD; More questions than answers**

- If known insults are not corollaries, what is etiology?
- Is it more common in some operations than others?
- Will it improve over additional postoperative time?
- Does it occur in younger patients or after short procedures?

**International Study of POCD**

- No relation of POCD to:
  - ASA status, lung, heart, PVD, HTN, head inj., stroke, a-fib, delirium, cancer, anesthetic technique, smoking, ETOH, EBL, periop fluids, type of operation, gender, long-term ICU stay, hypoxemia, hypotension

**Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness.**

- Retrospective cohort study of 575 participants tested annually at the Washington University Alzheimer’s Disease Research Center
- Three cohorts: surgical, no surgery/no illness, no surgery/illness
- Retrospective, matched-control group. Long-term annual testing.
- Attempted to overcome methodological/statistical deficiencies of previous studies.
Long-term cognitive decline in older subjects was not attributable to noncardiac surgery or major illness.

- Failed to find correlation between surgery and long-term decline.
- Suggests that accounting for pre-surgery cognitive trajectory removes association between surgery/illness and POCD.
- Unclear how to account for inevitable crossover
- Unclear how many were lost to follow-up to arrive at the final sample
- If incidence not different on annual testing, isn’t it still important in shorter-term?

Is there a connection we are missing?

- Within hours of exposure to NMDA blocker, developing rat brains show:
  - Cellular injury
  - Reduced ability to regenerate new cells
  - Impaired cell-to-cell communication
  - Auditory deficits
  - (Rat model at developmental stage equivalent to 0-2 year-old human brain)

Is there a connection we are missing?

- “…thyroid hormones negatively regulate expression of the amyloid-beta protein precursor (AbetaPP), which plays a key role in the development of AD.”


Is there a connection we are missing?

- Hypoxia, hypocapnia, and anesthetics trigger Alzheimer’s Disease.
- Could this be a similar molecular trigger for POCD?

Is it all about beta-amyloid protein?

Possible Etiologic Factors

- Preoperative
- Intraoperative
- Postoperative
**Preoperative**

- Psychiatric disorder
  - Psychosis
  - Dementia
  - Depression
  - Personality disorder


**Preoperative- theories**

- Poor medical status
  - Parkinson’s disease
  - Cerebrovascular disease
  - Hypoalbuminemia
  - Previous surgery
  - Sensory impairment

**Preoperative**

- Nutritional deficiency
  - Thiamine, etc.
- Drug influences
  - Alcohol abuse
  - Benzodiazepine abuse or withdrawal
  - Anticholinergic pre-med

**Intraoperative**

- Type of surgery (esp ortho, cardiac)
- Duration of surgery
- Hypoglycemia
- Electrolyte disturbance (esp. sodium)
- Temperature disturbance (hypo or hyperthermia have been implicated)
- Drugs: anticholinergics, inhalational anesthetics, polypharmacy
  - Meperidine, long-acting BNZ, BNZ withdrawal

**Intraoperative**

- Hyperglycemia
  - hyperglycemic = POCD incidence of 40% vs 29% in the normoglycemic group ($P = 0.01$).
  - Hyperglycemia was the strongest factor associated with POCD


**Intraoperative**

- Hypoxemia
- CBF
  - CBF found to be decreased after bypass.
- Hypotension
  - Although these are good theoretical bases, no-one has been able to show a direct correlation to POCD.
- Anemia (hemorrhage). This has been correlated to POCD
Cardiopulmonary Bypass
- Temporary depression of CBF
- Microembolization of vessels
  - (arterial filtration reduces incidence)
- Fall below limits of autoregulation
- Prolonged focal changes on EEG correlate with POCD; while increasing perfusion pressure reduced it.

Is it a lingering effect of the anesthetic drugs?
- The down-regulation of nerve growth factor (NGF) mRNA and protein expression in the cortex and thalamus after the propofol treatment, as well as a decrease of phosphorylated Akt were observed. The extrinsic apoptotic pathway was induced by over-expression of tumor necrosis factor (TNF) which led to the activation of caspase-3 in both examined structures. Neurodegeneration was confirmed by Fluoro-Jade B staining. Our findings provide direct experimental evidence that the anesthetic dose (25mg/kg) of propofol induces complex changes that are accompanied by cell death in the cortex and thalamus of the developing rat brain.

Does anesthetic type make a difference?
- The use of volatile anesthetics that are rapidly eliminated with minimal metabolic breakdown may reduce postoperative cognitive dysfunction and postoperative delirium by facilitating a faster recovery

General vs. Regional
- Rasmussen, Moller et. al. as part of International Study of POCD repeated earlier study in 2003. Included researchers in US, UK, Europe, and Netherlands.
  - Looked at 438 elderly (>60) patients.

ISPOCD follow-up
- Findings:
  - Mostly ortho procedures
  - POCD occurred in 10-20% of all patients at 1 week and 3 months.
  - No difference based on anesthesia type.
- Limitations:
  - High refusal/drop-out rate
  - Regional group received propofol sedation
  - GA group- didn’t specify technique

Does anesthetic type make a difference?
- No difference in POCD according to type of anesthetic.
  - Overall 5% long-term POCD.
Comparison of rates of POCD in patients having CEA with regional are similar to those of patients having CEA under general, in comparison to controls.


Does anesthetic type make a difference?

Comparison of propofol and sevo.
Very weak differences noted.
Sevo caused faster initial emergence and less early delirium.
No difference in POCD.


100 patients ASA status I-III; age 65-83, undergoing elective abdominal or urologic surgery > 2 hours

<table>
<thead>
<tr>
<th>Percentage with POCD at X interval</th>
<th>1 Day</th>
<th>6 Days</th>
<th>30 Days</th>
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<tbody>
<tr>
<td>Propofol</td>
<td>50%</td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td>Xenon</td>
<td>44%</td>
<td>12%</td>
<td>6%</td>
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Other factors are likely to contribute to the pathogenesis of POCD:
- Inflammatory processes triggered by the surgical procedure.
- Animal studies demonstrate a correlation between the inflammatory response in the hippocampus and the development of POCD in rodents.


Postoperative Factors
- Pain
- Hypoxia
- Hypocarbia
- Sepsis
- Sensory deprivation or overload (ICU environment)
- Electrolyte or metabolic derangement
Prevention

- Preoperative assessment
  - Detailed history of drugs
  - Medical problem evaluation
  - Detection of sensory or perceptual deficits
  - Mental preparation prior to surgery
  - Neuropsychologic testing
  - Thrombus prophylaxis
  - Optimize medical condition
  - Tailor anesthetic plan...

- Intraoperative precautions
  - Adequate oxygenation and perfusion
  - Correct the electrolyte imbalance
  - Adjust drug dose (BIS, etc. to minimize doses)
  - Minimize the variety of drugs
  - Avoid atropine, diazepam, scopolamine

- Postoperative care
  - Frequent orientation
  - Early mobilization
  - Environmental support (noise reduction, glasses/hearing aids used)
  - Treat pain
  - Identify risk-associated drugs
  - Reassure patient and family

- Geriatric-Anesthesiologic Intervention Program
  - Preop and postop assessment
  - Early surgery
  - Thrombus prophylaxis
  - Tight BP control
  - Oxygen therapy
    - Parikh SS & Chung F. Postoperative delirium in the elderly Anesthesia & Analgesia, 1995;80:1223-1232

Treatment of POCD

- Recognize and prevent causes
  - Rule out organic cause
    - Hypo/hyperglycemia
    - Hypoxemia
    - Electrolytes
    - Anemia
    - Sepsis
    - Dehydration
    - Malnutrition

- Remove contributing factors
  - Encourage patterned rest
  - Opioids/BNZ/DA antagonists
  - Pain
  - Polypharmacy
  - Control with drugs only if necessary
    - Narcoleptics (buterphenones/chlorpromazine) better than BNZ, unless BNZ withdrawal
    - Phsyostigmine
Summary

- POCD is variable in definition, but affects a significant number of patients
- May be associated with increased cost and functional decline
- Awareness of risk factors and measures to avoid those that are preventable may benefit the patient.