Postoperative Cognitive Dysfunction: Can we prevent it?

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Postoperative Cognitive Dysfunction

- Impairment of Memory
- Impairment of Attention
- Delayed functional recovery (psychomotor function)


U.S. Population by Age: 1900-2050

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

Spectrum of cognitive disorders

Differential Diagnosis

Postoperative Delirium

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

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!

Standardized Understanding is Elusive

Memory ➔ Cognitive Function ➔ Concentration ➔ Attention ➔ Function/ADLs

Standardized Understanding is Elusive

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

Synonyms of POCD

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

- Postoperative psychosis
  - Historical term. Various forms of cognitive disorder recognized since 1819
- Bedford - retrospective review of > 1,000 elderly patients. 10% POCD
  - (Bedford PD Adverse cerebral effects of anaesthesia on old people. *Lancet* 1955;2:259-63.)


Sequelae of Postoperative Cognitive Dysfunction

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

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).


### Independent Multivariate Predictors of One-Year Mortality

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Relative Risk</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Comorbidity</td>
<td>16.86</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Volatile vs. TIVA</td>
<td>2.97</td>
<td>0.022</td>
</tr>
<tr>
<td>Intraoperative Beta Blocker</td>
<td>1.67</td>
<td>0.004</td>
</tr>
<tr>
<td>Chronic Beta Blocker</td>
<td>1.53</td>
<td>0.019</td>
</tr>
<tr>
<td>Cumulative Deep Anesthesia Time (BIS &lt; 45, per hour)</td>
<td>1.34</td>
<td>0.007</td>
</tr>
<tr>
<td>Systolic Blood Pressure &lt; 80 mmHg (per minute)</td>
<td>1.04</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Beta blocker use was not protective Multivariate c-statistic = 0.806 (p = 0.001)

- intraoperative beta-blockers – hemodynamic stability
- chronic beta-blockers – higher comorbidity

Weldon et al. Anesthesiology 2002; 97: A-1097
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.

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. Dightra JR et al Br J Anaesth 1999;82(6))

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.


Predictors of POCD: 3 Months After Surgery

<table>
<thead>
<tr>
<th>Risk Factors for POCD</th>
<th>Univariate P value</th>
<th>Multivariate Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of Education</td>
<td>&lt; 0.001</td>
<td>0.86 (p=0.028)</td>
</tr>
<tr>
<td>Age</td>
<td>0.001</td>
<td>2.51 (p=0.057)</td>
</tr>
<tr>
<td>History of Stroke</td>
<td>0.003</td>
<td>NS</td>
</tr>
<tr>
<td>ASA Physical Status</td>
<td>0.009</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline Comorbidity</td>
<td>0.021</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA Status</td>
<td>0.028</td>
<td>NS</td>
</tr>
<tr>
<td>History of MI</td>
<td>0.046</td>
<td>NS</td>
</tr>
<tr>
<td>Surgery Type</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Gender</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline MMSE</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Anesthesia Time</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Multivariate c-statistic = 0.671 (p = 0.003)

Monk et al. Anesthesiology 2001; 95: A-50

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.
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%

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

Metabolic Encephalopathy

- Research recently is focusing on cytokines and other humoral markers of the stress response.
- Would suggest shorter and less-invasive surgery are beneficial

Neurological Injury

- Cerebral infarction
- Fat or air embolism
- Thrombus

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>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>25.8%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Control</td>
<td>3.4</td>
<td>2.8</td>
</tr>
<tr>
<td>p 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

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.
Is there a connection we are missing?

- "...thyroid hormones negatively regulate expression of the amyloid protein precursor (APP), 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

Pre-existing cognitive dysfunction

- Preexisting cognitive dysfunction was identified in approximately one-third of the patients prior to surgery.
- Preexisting cognitive dysfunction was a predictor of cognitive dysfunction 3 months and 1 yr after surgery.
- No evidence of anesthesia or surgery as direct causes.


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 BENZ, BENZ withdrawal

Hyperglycemia

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


Intraoperative

- CBF- found to be decreased after bypass
- Cerebral oximetry?
- Hypotension
  - Although these are good theoretical bases, nobody has been able to show a direct correlation 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.
Cardiopulmonary Bypass

- In the end, difference between cardiac and non-cardiac may likely be only related to differences in diagnostic criteria used.

Cardiac Surgery as a Protective event

- meta-analysis- cardiac surgery results in postoperative cognitive improvement
  - Reducing myocardial ischemia improves cognitive dysfunction?


Cardiac Surgery as a Protective event

- Transient myocardial ischemia caused cognitive dysfunction evidenced by impaired long term potentiation and increased expression of inflammatory biomarkers.
  - Effect attenuated by preconditioning with sevoflurane.
  - LTP impairment did not occur after a sham procedure.


Is it a lingering effect of the anesthetic drugs?

- Down-regulation of nerve growth factor (NGF) and protein expression in the cortex and thalamus after propofol.
- Extrinsic apoptotic pathway induced by over-expression of TNF which led to the activation of caspase-3.

- Neurodegeneration was confirmed by Fluoro-Jade B staining.
- Concluded that anesthetic dose (25 mg/kg) of propofol induces complex changes that are accompanied by cell death in the cortex and thalamus of the developing rat brain.


Is it a lingering effect of the anesthetic drugs?

- Isoflurane impaired spatial learning capacity, independent of tau phosphorylation or beta amyloid protein.

**Related to NMDA activation?**

- 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)

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**Related to NMDA activation?**

- Spacial learning found to be impaired in rats after 4-hr isoflurane exposure.
- NMDA activation found present, and NMDA inhibitor helped reduce POCD.

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**Could some drugs be protective?**

- Occurrence of POCD in rats after isoflurane exposure was demonstrated to be prevented with co-administration of lidocaine.

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**Does minimizing anesthetic help?**

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.

- Deep (BIS <45) Anesthesia Time: Significant Independent Predictor Of Mortality
  - Increased Relative Risk: 19.7% / Hr

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**Does minimizing anesthetic help?**

- 220 patients, mean 70 years THA or TKA
- 90% under spinal
- Opioid-sparing in all cases
- 1.5 days in hospital
- No incidence of post-op delirium

**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?**

- 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?**

- Extracorporeal Shockwave Lithotripsy under GA or spinal without sedation.
- POCD was almost three times as high after spinal anesthesia.
  - At 1 week, POCD was 11.9% after spinal vs. 4.1% after GA; at 3 months the incidence was 19.6% and 6.8% for spinal and GA, respectively

**Does anesthetic type make a difference?**

- Recent studies show slightly better performance from volatiles vs. propofol
Does anesthetic type make a difference?

- 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>
</tr>
</thead>
<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>
</tr>
</tbody>
</table>


No difference in POCD according to type of anesthetic.

- Overall 5% long-term POCD.


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.


So where are we now?

- There is currently minimal clinical evidence linking surgery or anesthetics to incident dementia. Rigorous clinical research is needed to resolve the controversy whether anesthetics or surgery is likely to cause persistent neurological decline or to precipitate dementia.


Prevention

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

Preventive Measures

- **Intraoperative precautions**
  - Minimally invasive surgery
  - Adjust drug dose (BIS to minimize doses)
  - Minimize the variety of drugs
  - Avoid atropine, diazepam, scopolamine
  - Minocycline hypothesized to be possibly helpful.

- **Cerebral oxygenation may be more important than peripheral saturation.**

- **Postoperative care**
  - Frequent orientation
  - Early mobilization
  - Environmental support (noise reduction, glasses/hearing aids used, promote sleep pattern)
  - Multi-modal non-opioid pain treatment
  - 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
Treatment of POCD

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

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.