Postoperative Cognitive Disorders: Does Anesthesia Harm the Brain?

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Research Support

- Anesthesia Patient Safety Foundation (APSF)
- I Heermann Anesthesia Foundation
- National Institute on Aging
- Alzheimer’s Association
Objectives

- Historical evidence for Postoperative Cognitive Disorders
- Definitions of Postoperative Cognitive Disorders
- Recent Delirium Research
  - Early development of a delirium screening battery
  - Does “light anesthesia” prevent delirium
- Current evidence for POCD following
  - Coronary Artery Bypass Surgery
  - Non-Cardiac Surgery
- Long-Term Effects of POCD
- Is Inhalation Anesthesia Detrimental in Elderly Patients?
Adverse Cerebral Effects of Anesthesia on Old People

- Review of records of 1193 patients:
  - Age 50 years or older
  - Operation under GA

- Mental deterioration in 120 (10%) patients

- Conclusions
  - Cognitive decline related to anesthetic agents and hypotension
  - “Operations on elderly people should be confined to unequivocally necessary cases”

Bedford. The Lancet 1955; 2:259
Postoperative Cognitive Disorders

- **Delirium**
  - 10-15% of elderly patients after GA
  - Up to 60% of patients with hip fracture

- **Mild neurocognitive disorder – POCD**
  - 10-50% after cardiac and noncardiac surgery

- **Dementia (rare)**
  - Multiple cognitive deficits
  - Impairment in occupational and social function
Time Frame of Delirium and POCD

- Emergence Delirium
- Post-Op Delirium
- Post-Op Cognitive Dysfunction

Pre-Op | OR | PACU | 24-72 hours Post-Op | Weeks-Months
Delirium: Definition

Disturbance of Consciousness
- Reduced clarity of awareness of the environment
- Reduced ability to focus, sustain, or shift attention
- “somnolent”, “lethargic”, “inattentive”

Time Course
- The disturbance develops over a short period of time
  - Usually hours to days
  - Tends to fluctuate during the course of the day
- Perioperative period associated with many risk factors
  - Medications, inflammatory response, environment etc.
Does Delirium Affect Long-Term Outcomes?

Inouye et al. (1998)
- Prospective study of delirium with primary outcome of death in geriatric patients
- Significant associations between delirium and death, nursing home placement, and the combined endpoint of death and nursing home placement

Maldonato (2002)
- Diagnosis of delirium was associated with length of stay that was twice as long as for patients in the same units without delirium
- Cost per ICU patient diagnosed with delirium was calculated at $22,000 more per patient

Demeure and Fain (2006)
- In 2004, approximately $6.9 billion of Medicare expenditures was attributed to the treatment of delirium

Leslie et al. (2008)
- National burden of delirium on the healthcare system may be as high as $152 billion each year
Systemic review of 25 articles to determine preoperative risk factors associated with delirium

- Selected if operative patients diagnosed prospectively using criteria from DSM III or IV

Delirium rates: 5.1% - 52.2% (hip fracture and aortic surgery)

Of the risk factors examined, evidence most robust for

- Cognitive impairment
- Psychotropic drug use
- Depression

Preoperative Executive Function and Depression Predict Postoperative Delirium

**Hypothesis**

- Individuals with preoperative cognitive impairment and/or depressive symptoms would be at the highest risk for the development of postoperative delirium.

**Ultimate goal**

- To develop a short cognitive test battery that can identify patients at risk for postoperative delirium.
Preoperative Executive Function and Depression Predict Postoperative Delirium

- Prospective cohort study
- 100 adult patients ≥ 50 years
- Major noncardiac surgery

Preoperative demographic data collected:
- Alcohol use
- Pain
- Age
- Education
- Charlson comorbidity score
- ASA physical status
- History of depression

Greene and Monk. Anesthesiology 2009; 110:788
Preoperative Executive Function and Depression Predict Postoperative Delirium

- Preoperative neuropsychological tests
  - 3MS (Modified Mini-Mental State Exam) – a measure of global cognitive function
    - Similar to MMSE but more detailed with scores of 1 – 100
  - Digit Symbol Substitution and Symbol Search (WAIS III)
    - Provides numerical measure of executive function
  - Trail Making Test
    - Measures a patient's ability to sequence and perform a difficult cognitive test
  - Geriatric Depression Scale – Short Form
    - A 15 point questionnaire to screen for depression
  - Entire test battery takes 15-20 minutes to complete

- Confusion Assessment Method (CAM) for delirium on POD 1-3

Greene and Monk. Anesthesiology 2009; 110:788
Confusion Assessment Method (CAM)

Developed and validated as a tool for non-clinicians to diagnose delirium in patients

1. Is there evidence of an acute change in mental status from the patient's baseline?

2. Does the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said?

3. Was the patient’s thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

4. Overall, how would you rate this patient’s level of consciousness?
   - Alert, Vigilant, Lethargic, Stupor, Coma

Patient screens positive if answers “Yes” to 1 and 2 and either 3 or 4.

### Table 5. Sensitivity Analyses Using the Preoperative Geriatric Depression Score–SF and/or the Trails B Time to Predict Postoperative Delirium

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDS-SF alone</td>
<td>56</td>
<td>80</td>
<td>35</td>
<td>91</td>
</tr>
<tr>
<td>Trails B time alone</td>
<td>75</td>
<td>82</td>
<td>44</td>
<td>95</td>
</tr>
<tr>
<td>Either GDS-SF or Trails B time</td>
<td>100</td>
<td>63</td>
<td>34</td>
<td>100</td>
</tr>
<tr>
<td>Both GDS-SF and Trails B time</td>
<td>31</td>
<td>99</td>
<td>83</td>
<td>88</td>
</tr>
</tbody>
</table>

Data are percentages.

GDS-SF = Geriatric Depression Score–Short Form; NPV = negative predictive value; PPV = positive predictive value.
Conclusions

- Trail Making Test (executive function) and Geriatric Depression Score are independent predictors of delirium after noncardiac surgery.

- These two tests can be completed in approximately 10 minutes.

- This short battery could screen for patients at risk for postoperative delirium.
  - Preoperative prediction of high-risk patients would facilitate the investigation of interventions to prevent postoperative delirium.

Greene and Monk. Anesthesiology 2009: 110;788
Can Perioperative Management Prevent Delirium?

- Preoperative treatment of depression

- Perioperative anesthetic management
  - Gabapentin
    - 900 mg po on AM of surgery and POD1-3
    - Delirium ↓ from 42% to 0% with treatment
      - Leung et al. Neurology 2006
  - Dexmedetomidine
    - ↓ the incidence of delirium in ICU patients
  - Minimize anesthetic polypharmacy
    - Regional technique with minimal or no adjunctive anesthetic agents
Does the Anesthetic Influence Postoperative Delirium?

Screening And Consent

Preoperative Data Gathering

Randomization

Deep Sedation OAA/S=0

Spinal Anesthesia and Propofol Infusion Titrated to Light or Deep Sedation as Guided by OAA/S

Light Sedation OAA/S=4,5

Pain Management with IV Morphine Start PCA Morphine

Pain Management with PCA Morphine Switched to Oral Opiates, NSAID, and Acetaminophen When Appropriate

Data Gathering After Discharge at 1 month, 3 months, and 1 year

Preoperative

Intraoperative

PACU

Hospital Stay

Follow-up

Level of sedation is determined using the observer’s assessment of alertness/sedation scale (OAA/S) score

- **Light sedation** is defined by an OAA/S score of 4–5 (BIS ≥ 80)
- **Heavy sedation** is defined by an OAA/S score of 0 (BIS = 50)
## Light Sedation Decreases Postoperative Delirium

<table>
<thead>
<tr>
<th></th>
<th>Heavy Sedation</th>
<th>Light Sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No delirium</td>
<td>37</td>
<td>48</td>
</tr>
<tr>
<td>Postop delirium</td>
<td>20 (35 %)</td>
<td>9 (16 %)</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>57</td>
</tr>
</tbody>
</table>

p=0.030, Fisher’s exact (2-sided)

Postoperative Cognitive Dysfunction: A mild neurocognitive disorder

- Deterioration of intellectual function presenting as impaired memory or concentration.
- Not detected until days or weeks after anesthesia
- Duration of several weeks to permanent
- Diagnosis is only warranted if:
  - corroborated with neuropsychological testing
  - evidence of greater memory loss than one would expect due to normal aging
“Hi. I’m, I’m, I’m ... You’ll have to forgive me, I’m terrible with names.”
Implications of Postoperative Neurocognitive Disorder

- Abrupt decline in cognitive function heralds:
  - Loss of independence
  - Withdrawal from society
  - Death

Seattle Longitudinal Study of Aging
Berlin Aging Study
POCD: Attention in Lay Media

Saving the Heart Can Sometimes Mean Losing the Memory

After the Bypass

Some patients suffer cognitive problems after they have had bypass surgery, especially if they were connected to heart-lung machines during the operation.

THE OPERATION

In most bypass operations, the heart is stopped. To maintain blood flow, the aorta is clamped on one side and blood is directed to a heart-lung machine to be oxygenated and returned through the unclamped side of the aorta.

THE POSSIBLE CULPRITS

1. IN THE HEART-LUNG MACHINE

Blood tends to clot when it leaves the body. Clots might be pumped back into the body and reach the brain.

2. IN THE AORTA

Fragments of fatty material that coat the aorta wall might be loosened by the act of clamping and unclamping, blocking small blood vessels of the brain, disrupting the blood supply to the surrounding tissue.

THE CONSEQUENCE

The fat fragments or blood clots may block small blood vessels of the brain, disrupting the blood supply to the surrounding tissue.

The affected brain cells cannot communicate with the parts of the body they serve, resulting in loss of function.
Biphasic Pattern of POCD after CAB

Change in Cognitive Index From Baseline

-2 -1 0 1 2

Not impaired at discharge
Impaired at discharge

Discharge 6-Weeks 6-Months 5 Years

Cognitive and Cardiac Outcomes 5 Years After Off-Pump vs On-Pump Coronary Artery Bypass Graft Surgery

Diederik van Dijk, MD, PhD  
Monique Spoor, MS  
Ron Hijman, PhD  
Hendrik M. Nathoe, MD, PhD  
Cornelius Borst, MD, PhD  
Erik W. L. Jansen, MD, PhD  
Diederick E. Grobbee, MD, PhD  
Peter P. T. de Jaegere, MD, PhD  
Cor J. Kalkman, MD, PhD  
for the Octopus Study Group

Context  Conventional coronary artery bypass graft surgery with use of cardiopulmonary bypass (on-pump CABG) is associated with excellent long-term cardiac outcomes but also with a high incidence of cognitive decline. The effect of avoiding cardiopulmonary bypass (off-pump CABG) on long-term cognitive and cardiac outcomes is unknown.

Objective  To compare the effect of off-pump CABG and on-pump CABG surgery on long-term cognitive and cardiac outcomes.

Design, Setting, and Participants  The Octopus Study, a multicenter randomized controlled trial conducted in the Netherlands, which enrolled 281 low-risk CABG patients between 1998 and 2000. Five years after their surgery, surviving patients were invited for a follow-up assessment.

Intervention  Patients were randomly assigned to receive either off-pump (n = 142) or on-pump (n = 139) CABG surgery.

Main Outcome Measure  The primary measure was cognitive status 5 years after surgery, which was determined by several standardized cognitive tests.
Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study

JT Møller  P Cluitmans  LS Rasmussen  P Houx  H Rasmussen  J Canet
P Rabbitt  J Jolles  K Larsen  CD Hanning  O Langeron  T Johnson  PM Lauven
PA Kristensen  A Biedler  H van Beem  O Fraidakis,  JH Silverstein
JEW Beneken  JS Gravenstein for the ISPOCD investigators

Collaborative research effort:
- Members from 8 European countries and USA
- 13 hospitals

Research conducted from 1994 - 1996
Long-Term POCD in the Elderly

Hypotheses

- Anesthesia and surgery in elderly patients (≥ 60 years) cause prolonged cognitive dysfunction
- The incidence of prolonged POCD increases with age
- Potential mechanisms of POCD
  - Hypoxemia is a major cause of POCD
  - Hypotension is a major cause of POCD
Long-Term POCD in the Elderly

Physiologic Monitoring

- $O_2$ saturation by continuous pulse oximetry
  - One night preop
  - Operating room
  - 24 hrs postop
  - Nights of POD 2-3

- Noninvasive blood pressure
  - Every 3 min in OR
  - Every 15 min in PACU
  - Every 30 min for 24 hrs after PACU discharge
Incidence of POCD in Patients and Controls

* p < 0.004

Lancet 1998; 351:857
Long-Term POCD in the Elderly

Conclusions and Questions

- Anesthesia and surgery cause long-term POCD

- Hypotension and/or hypoxemia not related to occurrence of POCD

- Variable incidence of early POCD at different centers
  - Differences in anesthetics, procedures, patients?
  - Are results generalizable to single institutions?

Lancet 1998; 351:857
A Prospective Study Evaluating The Relationship Between Age and POCD

- Single site - University of Florida: 1999 - 2002

- 1200 patients undergoing elective surgery
  - Young - 18 to 39 years of age
  - Middle-aged - 40 to 59 years of age
  - Elderly - 60 years and older

- Controls - primary family members

- Study design identical to ISPOCD study
  - Same psychometric test battery
  - Outcome Endpoints:
    - POCD (primary) and mortality (secondary)

## 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>0.0002</td>
<td>0.84 (p=0.031)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.0001</td>
<td>1.02 (p=0.0109)</td>
</tr>
<tr>
<td>History of Stroke</td>
<td>0.0005</td>
<td>3.14 (p=0.0298)</td>
</tr>
<tr>
<td>No POCD at Discharge</td>
<td>&lt;0.0001</td>
<td>0.32 (p&lt;0.0001)</td>
</tr>
<tr>
<td>Baseline Comorbidity</td>
<td>0.0639</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA Status</td>
<td>0.0472</td>
<td>NS</td>
</tr>
<tr>
<td>History of MI</td>
<td>0.0195</td>
<td>NS</td>
</tr>
<tr>
<td>ASA Physical Status</td>
<td>0.0293</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of Hospital Stay</td>
<td>0.0173</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>

Potential Mechanisms for POCD

- High-risk patients
- High-risk surgical procedures
- High-risk anesthetic techniques
Threshold Theory for Cognitive Decline

A: Protective factor (greater brain reserve capacity), lower test sensitivity, no impairment
B: Vulnerability factor (less brain reserve capacity), higher test sensitivity, impairment

Satz Neuropsychology 1993:(7);273.
Prevalence of AD

Potential Mechanisms for POCD

- High-risk patients - “Functional Cliff”
- High-risk surgical procedures
  - Cardiac Surgery
  - Orthopedic Surgery
- High-risk anesthetic techniques
Cerebral Microembolism Diagnosed by Transcranial Doppler during Total Knee Arthroplasty

Correlation with Transesophageal Echocardiography

Cheri A. Sulek, M.D.,* Laurie K. Davies, M.D.,† F. Kayser Enneking, M.D.,† Peter A. Gearen, M.D.,‡ Emilio B. Lobato, M.D.†
Cerebral Microemboli During TKA

- 22 adult patients - TKA with GA

- Intraoperative monitoring
  - Transcranial doppler ultrasonography
  - Transesophageal Echocardiography

- Results
  - TEE: emboli in L atrium - 36% (8 of 22)
  - TCD: emboli in 60% (9 of 15) of unilateral and 57% (4 of 7) of bilateral TKA
  - No focal neurologic deficits noted

Anesthesiology 1999; 91:672
Potential Mechanisms for POCD

- High-risk patients
- High-risk surgical procedures
- High-risk anesthetic techniques
**Are Anesthetic Agents Neurotoxic?**

Soluble protein remaining in filtrate after incubation of amyloid β42 with halothane (0-10mM), isoflurane (0-10mM), ethanol (0-100mM), or propofol (0-10μM) for 12 hours at 37°C.

**Conclusions:**
At all concentrations, inhaled agents enhance oligomerization and cytotoxicity of AD associated peptides.

Propofol inhibits oligomerization at low concentrations but enhances at very high concentrations.

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Eckenhoff. Anesthesiology 2004; 101:703
Alzheimer’s Disease Pathophysiology

- **Neuropathology**
  - Plaques containing amyloid ß (Aß) protein
  - Neurofibrillary tangles in cortex

- **Molecular pathology**
  - Amyloid protein (APOE allele 4)
  - Paired helical filaments (map tau)

- **Neurotransmitter pathology**
  - Acetylcholine

- **Abnormalities in oxidative metabolism**
Hypothetical pathway by which isoflurane induces a vicious cycle of apoptosis and Aβ generation and aggregation

Tg2576 Mouse Model of Alzheimer’s Disease

Tg2576 mice:

• Overexpress human APP\textsubscript{695}

• Develop memory deficits and plaques with age

• Show age-dependent AD-type neuropathology

• Suitable for examining the relationship Between Aβ and memory
Anesthesia with Isoflurane Increases Amyloid Pathology in Mice Models of Alzheimer’s Disease

Juan Perucho\textsuperscript{a}, Isabel Rubio\textsuperscript{b}, Maria J. Casarejos\textsuperscript{a}, Ana Gomez\textsuperscript{a}, Jose A. Rodriguez-Navarro\textsuperscript{a}, Rosa M. Solano\textsuperscript{a}, Justo Garcia De Yébenes\textsuperscript{b,*} and Maria A. Mena\textsuperscript{a}

\textsuperscript{a}Department of Neurobiology, CIBERNED, Madrid, Spain
\textsuperscript{b}Neurology, Hospital “Ramón y Cajal”, CIBERNED, Madrid, Spain
51 male mice in study
- 26 exposed to anesthesia
  - 11 Wild type (controls) and 15 Tg2576 mice
- 25 without anesthesia
  - 12 Wild type (controls) and 13 Tg2576 mice

Anesthetic technique
- Isoflurane – 4% for induction and 2% for maintenance with O₂
- Time of exposure 20-30 minutes (4 Tg2576 mice died at 30 min)
- Anesthetic exposures repeated twice a week for 3 months

Investigated the effects of repetitive exposure to isoflurane on:
- survival, behavior, cell death, Aβ deposition
Effect of Isoflurane Treatment on Survival

\[ p = 0.017 \]
Effects of Isoflurane Treatment on Apoptotic Cell Death

Ratio of pro-apoptotic/anti-apoptotic (Bax/Bc12) protein

p = 0.0134
Anesthesia with Isoflurane Increases Aβ Pathology - Conclusions

- Isoflurane treatment of Tg2576 mice (↑ risk for AD)
  - ↑ mortality
  - ↓ responsiveness after anesthesia
  - ↓ exploratory behavior
  - ↑ ratio of pro-apoptotic proteins in hippocampus
  - ↓ astroglial and ↑ microglial responses
  - ↑ Aβ aggregates and high molecular weight peptides

- Conclusions:
  - Isoflurane is probably not a general risk factor for AD
  - Inhaled anesthetics may be a risk in patients with special genetic or environmental risk factors for AD
Commentary

A Smoking Gun but Still No Victim

Maryellen F. Eckenhoff and Roderic G. Eckenhoff*

Department of Anesthesiology & Critical Care, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
Does Anesthetic Technique Matter? Regional vs. GA

- 10 RCTs comparing cognitive outcomes after GA vs. Regional

- JAMA 1995; 274:44-50: Epidural vs. GA for TKA
  - 262 patients – median age of 69 yrs.
  - No difference in cognitive function change from baseline at 1 week or 6 months
  - 5% incidence of POCD at 6 months
  - Type of anesthesia did not affect magnitude or pattern of POCD

- Acta Anaesthesiol Scand 2003; 47:260-6: Regional vs. GA for major surgery
  - 364 patients 60 years or older
  - No difference in cognitive function between groups at 3 months after surgery – 14.3% vs. 13.9%
Does Anesthetic Technique Matter?  
Regional vs. GA

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BUT TYPE AND AMOUNT OF SEDATION NOT CONTROLLED IN THESE STUDIES
Is Hypotension Responsible for POCD?

- Natural assumption: Hypotension is associated with ↑ POCD
- 235 older adults (50 yrs. or greater) schedule for primary total hip replacement
- All patients had epidural anesthesia
- Randomized to:
  - Mild hypotension: MAP = 55-70 mm
  - Severe hypotension: MAP = 45 - 55 mm

Anesthesiology 1999; 91: 926
Is Hypotension Responsible for POCD?

- No difference in the incidence of POCD between the groups:
  - Early (1 week po)
  - Late (4 months po)

- No difference in the rates of other adverse events:
  - Cardiac
  - Renal
  - Thromboembolic events
  - EBL and transfusion rates

Anesthesiology 1999; 91: 926
WHAT DO WE STILL NEED TO LEARN…

- Etiology of postoperative cognitive disorders
- Easy techniques to identify high-risk patients
- Prevention/Treatment
Superman in his later years

Dang!... Now where was I going?