Anesthesia, Surgery and Dementia

Kirk Hogan MD, JD
Department of Anesthesiology, UW-Madison
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No Conflicts
The Numbers

- 7 surgeries each per lifetime
- 70,000,000 procedures per year in USA
- 35%+ on patients > 65
- 2,000,000 + persistent cognitive changes after surgery
Overview

• History
• Postoperative delirium (POD)
• Postoperative cognitive dysfunction/decline (POCD)
• Postoperative cognitive improvement (POCI)
• Postoperative dementia
• Steps to take now
• Research priorities – known unknowns
Postoperative Cognitive Changes in History

- 1955: Bedford
- 1970 – 1990: Open cardiac surgery
- 1997 – present: Non-cardiac surgery
- 2004 – present: Alzheimer’s-like changes from anesthesia and surgery alone, and in combination, in vitro, cell culture, animals, human performance, biomarkers and imaging
What is postoperative delirium (POD)?

- In first several days after surgery, often after lucid interval
- Acute onset, rapidly evolving, fluctuating
- Inattention, disorganized thinking, memory loss
- Hyper-, hypo- or mixed psychomotor signs
- Nocturnal – circadian
- Confusion Assessment Method (CAM)
- Lasts days to weeks
- Has DSM-IV and ICD-10 codes
What are the risk factors for POD?

- Age
- Baseline cognitive status
- Poor nutrition
- Electrolyte and glucose abnormalities
- CNS medications
- Dehydration
- Alcohol and substance withdrawal
- Invasive, lengthy surgery
- Pain
What is the incidence of POD?

- As low as 10%
- As high as 70%
- Depending on age and procedure
- A marker of brain vulnerability
- A predictor of other postoperative cognitive changes:
  - Longer ICU stays
  - POCD, progression of MCI and AD
  - Increased risk of dementia 6 months to 5 years later
  - Institutionalization
  - Mortality
How is POD prevented and treated?

- Worse with IV than inhaled general anesthetics
- Regional anesthesia, esp. with sedation, is not preventive
- Modulate risk factors
- Avoid atropine, antihistamines, steroids, benzodiazepines, opioids
- Provide non-sedating analgesics
- Peripheral nerve blocks (PNBs)
- Local anesthetic infiltration (LAI)
- Haldol?
What is Postoperative Cognitive Dysfunction (POCD)?

• A decrease in neuropsychological **test performance** after anesthesia and surgery
• Memory, executive and intellectual function, speed
• Most often **asymptomatic**
• A patient with POCD is alert, oriented, without specific complaints
• Participants with pre-existing cognitive deficits are excluded from investigation
• Diagnosis by exclusion of other CNS lesions – stroke, seizure, altered metabolism, etc.
What is Postoperative Cognitive Dysfunction (POCD)?

| • No formal diagnostic criteria |
| • No DSM or ICD code |
| • Not in textbooks of Neurology or Neuropsychology |
| • Diagnosis often missed |
| • Slow, subtle onset |
| • Slow subtle recovery in many but not all patients |
| • May be transient or persistent |
What is the Incidence of POCD?

• Cardiac surgery – focus on surgery/anesthesia variables
  – 30-40% 6 weeks to 5 years after bypass
  – Microemboli
  – No difference on or off pump
• Non-cardiac surgery - focus on patient variables
  – 50% 2-7 days after surgery
  – 12- 30% at 3 months vs. 2.8% no surgery controls
  – 3 -10%+ at 1 year “persistent POCD”
What are the Implications of POCD?

- A marker of brain vulnerability
- Increased odds of mortality at 1 year
- Increased odds of retirement
- Increase dependence on social services
- POCD at 3 months correlates with 50% increased risk of dementia
What are the Risk Factors for POCD?

• Age
• Co-morbidities
• Educational achievement
• Genetics? - *APOE4* may predict early, but not persistent POCD
• Long, invasive, emergent, complicated, serial surgeries
• Deeper levels of anesthesia?
• Choice of anesthesia is **NOT** a risk factor for POCD
• Regional anesthesia **NO** protection
• Older inhaled agents worse than newer
• Benzodiazepines, “sleep architecture”
What are the Mechanisms for POCD?

- *In vitro* biophysical data
  - Inhaled anesthetics increase amyloid oligomerization
- *In vitro* cell culture data
  - Inhaled anesthetics increase Aβ generation
  - Activate caspase
  - Promote Aβ aggregation
  - Cause cytotoxicity and neuronal apoptosis
What are the Mechanisms for POCD: Anesthesia in Rodents?

- Histologic changes
  - Tau phosphorylation in hippocampus
  - Microgliosis
  - Cytotoxicity
- Behavioral changes
  - Loss of learning, increased mortality
  - Worse in aged rodents and AD transgenic rodents
  - Worse with certain combinations of anesthetics
What are the Mechanisms for POCD: Surgery in Rodents?

- Surgery (tibial fracture) + anesthesia vs. anesthesia alone vs. control
- Aseptic inflammatory response
- Damage associated molecular pattern (DAMP) molecules
- TNFα, IL-1B, IL-6, alarmins, purines, nucleic acids, HMGB1
- Activated macrophages and CNS microglia
- Abdominal surgery under local anesthesia increases hippocampal amyloid in aged WT and young AD Tg rodents, but not young WT rodents
- Changes prevented by γ secretase inhibitor
What is the pathogenesis of POCD?

- Direct toxicity of general anesthetics, regional anesthetics and sedatives AND/OR
- Peripheral and central nervous system inflammation
- Blood brain barrier endothelial disruption from anesthetics and inflammation
- Migration of macrophages into CNS, activation of CNS microglia, amplification of CNS inflammatory response
- Synaptic dysfunction, inhibition of neurogenesis, neuronal death
- Esp. in aged brain with glucose intolerance, vascular disease
What are Human Biomarkers of POCD?

- After cardiac and non-cardiac surgery:
- Increase in CSF Aβ, tau
- CSF S100b
- CSF IL-6, IL-10 and TNFα
- Preliminary data at best
What are Human Imaging Markers of POCD?

• Orthopedic surgery in healthy participants: 5-9 months later: decreased volume of cerebral grey matter, atrophic changes in hippocampus, enlarged lateral ventricles per MRI
• Parallel psychometric changes
• Silent pre-existing lesions
• Multiple prospective trials with psychometrics, MRI, amyloid and microglial PET before and after surgery
What is the Incidence of POCD after Surgery without Incision?

- Silbert et al. 2014
- Extracorporeal Shock Wave Lithotripsy (EWSL)
- Prospective, randomized, controlled
- Peerless test panel, statistical analysis
- General anesthesia vs. spinal anesthesia without sedation, no post-op analgesia
- Investigation halted after 100 patients and 6 years
- Overall POCD at 3 months 13.6%, not diff GA vs. RA
- POCD with NO centrally acting drugs
What are Barriers to Understanding POCD?

• Those at greatest risk are excluded from investigation
• No standard definition *i.e.*, magnitude and components of decline
• No standard experimental design *e.g.*, positive and negative controls (age, gender, comorbidity, “cognitive reserve”), attrition, etc.
• No standard study intervals
• No standard test battery, learning, floor/ceiling effects
• Few investigations amply powered
• No pre-operative cognitive trajectories – confined to single, “snapshot” baseline evaluation
What is Postoperative Dementia?

- New onset or progression of MCI/Alzheimer’s Spectrum Disorders (AD) by conventional definitions in-phase with surgery
- Other postoperative CNS lesions excluded
- Chronic, insidious, progressive
- Literature is sparse, retrospective, controversial
- Several studies suggest no association between general or regional anesthesia, or cumulative effects, with “development of AD”
- Very little literature on how best to anesthetize and operate on patients with AD
What are Risk Factors for Postoperative Dementia?

- Chen, 2014: matched for age, gender and index year reports 34% increased risk for AD with inhaled vs. intravenous general anesthesia
- Liu, 2013: progression of MCI to AD faster in patients who received inhaled general anesthesia vs. epidural or intravenous general anesthesia
What are Risk Factors for Postoperative Dementia – WRAP data?

- Surgery in 5 years before enrollment predicts lower cognitive test performance at Visit 1
- Surgery between Visit 1 and 2 predicts greater declines in cognitive performance between these visits
- Decrements in tests of memory are greater than decrements in tests of executive function and general abilities
- The cumulative number of surgeries correlates with the magnitude of the decline in Immediate Memory, suggesting that effects of surgery on cognition may accumulate across surgeries
- Though statistically significant, observed effects are small
What are Risk Factors for Postoperative Dementia – WRAP data?

- Generalized linear models adjusted for age, gender, education and Visit 1 performance to assess interactions of surgery and co-variates on cognitive factors between Visit 1 and Visit 2:
  - Working Memory: Family history and APOE (p=0.033)
  - Working Memory: Nitrous oxide (p=0.016)
  - Working Memory: ASA score (p=0.029) (lowest scores decline the most)
  - Verbal learning and Memory: APOE and nitrous oxide (p=0.048)
  - Executive function: APOE (p=0.06)
  - Speed and Flexibility: APOE (p=0.031)
  - Speed and Flexibility: ASA score (p=0.049) (highest scores decline the most)
What are Barriers to Understanding Postoperative Dementia?

• Does surgery increase the incidence of AD?
• Does surgery hasten the onset and/or speed the progression of AD?
• Prospective trials with long-term follow up
• Age at AD onset not clearly documented
• Challenges to research using EHRs
• Must combine psychometrics, general health profiles, biomarkers and imaging in longitudinal designs
• Correlation vs. causation
• Incorporate indices of anesthesia and surgery in all ongoing longitudinal cognitive aging investigations
What Clinical Steps Should We Take Before Surgery?

• Only consider needed surgery vs. cosmetic, sports, etc.
• Consider less-invasive, radio-guided, robotics, medical management options that minimize inflammation
• Pick your surgeon and anesthesiologist – go to busy facilities
• Informed consent from surgeon and anesthesiologist
• Asking about cognitive changes after surgery will trigger caregiver interest
• Be wary of Web sources of information
• Baseline neurologic exam
• Balance timing of surgery – avoid “stacking”, surgery while ill
What Clinical Steps Should We Take Before Surgery?

- Optimize physical condition: glucose, BP
- Diet: target weight, vitamins B, D, minerals and others
  - Minimal daily requirement
  - Optimal daily requirement?
  - Optimal daily requirement for surgery???
- Exercise: aerobic fitness, stamina
- Medications: peak effects, optimal levels
- Smoking, drinking
- “Prehabilitation”
What Clinical Steps Should We Take During Anesthesia?

- “Fast Track”
- Avoid benzodiazepine sedatives
- Avoid nitrous oxide
- Avoid older inhaled general anesthetics
- Regional anesthesia with minimal sedation
- Non-opioid analgesics
- PNBs and LAIs at the frontier – ask about, tricky, time-consuming, but it’s your brain and good safety profile
- Multi-modal analgesia
What Clinical Steps Should We Take After Surgery?

- Early ambulation
- Early discharge
- Home tele-medicine
- Aerobic exercise
- Fast track decreases early (12 day) but not late (3 month) POCD %
- Short procedure time, high level of surgeon experience, standardization, low blood loss, few complications
- Mental exercises
- Music, books on tape
What are the Research Priorities?

- Validated measures of cognitive performance must become standard before and after surgery
- Improved CNS monitoring during surgery
- Cognitive trajectories are crucial
- Extreme phenotypes
- Anesthesia and surgery are at least confounders in all ongoing cognitive investigations, and should be addressed face up
- Co-existing cognitive challenges in patients having surgery: “Chemo-brain”, head-trauma, PTSD, chronic illness, chronic pain
What are the Research Priorities?

• Plasma and CSF cognitive biomarkers using mass spectrometry (Mapstone, 2014)
• 0.25 uL, 1 second, 30,000 chemical entities with quantification
• Epigenetics – chemistry of gene switching, genetic “logic gates”, how we learn, how we remember, how we forget
• Effects of anesthesia and surgery in the afterlife
• Legal and ethical initiatives
• SMARTTots
• SMARTCoots
• Late life consequences of early surgery?
Medications for Prevention and Treatment?

• Improved preoperative preparation
• Improved inflammatory response modulation
• Stabilize the blood brain barrier
• Minocycline, NSAIDs, steroids, anti-chemokine antibodies, statins, etc.
• RCTs with strong psychometric designs
• Require teams of highly skilled players
Last Words of an Extreme Phenotype
WRAP Surgery Team

• Rebecca L. Koscik,
• Lisa C. Bratzke
• Katie J. Schenning
• John C. Boncyk
• Allen L. Wenzel
• Asenath A. La Rue
• Bruce P. Hermann
• Sterling C. Johnson
• Mark A. Sager