Can Depth of Anesthesia Monitoring Alter the Incidence of Mortality, POCD or Delirium?

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Disclosures: None
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The "Submarine Model" of Anesthesia
The Questions*

• Does “deeper” anesthesia cause increased mortality?

• Do anesthetics cause Post Op Cognitive Dysfunction - transiently? - permanently?

• If yes, does deeper anesthesia cause greater POCD?

• Does deeper anesthesia increase the risk of delirium?

* in adults
What does 1 + 1 equal?
Sensationalism; Pseudo-science; Self-interest; Lost objectivity
Q1: Does “deep” anesthesia cause increased mortality?
Anesthetic Management and One-Year Mortality After Non-Cardiac Surgery

-- 1064 patients studied prospectively
-- major non-cardiac surgery
-- BIS recorded; clinicians blinded
-- Endpoint: one year survival

Observations: Mortality at 1 year independently correlated with:
1. Co-morbidity score
2. Duration of intraoperative hypotension
3. “Cumulative deep hypnotic time” (BIS < 45)

Monk et al., Anesth Analg 100: 4-10, 2005
Anesthetic Management and One-Year Mortality After Non-Cardiac Surgery

Why?

Is it possible that some element of patient status predisposes the patient to more CNS depression from a hemodynamically equivalent anesthetic? Is the low BIS a marker of greater mortality risk rather than the cause?

Monk et al., Anesth Analg 100: 4-10, 2005
BIS monitors were loaned and sensors provided by Aspect Medical Systems, which provided no other support and did not participate in the study design and implementation.

Dr. Sigl assisted with the statistical analysis and the drafting of the manuscript but was not involved with the study design and implementation.
Editorial Board Reproached for Publication of BIS-Mortality Correlation

To the Editor:

We believe that the article by Monk et al. (1) should not have been published.

Drummond and Patel, Anesth Analg 101: 1238-9, 2005

(Disclaimer / Disclosure / Acknowledgement)
Anesthetic Management and One-Year Mortality After Non-Cardiac Surgery

Why?

Is it possible that some element of patient status predisposes the patient to more CNS depression from a hemodynamically equivalent anesthetic? Is the low BIS a marker of greater mortality risk rather than the cause?

Monk et al., Anesth Analg 100: 4-10, 2005
An unhealthy brain?

Early Mortality

Does a predisposition to mortality precede the anesthetic in some?

Does an “unhealthy” brain yield a lower BIS for any given anesthetic?
Cognitive Impairment: An Independent Predictor of Excess Mortality
A Cohort Study

Sachs et al., 55: 300-8, 2011

- 4000 primary care pts ≥ 60 yrs
- Cognitive test at enrollment
- “Both mild and moderate to severe cognitive impairment . . . associated with an increased risk for mortality.”

Decline in Cognitive Functioning Is Associated with a Higher Mortality Risk

Neuroepidemiology 28: 93–100, 2007
Is cognitive dysfunction is common in pre-surgical populations?

Preexisting Cognitive Impairment and Mild Cognitive Impairment in Subjects Presenting for Total Hip Joint Replacement

Anesthesiology 114: 1297-304, 2011

Lisbeth A. Evered, B.Sc., M.Biostats.,* Brendan S. Silbert, M.B., B.S., F.A.N.Z.C.A.,†

- Patients > 59 yrs (avg. 70)
- Cognitive impairment: 29% (44/152)
“Silent” Stroke
• “detected in 20% of healthy elderly people and up to 50% of patients in selected series.”

• “they are associated with subtle deficits in physical and cognitive function that commonly go unnoticed.”
Anesthetic Management and One-Year Mortality After Noncardiac Surgery

Subsequent work* concluded that silent stroke is a risk factor for POCD and that POCD is, in turn, a risk factor for earlier mortality.

Cognitive Impairment / Silent Stroke
(common among the elderly)

Premise: In some patients, a brain-related predisposition to mortality inevitably *precedes* the anesthetic!
Cognitive Impairment / Silent Stroke
(common among the elderly)

Early Mortality

Is a low BIS is a *marker* of mortality risk, rather than the *cause*?
The Missing Link

Do cognitive impairment and/or silent stroke cause a greater cerebral sensitivity to anesthetics? (i.e., a lower BIS for any given anesthetic?)

Intuitively easy to understand.

Support?
• Pre-Op Mini Mental State Examination

• Anesthesia: Propofol/ Remi; BIS “45-60”

• Cognitively impaired patients had:
  – Lower pre-induction BIS
  – Lower BIS at every interval in spite of lower doses
  – Slower wake-up
• “... found an association between cumulative duration of low BIS and mortality 

• ... [but it] was independent of both volatile anesthetic concentration and duration of anesthesia. [i.e., BIS did not correlate with anesthetic concentration.]”

• i.e., the folks who died had a more “sensitive” CNS.
Patients Who Died Received Less Anesthesia!

Median Difference: -0.03

Median Difference: -0.05

Mean Anesthetic Dose (MAC)
The Deep Anesthesia-Mortality Relationship

Predictive but not causal

An epiphenomenon reflecting poor preoperative condition that predisposes to late post-operative mortality.

C. J. Kalkman, Anesthesiology 114: 485-7, 2011
Elective major NCS (381 pts); ASA ≤ 4; > 40 yrs

Target BIS 55 vs 35

Stopped for futility (all three limbs)

“... no intervention reduced the risk of major morbidity or 1 yr mortality.”
Mortality Within 2 Years After Surgery in Relation to Low Intraoperative Bispectral Index Values and Preexisting Malignant Disease


- Existing cohort of 4087 SAFE-2 BIS monitored patients.
- When malignancy status included as a co-variate*, the low BIS-mortality correlation no longer evident
- Does a malignancy make you more susceptible to CNS depression by anesthetic agents?

* malignant status was not included in the 2005 study
Q1: Does “deep” anesthesia cause increased mortality?

No
But, there’s more to come . . . .

The Balanced Anaesthesia Study

The Balanced Anaesthesia Study attracted a 2013 NHMRC grant of more than $2.8 million, as well as a grant of $1.2 million from the New Zealand Health Research Committee. The study is led by Associate professor Timothy Short in New Zealand, and Professor Kate Leslie in Australia. Other investigators are Professor Matthew Chan (HK), Associate Professor Tomas Corcoran (WA), Professor Paul Myles (Vic), Professor Michael Paech.

The primary aim of this study is to determine the effect of light versus deep general anaesthesia on all-cause mortality at one year post-operatively in 6,500 moderate to high risk patients having major non-cardiac surgery. Secondary outcomes include awareness, myocardial infarction, cardiac failure, stroke, pulmonary embolism, deep venous thrombosis, pneumonia, sepsis, wound infection, renal/liver dysfunction, patient satisfaction, cancer recurrence and persistent post-operative pain.

Patients will be enrolled from approximately 26 sites in Australia, New Zealand and Hong Kong over a 4 year period with 1-year follow-up for the primary outcome.

Volatile agent based GA
Surgery > 2 hrs
BIS 50 or 35
Q2: Do anesthetics cause POCD in adults?
A word about detecting cognitive deficits . . . .
The Detection of Cognitive Deficits

Detection Threshold

Age

Cognitive Function

Normal

Allen et al., Am J Human Biol 17: 673–89, 2005
The Detection of Cognitive Deficits

Cognitive Function vs. Age

Detection Threshold

Anesthesia/Surgery may unmask rather than cause cognitive decay [Crosby]

Permanent POCD might represent the normal trajectory of cognitive decay
A word about detecting adverse effects . . . .
Dose – Response Relationship

Adverse Effect

Dose / Concentration
Dose – Response Relationship

POCD

Dose / Concentration

Threshold?
Delirium vs POCD

“Nutty”

**Delirium**
- Altered consciousness
  - hyperactive
  - hypoactive
- Disorientation
- Misperception (confusion)
- Memory impairment
- Inattention
- Fluctuating course
- Bedside diagnosis (inattention and disorganized thinking)

**POCD**
- Subtle deficits
  - memory
  - executive function
- Dx by Neuropsych. tests
  - word recall
  - pattern recall
  - trail making
  - word association
  - pegboard
  - attention (reaction time)
  - attention (task retention)

“Slow”
### Delirium vs POCD

<table>
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<tr>
<th>Delirium</th>
<th>POCD</th>
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<td><strong>“Nutty”</strong></td>
<td><strong>“Slow”</strong></td>
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| • Altered consciousness  
  - hyperactive  
  - hypoactive | • Subtle deficits  
  - memory  
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| • Disorientation | • Dx by Neuropsych. tests  
  - word recall  
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  - attention (reaction time)  
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| • Misperception  
  (confusion) | |
| • Memory impairment | |
| • Inattention | |
| • Fluctuating course | |
| • Bedside diagnosis  
  (inattention and disorganized thinking) | |
Q2: Do anesthetics cause POCD in adults?

A: The anesthesia / surgery experience certainly does cause POCD.
Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study


- Avg age: 68
- POCD: 26% at 1 week
  10% at 3 months
- (Non-surgical controls – CD: 3%)
What causes that POCD?

A. Anesthetic agents?
B. The inflammatory response to surgery?
C. Both of the above?
A. Anesthetic agents?

Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients


L. S. Rasmussen¹, T. Johnson², H. M. Kuipers³, D. Kristensen⁴, V. D. Siersma⁵, P. Vila⁶, J. Jolles⁷, A.

• POCD “greater” among GA pts at one week (20 vs 13%, p = 0.06) but not 3 months.

• The early difference suggests that anesthetics are doing something that is (at least) transient.

(* with sedation)
B. The inflammatory response to surgery?

Depletion of Bone Marrow–derived Macrophages Perturbs the Innate Immune Response to Surgery and Reduces Postoperative Memory Dysfunction

Anesthesiology 118: 527-36, 2013

Vincent Degos, M.D., Ph.D.,* Susana Vacas, M.D.,† Zhenying Han, M.D.,‡ Nico van Rooijen, Ph.D., Pierre Gressens, M.D., Ph.D.,‖ Hua Su, M.D.,# William L. Young, M.D.,** Mervyn Maze, M.B., Ch.B.

Inhibiting the inflammatory response reduced cognitive deficits!
Incidence of postoperative cognitive dysfunction after general or spinal anaesthesia for extracorporeal shock wave lithotripsy

B. S. Silbert¹,²*, L. A. Evered¹,² and D. A. Scott¹,²

“No significant difference in the rates of POCD [3 mon] when comparing general with spinal anaesthesia [with no sedation or post op opioid], suggesting that the surgical or procedural process itself may contribute to the development of POCD.”
What causes POCD?

A. Anesthetic agents?

B. The inflammatory response to surgery?

C. Both of the above?
What is the Mechanism of Anesthetic-Related POCD?

Unknown
Dendritic Spines vs. Age (Monkeys)

Duan et al., Cerebral Cortex 13: 950-61, 2003
Isoflurane: Retraction of Dendritic Spines (green)

Control

Green - Drebrin
Blue - DAPI

Brian Head, Piyush Patel, UCSD
Cultured neurons from PND 4-7 mice
Isoflurane 1.4% for 4 hours
Cytoskeletal depolymerization; \( \uparrow \) apoptosis

Green - Drebrin
Blue - DAPI
SOME ASSEMBLY REQUIRED: THE DEVELOPMENT OF NEURONAL SYNAPSES

Zheng Li and Morgan Sheng

Figure 6 | The sequence of molecular and morphological events in synapse assembly and maturation.

Q: Is POCD transient or permanent?
Minimal evidence . . . that patients continue to show POCD up to 6 months and beyond.
General anaesthesia does not contribute to long-term post-operative cognitive dysfunction in adults: A meta-analysis

J Guay (Univ of Montreal), Indian J Anaesthesia 55: 538-63, 2011

“The present meta-analysis does not support concerns that a single exposure to general anesthesia in an adult would significantly contribute to permanent POCD after non-cardiac surgery.”
“At 3 months after surgery, POCD was present in 5.7% of young, 5.6% of middle-aged, and 12.7% of elderly patients.

At 3 months, the prevalence of cognitive dysfunction was similar between age-matched controls and young and middle-aged patients but significantly higher in the elderly.”
Those were studies of G.A. patients over time

How about G.A. vs no anesthetic over time?
Cognition 6 Years after Surgical or Medical Therapy for Coronary Artery Disease

Ola A. Selnes, PhD,1 Maura A. Grega, MSN,2 Maryanne M. Bailey, BA,3 Luu D. Pham, MS,4 Scott L. Zeger, PhD,4 William A. Baumgartner, MD,2 and Guy M. McKhann, MD1,3,5

“Interpretation: Late cognitive decline does occur in patients who have undergone CABG, but the degree of this decline does not differ from that observed in patients of similar age with CAD who have not undergone CABG.”
“At 7.5 years follow-up, OPCAB patients had a similar or perhaps even better cognitive performance compared with PCI patients.”
• Three groups identified retrospectively from an Alzheimer’s Research Center data-base.

• Initially not demented, or mild or very mild dementia

  1. Non-cardiac surgery
  2. Major illness
  3. Neither

• “Cognitive trajectories did not differ”
Q: Is POCD transient or permanent?

A: Probably transient (3 - 6 months).
“But, my grand-dad has never been the same.”
The Detection of Cognitive Deficits

- Anesthesia/Surgery may unmask rather than cause cognitive dysfunction [Crosby]
- Permanent 
POCD might represent the normal trajectory of cognitive decay
POCD Risk Factors

- Age > 60
- Cardiac and hip surgery
- Less education
- Apoprotein ε4 allele et al.
- Prior stroke (even if no gross deficit)
- Preoperative cognitive impairment
- Alcohol abuse
- Post operative pain
- Delirium (inconsistent)
- Infection (Various sources)
“. . . . greater preoperative volumes of leukoaraiosis/lacunae were significantly contributed [sic] to postoperative executive* declines.”

* selective attention
The Detection of Cognitive Deficits

Permanent POCD might represent the normal trajectory of cognitive decay
Does anesthesia contribute to later dementia?
Mayo A.D. Registry subjects vs age and sex matched non-demented residents of Olmsted County (877 pairs)

- Medical records compared
- Anesthesia exposure (ca. 70%) and duration essentially identical
- “No significant association”
Is postoperative cognitive dysfunction a risk factor for dementia? A cohort follow-up study

J. Steinmetz¹*, V. Siersma³, L. V. Kessing², L. S. Rasmussen¹ and the ISPOCD Group

- POCD study patients 1994 - 2000; Avg. age – 67
  - Mental status at 1 wk and 3 mon
- Followed for 11 yrs (avg.)
- New onset dementia not different POCD vs non-POCD patients
Serial MRIs; atrophy and CD at 5-9 months but *not* later (!!)
Q: Is POCD transient or permanent?

A: Probably transient (3 - 6 months).
Is postoperative cognitive dysfunction a risk factor for dementia? A cohort follow-up study

J. Steinmetz\textsuperscript{1*}, V. Siersma\textsuperscript{3}, L. V. Kessing\textsuperscript{2}, L. S. Rasmussen\textsuperscript{1} and the ISPOCD Group

Br J Anaesth 110 (S1): i92–i97 (2013)

- IPSCOD 1 cohort (1988) followed for 11 years.

- Incidence of dementia \textbf{not different} between those who did and did not experience POCD.

REF
POCD Risk Factors

Should depth of anesthesia be on that list?

Q3: Does deeper anesthesia cause greater POCD?
What is the evidence that POCD is dose-related?

... and it should be if it is some form of toxicity.
Investigations of “Depth of Anesthesia” vs. POCD
(Six)
jdrummond@ucsd.edu
Dose - Response (POCD) Relationship

POCD

Dose / Concentration

Threshold ?
Depth of Anesthesia vs. POCD

Farag et al. (CCF), A&A 103: 633-40, 2006

- Patients (74) > 50 yrs
  - Elective spine, abd., pelvic surgery, 2-3 hrs
- Randomized: Low BIS (38.9) vs High BIS (50.7) (Target 50-60)
- Faster processing in low BIS group (p = 0.006)

Deeper anesthesia was associated with less POCD
Depth of anaesthesia and post-operative cognitive dysfunction

Steinmetz et al., Acta Anes Scand 54: 162–8, 2010

- 70 pts; > 60 yrs; non cardiac surgery
- Recorded CSI* (no anesthetic protocol)
- Cognitive tests before and at 7 days
- Pts with and w/o POCD had same average CSI and the same cumulative deep anesthesia time

* CSI = Cerebral State Index
Deeper Total Intravenous Anesthesia Reduced the Incidence of Early Postoperative Cognitive Dysfunction After Microvascular Decompression for Facial Spasm

Jianxiong An, MD,* Qiwu Fang, MD,† Changsheng Huang, MD,* Xiaoyan Qian, MB,†

J Neurosurg Anesthesiol 23: 12-17, 2011

- 40 pts / group; Propofol & remifentanil
- BIS 58 vs 38.5
- Neuropsych tests pre and day five
- Deeper group performed better

REF
Major head neck surgery (n=32)
Middle latency AEP guided vs standard care
MMSE*, Post Op Day 1 and 30
Less volatile agent
POCD difference at POD 1, but not POD 30

* Mini Mental Status Examination
Investigations of “Depth of Anesthesia” vs. POCD

(Six)

No difference in three.
Deeper was beneficial in two.
Deeper was harmful in one.
BIS-guided Anesthesia Decreases Postoperative Delirium and Cognitive Decline

Matthew T.V. Chan, MBBS, FANZCA,* Benny C.P. Cheng, MBBS, FHKCA,† Tatia M.C. Lee, PhD,‡ Tony Gin, MD, FRCA, FANZCA,* and the CODA Trial Group


- 921, non-cardiac surgery, avg. age 68
- BIS-guided (40-60) vs std. care
- Cog. function at 1 wk and 3 months
- Less propofol and volatile agent
- Avg. BIS: 53 vs 39
- POCD same at one week, less at 3 months
Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction

F. M. Radtke¹†, M. Franck¹†, J. Lendner¹, S. Krüger¹, K. D. Wernecke² and C. D. Spies¹*

- BIS-guided (575) vs BIS-blinded (580)
  - (no BIS target range)
- > 60 yrs; > 1 hr
- Average BIS: 39.0 vs 38.7
- But less burst-suppression and fewer episodes of very low BIS in BIS-guided group.
- POCD not different at days 7 (p = 0.06) and 90 (p = 0.37)

REF
What is the evidence that POCD is dose-related?

There is very little.
The Questions*

- Does “deep” anesthesia cause increased mortality?
- Do anesthetics cause Post Op Cognitive Dysfunction - transiently? - permanently?
- If yes, does deeper anesthesia cause greater POCD?
- Does deeper anesthesia increase the risk of delirium?

* in adults
Delirium vs POCD

**“Nutty”**

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| Misperception  
  (confusion) | |
| Memory impairment | |
| Inattention | |
| Fluctuating course | |
| Bedside diagnosis  
  (inattention and disorganized thinking) | |
Q4: Does deeper anesthesia increase the risk of delirium?

Three of four studies suggest, “Yes”
RCT, D/B; SAB + propofol sedation
mental status exam x 3 d; 57 pts/group

- BIS Approx. 50 vs. BIS ≥ 80

Delirium 40% 19%
Duration (days) 1.4 0.5

- Dose relationship suggests that anesthesia (propofol) is causing delirium
Sedation Depth During Spinal Anesthesia and the Development of Postoperative Delirium in Elderly Patients Undergoing Hip Fracture Repair


Frederick E. Sieber, MD; Khwaji J. Zakriya, MBBS; Allan Gottschalk, MD, PhD;

- BIS
  - Approx. 50 vs. BIS ≥ 80

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<td>Delirium (%)</td>
<td>40%</td>
<td>19%</td>
</tr>
<tr>
<td>Duration (days)</td>
<td>1.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Age</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Dementia* (%)</td>
<td>37</td>
<td>33</td>
</tr>
<tr>
<td>Independent (%)</td>
<td>56</td>
<td>74</td>
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*Preop MMSE
BIS-guided Anesthesia Decreases Postoperative Delirium and Cognitive Decline

Matthew T.V. Chan, MBBS, FANZCA,* Benny C.P. Cheng, MBBS, FHKCA,† Tatia M.C. Lee, PhD,‡ Tony Gin, MD, FRCA, FANZCA,* and the CODA Trial Group


- 921, avg. age 68, non-cardiac surgery
- BIS-guided (40-60) vs std care (53 vs 39)
- Less propofol and volatile agent
- Delirium assessed “in hospital”
- CAM (Confusion Assessment Method)
- Less delirium in BIS group: 16% vs 24%
Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction

BJA 110: 98-105, 2013

F. M. Radtke\textsuperscript{1†}, M. Franck\textsuperscript{1†}, J. Lendner\textsuperscript{1}, S. Krüger\textsuperscript{1}, K. D. Wernecke\textsuperscript{2} and C. D. Spies\textsuperscript{1*}

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  - (no BIS target range)
- > 60 yrs; > 1 hr
- Average BIS: 39.0 vs 38.7
- But less burst-suppression and fewer episodes of very low BIS in BIS-guided group.
- Delirium less in BIS group, 17\% vs 21\% (p = 0.036)
BIS monitored vs “ETAG” monitored
DOA (BIS) very similar in the two groups
Trend (ns) to less delirium in the BIS group

... details to follow in a few moments.
Four Studies of Depth vs Delirium

Three suggest that “deeper” anesthesia or sedation is associated with increased delirium.
Four Studies of Depth vs Delirium

Three suggest that “deeper” anesthesia or sedation is associated with increased delirium.

In the ICU, delirium is associated with increased mortality.

Is delirium the cause or a marker of increased propensity?
“Low average volatile anesthetic dose, intraoperative transfusion, ASA physical status, and [co-morbidity score] were identified as independent predictors of delirium . . . .

The association between low anesthetic concentration and delirium . . . . could reflect that patients with poor health are both more sensitive to the effects of volatile anesthetic drugs and are also more likely to develop postoperative delirium.”
Four Studies of Depth vs Delirium

Three suggest that “deeper” anesthesia or sedation is associated with increased delirium.

In the ICU, delirium is associated with increased mortality.

Is delirium the cause or a marker of increased propensity?

(Hazard to self, bed-bound, no physiotherapy)

? Monitor & limit depth of anesthesia in the at risk population.
Risk Factors for Delirium

- Age
- Preoperative cognitive impairment (refs)
- Psychiatric disorders
- Alcohol abuse
- Preoperative impairment of A.D.L.
- Low BMI (< 20)
- Indoor injury (hip #)
- Pre-operative waiting time (hip #)
- Fever
- Vascular surgery

(Various sources)
Preop cognitive dysfunction predicted post op delirium
Risk Factors for Delirium

- Age
- Preoperative cognitive impairment
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- Preoperative impairment of A.D.L.
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