Does Anesthetic Management Really Affect Long-Term Outcomes?

Terri G. Monk, M.D.
Professor
Department of Anesthesiology
Duke University Medical Center
Durham, NC
Research Support

- Anesthesia Patient Safety Foundation (APSF)
- I Heermann Anesthesia Foundation
- NIA K01 award
- Aspect Medical Systems
- Hospira Inc.
Lecture Topics

- Current evidence for association between perioperative anesthetic management and outcomes
  - Recovery from anesthesia
  - Postoperative awareness
  - Hypnotic “depth of anesthesia”

- Potential mechanisms for long-term influence of anesthesia on outcomes
Optimal Depth of Unconsciousness

Lighter Levels:
- Inadequate Anesthesia

Deeper Levels:
- Cardiovascular Effects
- Recovery Quality
- Increased Drug Use $
- Neurocognitive Dysfunction
- Mortality
Does the Use of a Brain Function Monitor Improve Outcome?

Do You Really Need a Brain Monitor?
Bispectral Index for Improving Anaesthetic Delivery and Postoperative Recovery: Cochrane Review

Objective: Does the incorporation of BIS into the standard practice of managing anaesthesia:

- Reduce consumption of anaesthetic agents
- Recovery time
- Incidence of recall awareness
- Total cost of anaesthesia management

Cochrane Review 2007: Issue 4
Bispectral Index for Improving Anaesthetic Delivery and Postoperative Recovery: Cochrane Review

**Methods:**

- All RCTs dealing with the use of BIS or clinical signs in the titration of anaesthetic agents
  - Adult patients ≥ 18 years
  - Any type of surgery under general anaesthesia
- Included only 20 studies
Bispectral Index for Improving Anaesthetic Delivery and Postoperative Recovery: Cochrane Review

**Conclusions:**

- Anaesthesia, guided by BIS, kept within the recommended range, could improve anesthetic delivery and postoperative recovery from relatively deep anesthesia.

- BIS-guided anaesthesia has a significant impact on reducing the incidence of intraoperative recall in surgical patients with *high risk of awareness*.

- Insufficient evidence to support the cost-benefit of BIS monitoring.
A man named Clay, who undergoes heart surgery while experiencing a phenomenon called "anesthetic awareness," leaving him awake but paralyzed throughout the operation.

“‘Awake’ will do to surgery what ‘Jaws’ did to swimming in the ocean.”
The “Experts”

Incidence: 1-2 per 1,000

“To prove that the BIS monitor can prevent awareness would require a study of over 40,000 patients …”

…. and will never be done

…. will ruin your research career
Bispectral Index Monitoring to Prevent Awareness during Anaesthesia: *The B-Aware Trial*

What if we target high-risk patients?

- C Section under GA
- High-risk cardiac
  - EF <30%; severe AS; pulmonary HTN; urgent surgery
- Hemodynamically unstable
  - trauma; blood loss; poor cardiac function
- Rigid bronchoscopy
- Other
  - PHx awareness, chronic drug therapy

*Incidence of Awareness: 1:100*

*Myles PS, et al. Lancet 2004*
And look for a big difference between groups ….

- **Not**: 0.2% to 0.1%

- **But**: 1% to 0.1%

⇒ sample size: 2300 patients

(12 cases vs. 1-2 cases)

80% power
Bispectral index monitoring to prevent awareness during anaesthesia: *the B-Aware Trial*


**Research Question:**

“*Does BIS monitoring prevent awareness in high-risk patients under general anesthesia?*”
B-Aware Trial: design

2500 high-risk pts

BIS  Routine Care

 Interviews (awareness)  

\{ 4 hrs  \
\{ 24 hrs  
\{ 30 days  

- Blinded assessors and blinded EAC
Time to Eye-Opening

Cumulative incidence

hazard ratio (HR) 1.19, P=0.004
adjusted HR* 1.20, P=0.004
13 Cases of Awareness

**Laparotomy:** Remembers going “half asleep”, then hearing shouting (“… do things faster… because things are crashing…”). He felt pain and was anxious, dizzy and breathless, and could not move.

**CABG:** Heard noises and voices during surgery; had severe pain of “people trying to tear my chest apart”.

**Lung Tx:** Heard conversations regarding the war in Afghanistan, recalling her disagreement with the views being put forward; unable to move or speak. Also remembers a suction tube being placed in her throat, which was uncomfortable, and someone saying “there are lots of secretions”.

**Whipple’s:** Heard the anesthesiologist say “the pressure is really low”, and the surgeon respond “can you do something about it”. Recalls movement and pain within the abdomen. Tried to, but could not move.
Bispectral index monitoring to prevent awareness during anaesthesia: *the B-Aware Trial*

*Myles PS, et al. Lancet 2004*

<table>
<thead>
<tr>
<th></th>
<th>BIS Group (n=1227)</th>
<th>Routine Care Group (n=1238)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed awareness</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>→ 5-fold reduction</td>
<td></td>
</tr>
<tr>
<td>RRR: 82% (95% CI: 17-98%), P = 0.022</td>
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</table>
Awareness Cases with BIS

Awareness at this time

Off-pump Coronary Artery Bypass Surgery

Rigid bronchoscopy & esophagoscopy
<table>
<thead>
<tr>
<th>Group</th>
<th>BIS Group (n=1227)</th>
<th>Routine Care (n=1238)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dreaming at 4 hrs</td>
<td>2.7%</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

P = 0.005
Grant Wood 1930
Art Institute of Chicago
Anesthesia Awareness and the Bispectral Index: B-Unaware Trial

- 2000 patients randomly assigned to:
  - BIS between 40-60 or
  - End-tidal anesthetic gas (ETAG) of 0.7 to 1.3 MAC

- Postoperative assessments for awareness
  - 24 hrs, 24-72 hrs, and 30 days postop

- Audible alarms set in each group

- Sign on anesthesia machine asking practitioners to “check the BIS value or end-tidal anesthetic gas (ETAG) concentration and to consider whether the patient might have intra-operative awareness”
  - Probable Hawthorne Effect – a temporary change in behavior in response to a change in environmental conditions

Most of Us Overdose Elderly

- Is the ETAG measurement appropriate?

- Gas monitors
  - Assume patient is 40 yrs old
  - Do not know what other drugs given
  - Do not know opioids & epidurals lower MAC
  - Underestimate brain concentration on emergence

- Mean age of patients in B-Unaware study was 59 ± 14 years

- Elderly patients were overdosed using MAC
Anesthesia Awareness and the Bispectral Index: B-Unaware Trial

- Two cases of definite awareness in each group
  - BIS > 60 in one case
  - ETAG concentration < 0.7 MAC in three cases
  - Episodes when BIS was not recording in BIS group

- Study did not show a lower incidence of anesthesia awareness using BIS monitoring
  - 2/1000 patients in each group

BIS Values and ETAG Concentrations over the Course of the Anesthesia in Patients with Definite Anesthesia Awareness in the BIS-Guided Group

Patient 3

Patient 4

Anesthesia Awareness and the Bispectral Index: *B-Unaware Trial*

- Letter’s to the editor
  - Inadequate sample size – study enrolled patients with a low risk of awareness
    - Would lead to reduction of events – only 4 in 2000 patients (compared to 13 in 2500 in the B-Aware trial with high-risk patients)
  - ETAG-protocol is not routine in clinical practice
  - Not possible to monitor for awareness during TIVA
  - A monitor will “not alter the anesthesia outcome unless the information derived from it is acted on”

Is Anesthesia Associated with One-Year Mortality?
Prospective Observational Trial

- Single-Center (USA)
  - 1064 adults undergoing GA for non-cardiac surgery
  - Demographic, hemodynamic, intraoperative factors analyzed for association with one-year mortality

- 1 Year Mortality Rate = 5.5%

- Cox Proportional Hazard Modeling
  - Evaluate categorical & continuous cofactors
  - Significant univariate predictors determined
  - Forward step-wise multivariate model
  - 95% Confidence Intervals via Bootstrapping

Monk et al. Anesth Analg 2005;100:4-10
Prospective longitudinal study evaluating the effect of patient characteristics, procedure and anesthetic variables on outcome was evaluated using multivariate modeling.

- Co-morbidity Scores, Demographics, Patient History
- Medications, Anesthetic Agents / Duration, Surgery Type
- Cumulative Deep Anesthesia Time (BIS < 45)
- Intraoperative Hemodynamics
# Independent Multivariante Predictors of One-Year Mortality

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Relative Risk [Bootstrapped 95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson Comorbidity Score (3+ vs 0-2)</td>
<td>16.116 [10.110 – 33.717]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cumulative Deep Hypnotic Time (BIS &lt; 45) (per hour)</td>
<td>1.244 [1.062-1.441]</td>
<td>0.0121</td>
</tr>
<tr>
<td>Hypotension SBP &lt; 80 mm Hg (per minute)</td>
<td>1.036 [1.006-1.066]</td>
<td>0.0125</td>
</tr>
</tbody>
</table>

*c-statistic: 0.847 [95%CI: 0.788-0.906, p < 0.001]*

Monk et al. Anesth Analg 2005;100:4-10
Mortality Within 2 Years After Surgery in Relation to Low Intraoperative Bispectral Index Values and Preexisting Malignant Disease

Maj-Lis Lindholm, PhD, RN*  
Stefan Träff, MD†  
Fredrik Granath, PhD‡  
Scott D. Greenwald, PhD§  
Anders Ekbom, MD, PhD†  
Claes Lennmarken, MD, PhD†  
Rolf H. Sandin, MD, PhD*  

BACKGROUND: A correlation between deep anesthesia (defined as time with Bispectral Index (BIS) <45; T_{BIS} <45) and death within 1 yr after surgery has previously been reported. In order to confirm or refute these findings, we evaluated T_{BIS} <45 as an independent risk factor for death within 1 and 2 yr after surgery and also the impact of malignancy, the predominant cause of death in the previous report.

METHODS: Mortality within 2 yr after surgery, causes of death and the occurrence of malignant disease at the time of surgery were identified in a cohort of 4057 BIS-monitored patients. Statistically significant univariate predictors of mortality were identified. In order to allow for comparison with previous data, the following multivariate analysis was first done without, and thereafter with, preexisting malignancy status, the predominant cause of death.

RESULTS: One-hundred-seventy-four (4.3%) patients died within 1 yr and another 92 during the second year (totaling 6.5% in 2 yr). T_{BIS} <45 was a significant predictor of 1- and 2-yr mortality when preexisting malignant disease was not among the co-variates (hazard ratio [HR] 1.13 [1.01-1.27] and 1.18 [1.08-1.29], respectively). Further exploration confirmed the significant relation between postoperative mortality and T_{BIS} <45 to patients with preexisting malignant diagnoses associated with extensive surgery and less favorable prognosis. The most powerful predictors of 2-yr mortality in the model, including preexisting malignancy, were ASA physical

Anesth Analg 2009; 108:508-12
Is Depth of Anesthesia Associated with One-Year Mortality?

- Multi-center Prospective Trial (Sweden)
  - 4087 General Anesthetics, Non-cardiac Surgery
  - Malignancy data from National Registry of Cancer

- 1 Year Mortality Rate = 4.3%

- 2 Year Mortality Rate = 6.5%

- Deep Anesthesia Time (BIS < 45):
  - Significant Independent Predictor Of Mortality
    - At both 1 years and 2 years

## Causes of Death in First 2 Years after Surgery

<table>
<thead>
<tr>
<th></th>
<th>Year 1 (n = 174)</th>
<th>Year 2 (n = 92)</th>
<th>Total (n = 266)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>130 (75%)</td>
<td>60 (65%)</td>
<td>71%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>30 (17%)</td>
<td>21 (11%)</td>
<td>19%</td>
</tr>
<tr>
<td>Organ Failure</td>
<td>8 (5%)</td>
<td>4 (4%)</td>
<td>5%</td>
</tr>
<tr>
<td>Homicide or Suicide</td>
<td>3</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>4</td>
<td>3%</td>
</tr>
</tbody>
</table>

Hazard Model of 2-Year Mortality

Accounting for Time-Varying Importance of Risk Factors

• Predictors of 2 year mortality without Cancer in the model
  • ASA Score Class IV   HR 11.5 (4.4 – 30.4)
  • Age > 80 years           HR 5.0 (3.1 – 8.2)
  • $T_{BIS} < 45$            HR 1.18 (1.1 – 1.3)

• When Cancer added to the model, there was no significant relationship between $TBIS < 45$ and mortality

<table>
<thead>
<tr>
<th>Cancer Status</th>
<th>RR per hour BIS &lt; 45</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1</td>
<td>Year 2</td>
</tr>
<tr>
<td>M0</td>
<td>0.78</td>
<td>0.93</td>
</tr>
<tr>
<td>M1</td>
<td>0.89</td>
<td>1.33</td>
</tr>
<tr>
<td>M2</td>
<td>1.09</td>
<td>1.20</td>
</tr>
<tr>
<td>Total</td>
<td>1.04</td>
<td>1.16</td>
</tr>
</tbody>
</table>

M0 = no history of pre-existing malignancy  
M1 = not M0 or M2  
M2 = malignancies with surgery time > 90 min and associated with ↓ life span

Mortality within 2 years of Surgery in Relation to Low BIS and Malignancy

Conclusions:

• Confirms statistical relationship between 1 year mortality and $T_{\text{BIS}} < 45$
• Extends this relationship to 2 years after surgery
• Most important associations between co-morbidity and death (ASA, age, pre-existing malignancy)
• The relationship between $T_{\text{BIS}} < 45$ and mortality may not be causal
• If there is a causal impact from $T_{\text{BIS}} < 45$, the effect is probably very weak

Presence of electroencephalogram burst suppression in sedated, critically ill patients is associated with increased mortality

Paula L. Watson, MD; Ayumi K. Shintani, MPH, PhD; Richard Tyson, MD; Pratik P. Pandharipande, MD, MScI; Brenda T. Pun, RN, MSN, ACNP; E. Wesley Ely, MD, MPH

Objectives: This study investigates the possibility of a relationship between oversedation and mortality in mechanically ventilated patients. The presence of burst suppression, a pattern of severely decreased brain wave activity on the electroencephalogram, may be unintentionally induced by heavy doses of sedatives. Burst suppression has never been studied as a potential risk factor for death in patients without a known neurologic disorder or injury.

Design: Post hoc analysis of a prospectively observational cohort study.

Setting: Medical intensive care units of a tertiary care, university-affiliated medical center in the eastern United States.

The main results are as follows: of the overall cohort demonstrating a high severity of illness (Acute Physiology and Chronic Health Evaluation II scores of 27.4 ± 9.7) and 99% receiving sedation. Of those with burst suppression, 29 of 49 (59%) died within 6 months compared with 26 of 76 (33%) who did not demonstrate burst suppression. Using time-dependent Cox regression to adjust for clinically important covariates (age, Charlson comorbidity score, baseline dementia, Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment, coma, and delirium), patients who experienced burst suppression were found to have a statistically signifi-
Burst Suppression in ICU is Associated with Increased Mortality at 6 Months

- **Objective:** To investigate the relationship between oversedation and mortality in mechanically ventilated patients in the ICU

- **Methods:** Post hoc analysis of 125 patients
  - Most common diagnosis – sepsis/pneumonia
  - Sedation not controlled – benzodiazepines ± propofol
  - Daily BIS monitoring

- **Results:**
  - Burst supression occurred in 39% of patients
  - Morality Rate in first 6 months
    - 59% (29 of 49 patients) with burst suppression
    - 33% (25 of patients) without burst suppression
    - Hazard’s ration = 2.04, CI = 1.12-3.70, p = 0.02

- **Conclusion:** The presence of burst supression was an independent predictor of increased death at 6 months

Watson et al. CCM 2008: 36:12
How could anesthesia management affect patient outcomes as long as one year after surgery?
Does Excessive Anesthetic Depth Affect Long-Term Outcomes?

↑ Sensitivity of brain to anesthetic effects in:

- Elderly
- Individuals with advanced cancer
Aging Brain loses neurons
Brain loses 10% of its weight by age 90 years

66 year old male

86 year old brain
Does Excessive Anesthetic Depth Affect Long-Term Outcomes?

- Brain of elders or those with advanced cancer may be more sensitive to anesthetics
- Excessive anesthesia predisposes patient to proximal complications
  - Postoperative delirium
  - Silent regurgitation
  - Postoperative pulmonary problems
Does Excessive Anesthetic Depth Affect Long-Term Outcomes?

- **Elderly brain is more sensitive to anesthetics**
  - Cancer may alter blood-brain barrier too
- **Excessive anesthesia predisposes patient to proximal complications**
  - Postoperative delirium
  - Silent regurgitation
  - Postop pulmonary problems
- **Inhalational anesthetics may be neurotoxic !!**
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.

Gray area represents clinical anesthesia doses

Eckenhoff. Anesthesiology 2004; 101:703
Hypothetical pathway by which isoflurane induces a vicious cycle of apoptosis and Aβ generation and aggregation

- Isoflurane
- Aβ aggregation
- Caspase Activation and Apoptosis
- BACE
- γ-secretase
- APP processing
- Aβ generation/accumulation
Anesthetic effects on elderly brain

Excessive anesthesia predisposes patient to proximal complications

- Postoperative delirium
- Silent regurgitation
- Postop pulmonary problems

Inhaled anesthetics may be neurotoxic

Altered inflammatory state
THE SECRET KILLER

The surprising link between inflammation and heart attacks, cancer, Alzheimer’s and other diseases

What you can do to fight it
How does Anesthesia and Surgery Affect the Inflammatory Response?

- Perioperative period has a heightened inflammatory state
  - ↑ release of pro-inflammatory cytokines
  - ↓ levels of anti-inflammatory cytokines
  - ↑ production of:
    - Arachidonic acid metabolites
    - Superoxide radicals

- Individual genetic profiles may predispose certain patients to an enhanced inflammatory response

Tomasdottir et al. Anesth Analg 2003;97:944
Perioperative Inflammation and Long-Term Risk: A Hypothetical Model

Meiler, Monk et al. APSF Newsletter: 2003; 18(3):33
Anesthetic Level & Inflammation

- 100 orthopedic patients
  - Randomized to: Standard Practice (SP) or BIS-guided care (50-60)

- Anesthesia Time: 2.0 hr

- BIS-guided patients:
  - used less sevoflurane (End-tidal: 1.3% vs 1.85%)
  - Significantly less time BIS<45 (18% vs 57 % of case)

- Inflammatory marker (hsCRP) increased in SP group for first 2 days.

Kerssens et al. Anesthesiology 2007; 107: A1860
“Anesthetic management, directly or indirectly, may contribute to the biology of remote adverse events”

“Practicing anesthesiologists may be able to influence long-term outcomes by adjusting anesthetic and adjuvant regimens”

“If anesthesiologists can cause even a small improvement in long-term outcome (one-year), thousands of lives could be saved each year.”

Multicenter randomized prospective trials are needed to determine the impact of anesthesia on long-term outcomes.