Monitoring of the Brain during Anaesthesia:
current status of the field

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STOP
Anesthesia Awareness

1 CASE IS 1 TOO MANY
Intraoperative awareness
(explicit memory formation, conscious recall)

...my awareness during surgery has dramatically changed my whole life. Not a minute goes by that I don't remember the horror of my surgery. In many respects my life has been a nightmare since my surgery.
Determining if awareness has occurred: the structured Brice interview

1. What is the last thing you remember before going to sleep?
2. What is the first thing you remember waking up?
3. Do you remember anything between going to sleep and waking up?
4. Did you dream during your procedure?
5. What was the worst thing about your operation?
Intraoperative awareness: incidence in modern anesthesia practice

- 11785 patients, general anaesthesia
  Interviewed 3 times:
  before they left the post-anaesthesia care unit
  1-3 days after the operation and 7-14 days after the operation.
- 18 cases of awareness
  one case of inadvertent muscle blockade occurred before unconsciousness.
- **Incidence of awareness:**
  - 0.18% in cases in with neuromuscular blocking drugs
  - 0.10% in the absence of such drugs.
- 17 cases of awareness were identified at the final interview
- no more than 11 would have been detected if an interview had been done only when the patients left the post-anaesthesia care unit.
ELECTROENCEPHALOGRAPHICALLY CONTROLLED ANESTHESIA IN ABDOMINAL SURGERY

CHARLES W. MAYO, M.D.
REGINALD G. BICKFORD, M.B.
and
ALBERT FAULCONER Jr., M.D.
Rochester, Minn.

JAMA, 1950, 144;13:1082-83
Aspect A-1000 – the first BIS monitor...
Spectral Analysis
(Fast Fourier Transform)
Aspect/Covidien BIS monitor...
some competitors....
BIS tracks anesthetic concentration of GABA-ergic anaesthetics

Bouillon TW et al, Anesthesiology, 2004)
BIS trend (one hour anesthetic)
BIS-monitoring: evidence-based or confidence-based?
Reduction in the incidence of awareness using BIS monitoring

A. Ekman¹, M-L. Lindholm¹, C. Lennmarken² and R. Sandin¹
¹Department of Anaesthesia and Intensive Care, Regional hospital, Kalmar, and The Karolinska Institute, Stockholm, and ²Department of Anaesthesia and Intensive Care, University Hospital, Linköping, Sweden

• prospective cohort of 4945 consecutive surgical patients monitored with BIS (target: 40-60)
• interviewed for ER on three occasions.
• compared with a historical group of 7826 similar cases
• Explicit Recall:
  • 2 patients (0.04%) in the BIS-group
  • 14 patients (0.18%) in the control group (P<0.038)
Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial

P S Myles, K Leslie, J McNeil, A Forbes, M T V Chan, for the B-Aware trial group*


• Question: does BIS monitoring prevent awareness in high-risk patients under general anaesthesia?

• High risk:
  • cesarean section, high-risk cardiac surgery, trauma surgery, rigid bronchoscopy

• Multicenter RCT: 20 sites around Australia, NZ and SE Asia

• Randomized 2500 patients over 2 years
Australasian ‘B-aware’ trial: Results

- Patients were assessed by a blinded observer for awareness:
  - at 2-6 h, 24-36 h, and 30 days after surgery.
- 1227 patients ‘BIS-guided’ and 1238 routine care results awareness:
  - 2 reports in the BIS"-guided group
  - 11 reports in the routine care group (p=0.022)
- BIS-guided anesthesia reduced the risk of awareness by 82% (approximate 95% CI, 17 - 98 percent).
- BIS monitoring was associated with decreased time to eye opening (P<0.01)
Anesthesia Awareness and the Bispectral Index

Michael S. Avidan, M.B., B.Ch., Lini Zhang, M.D., Beth A. Burnside, B.A., Kevin J. Finkel, M.D., Adam C. Searleman, B.S., Jacqueline A. Selvidge, B.S., Leif Saager, M.D., Michelle S. Turner, B.S., Srikar Rao, B.A., Michael Bottros, M.D., Charles Hantler, M.D., Eric Jacobsohn, M.B., Ch.B., and Alex S. Evers, M.D.
Anesthesia Awareness Monitor No Better Than Older Methods, Study says

Featured Article
Main Category: Pain / Anesthetics
Also Included In: Medical Devices
Article Date: 14 Mar 2008 - 1:00 PDT

New Technology No Better at Spotting 'Anesthesia Awareness'

Study comparing bispectral index monitoring to standard methods found little difference

By Amanda Gardner
Posted 3/12/08

WEDNESDAY, March 12 (HealthDay News) -- A much-touted technology designed to detect when patients are regaining consciousness while under anesthesia during surgery doesn't appear to work any better than standard methods.
Study design
Avidan et al., NEJM, March 13, 2008

• 2000 patients at high risk for awareness
• Randomized to:
  – BIS-guided protocol (BIS 40-60)
  – End-tidal anesthetic gas guided (0.7-1.3 MAC)
• Outcome: awareness (Brice interview 3x)
  – 0 - 24 h
  – 27 - 72 h
  – Day 30 post-surgery
Results
Avidan et al., NEJM, March 13, 2008

• BIS-guided: 967 patients, ETAG guided: 974
• 2 cases of definite anesthesia awareness occurred in each group
  – (absolute difference, 0%; 95% [CI], −0.56 to 0.57%).
• The BIS value was > 60 in one case of definite anesthesia awareness, and the ETAG concentrations were < 0.7 MAC in 3 cases
• mean time-averaged ETAG concentration:
  – 0.81 ± 0.25 MAC in the BIS group
  – 0.82 ± 0.23 MAC in the ETAG group
Conclusions
Avidan et al., NEJM, March 13, 2008

• Anesthesia awareness can not predictably be prevented with BIS monitoring
• BIS was not shown to be superior to a protocol based on ETAG concentrations for preventing anesthesia awareness.
• Reliance on BIS technology may provide patients and health care practitioners with a false sense of security about the reduction in the risk of anesthesia awareness.
‘definite awareness’, BIS-guided (n=2)
Avidan et al., NEJM, March 13, 2008
Aspect Medical Systems, Inc. (Public, NASDAQ:ASPM) - Add to Portfolio - Discuss ASPM

6.11 Open: 6.21 Mkt Cap: 104.13M P/E: 60.83 Dividend: N/A
High: 6.24 52Wk High: 17.58 F P/E: N/A Yield: N/A
Low: 5.97 52Wk Low: 4.86 Beta: 2.89 Shares: 17.04M
Mar 18 - Close Vol: 0.00 Avg Vol: 335,000.00 EPS: 0.10 Inst. Own: 95%

After Hours: 6.11 0.00 (0.00%) - Mar 18, 4:45PM ET

Zoom: 1d 5d 1m 3m 6m YTD 1y 5y 10y Max

Mar 12 - Mar 18, 2008: -4.71 (-43.53%)
Prevention of Intraoperative Awareness in a High-Risk Surgical Population

BAG-recall Methods

- **Multicenter RCT** (St. Louis, MO, Ann Arbor, MI, Winnipeg, MB):
  - 6041 patients at high risk for awareness
  - BIS-guided (60 - 40) vs. etAG-guided (0.7 -1.3 MAC)
  - assessment of awareness @ 24 -72 h and 30 days
BAG-recall Results

Definite awareness (9 in total):

• etAG: 2/2861 (0.07 %)

• BIS: 7/2852 (0.24 %), p=0.98
Michigan Awareness Trial

- single center, 3 locations
- ‘unselected’ patients (not high-risk)
- blinded assessed for awareness (Brice):
  - at 2-6 h, 24-36 h, and 30 days after surgery.
- 18,836 patients in randomized in total
- ‘definite’ awareness (post-hoc analyses):
  - ‘no intervention’ group: 0.15% (5/3384)
  - anesthetic concentration group: 0.12% (11/9376)
  - BIS-guided group: 0.05% (3/6076)
- BIS monitoring was not associated with decreased time to eye opening or less PONV

Mashour GA et al., Anesthesiology 2012
Michigan Awareness Trial

Fig. 3. Secondary outcomes of definite or possible awareness in *post hoc* groups.

Mashour GA et al., *Anesthesiology* 2012
RCTs on the effect of BIS monitoring on the incidence of intraoperative awareness

<table>
<thead>
<tr>
<th>RCT</th>
<th>author</th>
<th>year</th>
<th>BIS</th>
<th>control</th>
<th>Total n</th>
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<tbody>
<tr>
<td>B-aware (multicenter)</td>
<td>Myles et al.</td>
<td>2004</td>
<td>2</td>
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<td>B-unaware (monocenter)</td>
<td>Avidan et al.</td>
<td>2008</td>
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<td>2</td>
<td>1941</td>
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<td>BAG-recall (multicenter)</td>
<td>Avidan et al.</td>
<td>2011</td>
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<td>2</td>
<td>5713</td>
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<td>Michigan Awareness Study</td>
<td>Mashour et al.</td>
<td>2012</td>
<td>11</td>
<td>8</td>
<td>18836</td>
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<tr>
<td>Zhang (TIVA Only)</td>
<td>Zhang et al.</td>
<td>2011</td>
<td>4</td>
<td>15</td>
<td>5228</td>
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<tr>
<td>total</td>
<td></td>
<td></td>
<td>26</td>
<td>38</td>
<td>10119</td>
</tr>
</tbody>
</table>
“My brain? That’s my second favourite organ.”
‘Deep Anaesthesia’ is Bad for the Brain – Deep Anaesthesia Kills

Are we creating a new scare?
The Hidden Dangers of Going Under

Anesthesia may have lingering side effects on the brain, even years after an operation

By Carina Storrs | Mar 18, 2014

Two and a half years ago Susan Baker spent three hours under general anesthesia as surgeons fused several vertebrae in her spine. Everything went smoothly, and for the first six hours after her operation, Baker, then an 81-year-old professor at the Johns Hopkins Bloomberg School of Public Health, was recovering well. That night, however, she hallucinated a fire raging through the hospital toward her room. Petrified, she repeatedly buzzed the nurses’ station, pleading for help. The next day she was back to her usual self. “It was the most terrifying
These associations suggest that intraoperative anesthetic management may affect outcomes over longer time periods than previously appreciated...

**Anesthetic Management and One-Year Mortality After Noncardiac Surgery**

Terri G. Monk, MD, MS*, Vikas Saini, MD, FACC†, B. Craig Weldon, MD*, and Jeffrey C. Sigl, PhD‡

*Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, †The Cardiovascular Specialists LLC, Hyannis, Massachusetts, ‡Aspect Medical Systems, Newton, Massachusetts

**Independent predictors of 1 yr mortality (5.5%):**

- **Patient comorbidity** RR = 16.1 (P < 0.001)
- ‘**Cumulative deep hypnotic time**’ (BIS < 45): RR = 1.24/h (P=0.0121)
- **Intraoperative systolic hypotension:** RR = 1.036/min (P=0.0125)

“These associations suggest that intraoperative anesthetic management may affect outcomes over longer time periods than previously appreciated…”
<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>30</td>
<td>51.7</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>10</td>
<td>17.2</td>
</tr>
<tr>
<td>Renal/liver failure</td>
<td>3</td>
<td>5.2</td>
</tr>
<tr>
<td>Multiple organ failure</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Acquired immunodeficiency syndrome</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Aspiration</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Pulmonary emboli</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Sepsis/infection</td>
<td>1</td>
<td>1.7</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>12.1</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Values are n (%).
Risk of Death Associated with Hours with BIS < 45 with Respect to Cancer Status Before Surgery and Time Since Surgery

<table>
<thead>
<tr>
<th>Cancer status</th>
<th>Year 1 (95% CI)</th>
<th>Year 2 (95% CI)</th>
<th>Total (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>0.78 (0.56–1.07)</td>
<td>0.93 (0.66–1.30)</td>
<td>0.84 (0.64–1.09)</td>
</tr>
<tr>
<td>M1</td>
<td>0.89 (0.60–1.31)</td>
<td>1.33 (0.94–1.89)</td>
<td>1.07 (0.79–1.47)</td>
</tr>
<tr>
<td>M2</td>
<td>1.09 (0.97–1.22)</td>
<td>1.20 (1.05–1.37)</td>
<td>1.12 (1.02–1.24)</td>
</tr>
<tr>
<td>Total</td>
<td>1.04 (0.92–1.16)</td>
<td>1.16 (1.02–1.32)</td>
<td>1.08 (0.99–1.18)</td>
</tr>
<tr>
<td>cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>advanced</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative risk per hour with BIS less than 45 (95% Confidence intervals), adjusted for all variables presented in Table 2.

BIS = Bispectral Index; CI = confidence interval.

secondary analysis of the B-Aware Trial (Lancet, 2004)
median follow-up time 4.1 years
548 patients (22.2%) had died since surgery
  • 220 patients (8.9%) had an MI
  • 115 patients (4.7%) had a stroke
hazard ratio for death in patients who recorded BIS values < 40 for 5 min was 1.41 compared with other BIS-monitored patients (95% CI: 1.02–1.95; P 0.039)
We found an association between cumulative duration of low BIS and mortality in cardiac surgery. This association was independent of both volatile anesthetic concentration and duration of anesthesia. This suggests intermediate-term mortality after cardiac surgery is not causally related to excessive anesthetic dose.
Concurrence of Intraoperative Hypotension, Low Minimum Alveolar Concentration, and Low Bispectral Index Is Associated with Postoperative Death


• Retrospective observational study (13,198 patients) from three clinical trials (B-Unaware, BAG-RECALL, Michigan Awareness Control Study)

• “triple low” state: intraoperative concurrence of:
  MAP <75 mmHg, MAC <0.8, BIS<45

• after propensity matching, cumulative duration of triple low was significantly associated with an increased risk of mortality at 30 days (hazard ratio, 1.09; 95% CI, 1.07 to 1.11, per 15 min)
Percent of the study population surviving up to 90 days after surgery.
Patients who experienced greater than 15 cumulative minutes of concurrently low MAP, MAC, and BIS values had decreased postoperative survival to 90 days.

TL = triple low.

(Anesthesiology 2015; 123:00-85)
are these associations causal, epiphenomena (markers of severity and poor prognosis) or coincidental?
‘Balanced’ trial

- prospective, randomized, double blind, parallel assessment, intention-to-treat, safety and efficacy study
- Patients will be monitored with BIS, randomised to BIS targets of either 50 or 35
- Inclusion criteria are: age $\geq 60$ years, moderate or high risk (ASA 3 or 4), surgery lasting $\geq 2$ hours, all general anaesthesia including with major regional block
- primary outcome: survival at one year after surgery
  - one year mortality is expected to be 10%.
  - sufficient power to detect 20% reduction $\Rightarrow 6500$ patients
Monitoring of the Brain during Anaesthesia: Take home messages:

- All processed EEG monitors (BIS, entropy) are able to ‘track’ brain concentrations of GABA_α agonists (propofol, volatile anesthetics).
- Conflicting evidence for reduction incidence of awareness in with BIS monitoring (both unselected and high-risk patients).
- ASA Practice Guideline (2005) still valid:
  - ...*EEG monitoring to prevent awareness is not ‘standard of care’: anesthesiologist decides indication*...
  - Intravenous anesthesia with NMB may be the exception.
- Insufficient evidence for harmful effect of ‘deep anesthesia’
  -Awaiting trials (BALANCED)