Depth of Anesthesia and Outcomes of Care

Mary Golinski PhD CRNA
2017
SDANA
? ~ Does ‘deep anesthesia’ result in morbidity/mortality or does poor health, anesthetic agent sensitivity, and other variables (i.e. hypotension) lead to poor outcomes?
Understanding ‘Relative Anesthetic Overdose’

- MOA of drugs, pharmacokinetic profile – mostly known
  - Dose requirements vary person to person
  - Based on population estimates - preventing movement, recall, instability
- Make a typical estimate (mg/kg) ~ how much to give
  - Appropriate for ‘90%’
- Adjusting for several demographic variables
  - Not possible to predict exact dose requirements
    - Appropriate for one person, excessive for another
      - ? sensitivity
- RAO - dose of anesthetic that is appropriate for most results in excessively deep for others
  - OR even same person and different situations, doses vary
Assessing ‘depth’

Historically and Currently

- Autonomic signs
- Hypertension
- Tachycardia
- Tearing
- Sweating

PRST Score
Autonomic Nervous System Index of Consciousness

- Blood Pressure
- Heart Rate
- Sweating
- Secretion of Tears
Defining ‘depth of’ and ‘light anesthesia’

- In the absence of EEG
  - Depth is based on
    - Clinical signs
    - Hemodynamic responses
    - End tidal inhalation agent
    - **Effect site concentration of IV agents**

- Light anesthesia based on -
  - Traditional signs and if using BIS: 50-60
With effect-site targeting the goal is to achieve a user-defined target effect-site concentration as rapidly as possible, by manipulating the plasma concentration around the target.

The systems contain microprocessors, programmed with an adult pharmacokinetic model, to calculate and implement the required infusion rates and to monitor the driving motor to calculate the volume of drug actually being administered and to perform a simple calculation of the estimated plasma concentration from this.
The surface electroencephalogram (EEG) for determining depth

- A complex physiologic signal is a waveform that represents the sum of all brain activity produced by the cerebral cortex.

- The normal waveform is notable for two characteristics:
  - Small amplitude (20-200 microvolts)
  - Variable frequency (0-50 Hz)
EEG changes in response to

- the effects of anesthetic and sedative/hypnotic agents

Individual drugs can induce some unique effects on the EEG, the overall pattern of change is quite similar for many of these agents.

During general anesthesia, typical EEG changes include:
- An increase in average amplitude (power)
- A decrease in average frequency
General pattern of EEG changes observed during increasing doses of anesthesia

As anesthetic effect increases, EEG frequency typically slows resulting in transition through frequency-based classes: Beta -> Alpha -> Theta -> Delta.
Bispectral index – a processed EEG parameter with extensive validation and demonstrated clinical utility

Derived utilizing a composite of measures from EEG signal processing techniques
- bispectral analysis
- power spectral analysis
- and time domain analysis

3 measures combine via an algorithm to optimize the correlation between the EEG and the clinical effects of anesthesia, and quantified using the BIS Index range
- Monitoring the ‘hypnotic component of anesthesia’
  - Generation of dimensionless numeric on a continuous scale
  - Device specific
  - Example:
    - 0 = electrocortical silence
    - 100 = normal cortical activity
'Although no technology including pulse oximetry, has definitively shown to reduce mortality, it has been suggested that ‘monitoring of depth’ of anesthesia **should** allow exact dosage of anesthetic drugs and therefore reduce cardiovascular side effects caused by an overdosage.'
What is a depth monitor really telling us?

- Depth monitors: Inconsistent use and Controversial Utility
  - Represents an **optimal** level of general anesthesia and using algorithms, assessing depth
  - We know standard doses for the majority; we know when to give more, hemodynamic stabilizers, decrease doses....

- **For those sensitive - are we risking ‘over-dosage?’**
  - Depth monitor metric doesn’t identify ‘sensitivity’

- Remember GA {state of unconsciousness}
  - 3 components:
    - analgesia (pain relief)
    - amnesia (loss of memory)
    - immobilization
A Very Cerebral Question – How do we know WHO is sensitive?

WHO are the ‘sensitive’ ones?

Intraoperative awareness risk, anesthetic sensitivity, and anesthetic management for patients with natural red hair: a matched cohort study

Le risque d’éveil peropératoire, la sensibilité aux anesthésiques et la gestion anesthésique chez les patients naturellement roux: une étude de cohorte appariée

Stephen C. Gradwohl, MD · Amrita Aranake, MD · Arbi Ben Abdallah, PhD · Paul McNair, BS · Nan Lin, PhD · Bradley A. Fritz, BS · Alex Villafranca, MS · David Glick, MD · Eric Jacobsen, MBChB · George A. Mashour, MD, PhD · Michael S. Avidan, MBChB

Received: 29 May 2014/ Accepted: 16 December 2014/Published online: 14 February 2015
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RESULTS:

- The relationship between pharmacokinetically stable volatile anesthetic concentrations and bispectral index values differed significantly between red-haired patients and controls (P < 0.001), but without clinical implications.

CONCLUSION:

- There were no demonstrable differences between red-haired patients and controls in response to anesthetic and analgesic agents or in recovery parameters. These findings suggest that peri operative anesthetic and analgesic management should not be altered based on self-reported red-hair phenotype.
Impact of right-handedness on anaesthetic sensitivity, intra-operative awareness and postoperative mortality


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Summary
Anatomical, neurological and behavioural research has suggested differences between the brains of right- and non-right-handed individuals, including differences in brain structure, electroencephalogram patterns, explicit memory and sleep architecture. Some studies have also found decreased longevity in left-handed individuals. We therefore aimed to determine whether handedness independently affects the relationship between volatile anaesthetic concentration and the bispectral index, the incidence of definite or possible intra-operative awareness with explicit recall, or postoperative mortality. We studied 5585 patients in this secondary analysis of data collected in a multicentre clinical trial. There were 4992 (89.4%) right-handed and 593 (10.6%) non-right-handed patients. Handedness was not associated with (a) an alteration in anaesthetic sensitivity in terms of the relationship between the bispectral index and volatile anaesthetic concentration (estimated effect on the regression relationship –0.52 parallel shift; 95% CI –1.37 to 0.23; p = 0.17); (b) the incidence of intra-operative awareness with 26/4992 (0.52%) right-handed vs 1/593 (0.17%) non-right-handed (difference = 0.35%; 95% CI –0.45 to 0.63%; p = 0.35); or (c) postoperative mortality rates (90-day relative risk for non-right-handedness 1.19, 95% CI 0.76–1.86; p = 0.45). Thus, no change in anaesthetic management is indicated for non-right-handed patients.
Extremes of age = sensitivity?

- Drugs most common cause of orthostatic hypotension, either by volume depletion or vasodilation
- Elderly are susceptible
  - Reduced baroreceptor sensitivity
  - Decreased cerebral blood flow
  - Renal sodium wasting
  - Impaired thirst mechanism
Trying to answer the question...

- Volatile agents interact with ion channels, receptors, various structures within brain and our nervous system.

- The same in each of us?
  - Red hair
  - Left handed
  - Elderly
  - Very young
Where information is lacking

- Our drugs – exert effects
  - Reducing a ‘dose’ ~ often a judgment call based on numerous things
    - Procedure, co morbidities, history, physiologic response, other
  - HOWEVER – no direct monitor to measure (the magnitude of) DRUG EFFECTS ON BRAIN FUNCTION

- Think about this: Could poor outcomes be related to drugs destroying brain function?
What are we left with?

- Non consensus – what is the gold standard for the measurement of optimal depth?
  - HOW MUCH IS enough AND for WHO?

- Depth of anesthesia monitors use **clinical endpoints** as ‘effectiveness measures’

- Monitor on – numeric identified – was there……
  - loss of consciousness, lack of memory, lack of awareness, recovery to consciousness?
  - Answer ‘YES’ = everything must be good, right?
More About – THE EEG
EEG, monitors brain activity:
- directly OR through the skull

Used:
- to help diagnose certain seizure disorders, brain tumors, brain damage from head injuries, inflammation of the brain and/or spinal cord, alcoholism, certain psychiatric disorders, and metabolic and degenerative disorders that affect the brain

EEGs are also used to evaluate sleep disorders, monitor brain activity when a patient has been fully anesthetized or loses consciousness, and confirm brain death.
Electroencephalography (EEG)

- IS THE summation and recording of postsynaptic potentials from the pyramidal cells of the cerebral cortex
  - Typically classified by frequency
- Can be recorded off the scalp and forehead using surface and needle electrodes. EEG can take the following forms:
  - 1. Raw EEG
  - 2. Computer processed EEG
  - 3. Bispectral Analysis (BIS)
Burst-suppression (BS) is an electroencephalography (EEG) pattern consisting of alternative periods of slow waves of high amplitude (the burst) and periods of so-called flat EEG (the suppression) (Swank & Watson, 1949).

Generally associated with:
- comatose states of various etiologies:
  - hypoxia, drug-related intoxication,
  - hypothermia AND
- childhood encephalopathies
- but also anesthesia
Depth monitors

- Raw EEG data are obtained through one of several specially designed BIS™ sensors placed on the forehead.
- Sensor non-invasively collects the raw EEG data that indicates the multifaceted electrical activity of the brain in real time.
- The scientifically validated BIS algorithm then filters, analyzes and correlates this data, quantifying only the change in the bispectrum and other EEG features that apply to the individual’s current clinical state.
- The results are continually consolidated and displayed as the clinically validated BIS Index, a number between 0 and 100 that indicate the patient’s response to anesthetic agents.
The Clinical ‘ART’ of Anesthesia

- requires keen awareness and observation and even ‘calibration’ of surgical stimuli and responses (verbal responses, movement, tachycardia) against the dose and concentration of anesthetic drugs used to reduce the probability of response, constantly adjusting the administered dose to achieve the desired anesthetic depth!

- And MINIMIZE poor outcomes related to depth of anesthesia! AND/OR over dosage
Soooo...........what do the current trials report?

- Does deep anesthesia cause poor outcomes? Does depth of anesthesia monitoring / EEG improve outcomes? Because we lighten up when evidence suggests deep? Or is a high acuity patient overly sensitive?

What comes first? The chicken or the egg?
Current monitoring modalities available for depth information
All published studies used the bispectral index monitor to measure anesthetic depth.

- Majority of published observational studies were post hoc analyses of studies undertaken for other purposes.
  - Most of these studies report a statistically significant association between deep general anesthesia BIS 45 and death.
  - Some suggest association between deep GA and MI or postoperative cognitive decline.
The combination of low BIS values and low delivered anesthetic concentrations (thus defining increased anesthetic sensitivity) may identify patients at particularly high risk.

3 RCTs:
- 1 reports worse outcomes in the BIS = 50 group compared with BIS = 80.
- 2 report no difference in mortality between BIS = 35 AND BIS = 50/55.
Anesthetic management and one-year mortality after non cardiac surgery

Table 2. Univariate Predictors of 1-yr Postoperative Mortality

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Relative risk (odds ratio) [95% CI]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidity (3+ versus 0–2)</td>
<td>13.901 (7.722–25.027)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASA physical status (Class 3, 4 versus Class 1)</td>
<td>8.300 (2.099–34.289)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Age (65+ versus 18–39 yr)</td>
<td>4.459 (2.032–9.784)</td>
<td>0.0002</td>
</tr>
<tr>
<td>History of hepatic disease</td>
<td>3.591 (1.764–7.310)</td>
<td>0.0004</td>
</tr>
<tr>
<td>History of previous myocardial infarction</td>
<td>3.529 (1.733–7.183)</td>
<td>0.0005</td>
</tr>
<tr>
<td>History of heart disease</td>
<td>2.174 (1.128–4.192)</td>
<td>0.0204</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.944 (1.162–3.254)</td>
<td>0.0114</td>
</tr>
<tr>
<td>Cumulative deep hypnotic time (per h)</td>
<td>1.335 (1.132–1.574)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Surgical duration (per h)</td>
<td>1.218 (1.056–1.405)</td>
<td>0.0067</td>
</tr>
<tr>
<td>Intraoperative systolic blood pressure &lt;80 mm Hg (per min)</td>
<td>1.044 (1.016–1.072)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.968 (0.937–1.000)</td>
<td>0.0494</td>
</tr>
<tr>
<td>Preoperative diastolic blood pressure</td>
<td>0.963 (0.942–0.985)</td>
<td>0.0010</td>
</tr>
<tr>
<td>Educational level (yr)</td>
<td>0.878 (0.794–0.972)</td>
<td>0.0118</td>
</tr>
<tr>
<td>Preoperative Mini-Mental State Examination (per unit)</td>
<td>0.829 (0.700–0.982)</td>
<td>0.0298</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimally invasive or superficial versus intracavitary</td>
<td>0.308 (0.123–0.774)</td>
<td>0.0123</td>
</tr>
<tr>
<td>Orthopedic versus intracavitary</td>
<td>0.217 (0.086–0.545)</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

CI = confidence interval.
Multivariate Predictors of 1 year Mortality

Assessed entire study population

- Found 3 significant INDEPENDENT predictors of 1 year mortality
  - Charleston Comorbidity Score 3+ \( p < 0.0001 \)
  - Cumulative deep hypnotic time per hour \( p < 0.0121 \)
  - Systolic Blood Pressure < 80 mmHg (per min) \( p < 0.0125 \)
Dexamethasone, light anaesthesia, and tight glucose control (DeLiT) randomized controlled trial.


BACKGROUND:
- The inflammatory response to surgical tissue injury is associated with perioperative morbidity and mortality. We tested the primary hypotheses that major perioperative morbidity is reduced by three potential anti-inflammatory interventions: (i) low-dose dexamethasone, (ii) intensive intraoperative glucose control, and (iii) lighter anaesthesia.

METHODS:
- We enrolled patients having major non-cardiac surgery who were ≥40 yr old and had an ASA physical status ≤IV. In a three-way factorial design, patients were randomized to perioperative i.v. dexamethasone (a total of 14 mg tapered over 3 days) vs placebo, intensive vs conventional glucose control 80-110 vs 180-200 mg dl(-1), and lighter vs deeper anaesthesia (bispectral index target of 55 vs 35). The primary outcome was a collapsed composite of 15 major complications and 30 day mortality. Plasma high-sensitivity (hs) C-reactive protein (CRP) concentration was measured before operation and on the first and second postoperative days.
RESULTS:

- The overall incidence of the primary outcome was about 20%. The trial was stopped after the second interim analysis with 381 patients, at which all three interventions crossed the futility boundary for the primary outcome. No three-way ($P=0.70$) or two-way (all $P>0.52$) interactions among the interventions were found. There was a significantly smaller increase in hsCRP in patients given dexamethasone than placebo [maximum 108 (64) vs 155 (69) mg litre$^{-1}$, $P<0.001$], but none of the other two interventions differentially influenced the hsCRP response to surgery.

CONCLUSIONS:

- Among our three interventions, dexamethasone alone reduced inflammation. However, no intervention reduced the risk of major morbidity or 1 yr mortality.
Consider this

- **Stopped for futility:**
  - Dexamethasone, light anaesthesia, and tight glucose control (DeLiT) randomized controlled trial.
    - *BrJ Anaesth* 2013;111:209-21
A few recent, large, well-publicized trials in critical care medicine have been stopped for futility. In the critical care setting, stopping for futility means that independent review committees have elected to stop the trial early – based on predetermined rules – since the likelihood of finding a treatment effect is low.
Long term relevance to patient outcome or ‘how is it that anesthesia can influence 1 year mortality?’

- **PRE CLINICAL** and Clinical trials
  - Anesthesia invokes inflammatory response
  - Increases deposition of Alzheimer proteins
  - Induces neuro-apoptosis (rat pups)
  - Causes prolonged cognitive dysfunction (emergence delirium, other)

- **Volatile or Intravenous?**
  - BOTH
  - Morphine – angiogenesis
  - Volatile – inhibit natural killer cell activity, cancer metastasis
  - Other – immune suppression, direct tissue toxicity
A holistic approach to anesthesia-induced neurotoxicity and its implications for future mechanistic studies.

Zanghi CN¹, Jevtic-Todorovic V².

Author information

Abstract
The year 2016 marked the 15th anniversary since anesthesia-induced developmental neurotoxicity and its resulting cognitive dysfunction were first described. Since that time, multiple scientific studies have supported these original findings and investigated possible mechanisms behind anesthesia-induced neurotoxicity. This paper reviews the existing mechanistic literature on anesthesia-induced neurotoxicity in the context of a holistic approach that emphasizes the importance of both neuronal and non-neuronal cells during early postnatal development. Sections are divided into key stages in early neural development; apoptosis, neurogenesis, migration, differentiation, synaptogenesis, gliogenesis, myelination and blood brain barrier/cerebrovasculature. In addition, the authors combine the established literature in the field of anesthesia-induced neurotoxicity with literature from other related scientific fields to speculate on the potential role of non-neuronal cells and to generate new future hypotheses for understanding anesthetic toxicity and its application to the practice of pediatric anesthesia.

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Indirect physiologic effects

- Discovered in human clinical trials/research
  - Increases in Alzheimer biomarkers
  - Indirect due to cardiovascular/neuronal depression causing tissue hypoperfusion, hypoxia
  - Pro-inflammatory cytokines

Cerebral Oximetry

- Association between low cerebral oxygenation during anesthesia and poor cognitive function, delayed discharge, other
- Loss of cerebral autoregulation
When administered as part of the anesthetic, does the pain relief offered promote cancer recurrence by a peripheral effect?
Less is Better?

Table I – Some Side Effects of Opiates

- Depression of respiration
- Itching
- Nausea and vomiting
- Constipation
- Urinary retention
- Chest wall rigidity
- Cough suppression
- Pupillary constriction
- GI/GU sphincter constriction
- Dysphoria
- Depression of stress response
- Cardiovascular effects
- Immune suppression
The Effect of BIS Monitoring on Long term Survival in the B Aware Trial

- The B Aware Trial Large multi center
  - Compared the incidence of awareness during anesthesia BIS v Routine care
  - Random allocation
  - 42% cardiac surgery
  - 43% propofol maintenance
  - Included high risk

- FINDINGS:
  - Of 2463 eligible and consenting patients, 1225 were assigned to the BIS group and 1238 to the routine care group. There were two reports of awareness in the BIS-guided group and 11 reports in the routine care group (p=0.022). BIS-guided anaesthesia reduced the risk of awareness by 82% (95% CI 17-98%).
Long term follow up and post hoc analysis of the B Aware Trial

- Using BIS = less drug
- Avoidance of low BP and organ toxicity - theorized
- Does this translate into reduction in M & M?
- Testing the hypothesis
  - Survival would be improved in those receiving BIS guided anesthesia over those undergoing routine care
- Supporting the hypothesis:
  - Monitoring with BIS and absence of BIS values <40 for > 5 minutes were associated with improved survival and reduced morbidity in patients enrolled in the B aware trial
CONCLUSION

- The use of light propofol sedation decreased the prevalence of postoperative delirium by 50% compared with deep sedation.
- Limiting depth of sedation during spinal anesthesia is a simple, safe, and cost-effective intervention for preventing postoperative delirium in elderly patients that could be widely and readily adopted.
“Postoperative cognitive dysfunction and delirium ~ does deep anesthesia cause both and both cause poor outcomes?"

RAO/Deep anesthesia = Cognitive Dysfunction or Delirium = M/M

Another area of needed research
Delirium - defined and described in the Diagnostic and Statistical Manual of Mental Disorders

The key characteristics: a change in mental status characterized by a reduced awareness of the environment and a disturbance in attention.

- May be accompanied by other, more florid, perceptual symptoms (hallucinations) or cognitive symptoms including disorientation or temporary memory dysfunction.

- May express hypoactive, hyperactive, or mixed psychomotor behaviors

- Severity may vary, can be graded, and may have prognostic value

By definition, although the disorder develops acutely, the condition will wax and wane during the course of a day. These symptoms are not exclusive to delirium. Patients who have baseline dementia, psychosis, or anxiety/depressive disorder may present diagnostic challenges.

Postoperative cognitive dysfunction (POCD) - more difficult to define.

Refers to deterioration in cognition temporally associated with surgery. While the diagnosis of delirium requires a detection of symptoms, the diagnosis of POCD requires preoperative neuropsychological testing (baseline) and a determination that defines how much of a decline is called cognitive dysfunction.

Spectrum of abilities referred to as cognition is diverse, including learning and memory, verbal abilities, perception, attention, executive functions, and abstract thinking. It is possible to have a decrement in one area without a deficit in another. Self-reporting of cognitive symptoms has been shown to correlate poorly with objective testing, so valid pre- and postoperative testing is essential to the diagnosis of POCD.
The original question remains: If actions are taken to avoid low processed EEG index values will there be improved outcomes?
The yet unsupported hypotheses

- Actions we take to correct hypotension or the actual ‘causes’ of hypotension treated - may improve outcomes

- Relative anesthetic overdose is detrimental and implies agents have a toxic and dose dependent effect on the brain and other vital organs
  - Supported by some
    - Youth, elderly, animals (pre clinical trials),
Brain dysfunction may result in relative anesthetic overdose (concentrations delivered usually on the basis of normal brain function) may be bad for abnormal BRAIN function!

Significant cerebral injury and disease typically exhibit low index values -- and independently of that -- equates to poor outcomes of care.
If any hypothesis is supported ~

The question is WHAT IS THE MECHANISM?

Planes of Anesthesia

- Planes are used to describe depth of anesthesia during the maintenance stage
- Plane 1: light
- Plane 2: medium
- Plane 3: deep
- Plane 4: too deep

<table>
<thead>
<tr>
<th></th>
<th>LIGHT</th>
<th>ADEQUATE/DEEP</th>
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<tbody>
<tr>
<td>Nystagmus present</td>
<td>No nystagmus</td>
<td></td>
</tr>
<tr>
<td>Eye position rostral</td>
<td>Central</td>
<td></td>
</tr>
<tr>
<td>Lacrimation, (tearing)</td>
<td>Less moist (eye should remain moist)</td>
<td></td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Muscle relaxation</td>
<td></td>
</tr>
<tr>
<td>Vocalization</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Movement</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Strong palpebral reflex</td>
<td>Reduced palpebral reflex</td>
<td></td>
</tr>
<tr>
<td>Frequent spontaneous blink</td>
<td>No or occasional spontaneous blink</td>
<td></td>
</tr>
<tr>
<td>Change in respiratory pattern, rate, and or depth indicates a change in plane and is considered by some to be the most reliable sign.</td>
<td></td>
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</tbody>
</table>
Is a lower dose of anesthetic better?

<table>
<thead>
<tr>
<th>Respiration</th>
<th>Eyeball Activity</th>
<th>PUPILS</th>
<th>Area of Swallowing</th>
<th>Area of Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No Pre-Anaesthetic Medication</td>
<td>Morphine</td>
<td>Morphine Alone</td>
</tr>
<tr>
<td>Stage 1</td>
<td></td>
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<tr>
<td>Stage 2</td>
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</table>
What should we be doing next?

- A Large Randomized Controlled Trial?

**MAIN TYPES OF STUDY DESIGN**

- Study Design
  - Observational
  - Experimental
  - Longitudinal
  - Cross-sectional
    - Retrospective Cohort
    - Prospective Cohort
    - Case-control
Noted pilot study

- Short et al
  - A pilot study for a prospective, randomized, double blind trial of the influence of anesthetic depth on long term outcome
  - Anesth Analg
    2014;118:981-6
Remember the purpose of a pilot

Reasons for conducting Pilot study

Main Reasons:

1. **Process**: This assesses the feasibility of the process that are key to the success of the main study.
2. **Resources**: This deals with assessing time & resource problems that can occur during the main study.
3. **Management**: This covers potential human & data management problems.
4. **Scientific**: This deals with the assessment of the response, effect & variance of the effect.

Pyramid of research designs:

- Meta Analyses / Expert Panel Reviews of Research Evidence
- Replicated RCTs or Quasi-Experimental Designs
- Single Randomized Control Trial (RCT)
- Single Quasi-Experiments
- Single Group Pre- to Post-test Designs

Pilot Studies | Case Studies | Observation
A pilot study for a prospective, randomized, double-blind trial of the influence of anesthetic depth on long-term outcome.

Short TG, Leslie K, Campbell D, Chan MT, Corcoran T, O'Loughlin E, Frampton C, Myles P.

Abstract

BACKGROUND: Deep general anesthesia has been associated with increased mortality in 5 observational studies. The association may be causal or an epiphenomenon due to increased anesthetic sensitivity in high-risk patients. We conducted a pilot study to assess the feasibility of performing a definitive randomized controlled trial. The aims of the study were to determine whether anesthetic depth targeting in a high-risk group was feasible and to document anesthetic doses and arterial blood pressures associated with "deep" and "light" general anesthesia.

METHODS: ASA physical status III and IV patients, aged ≥ 60 years, having surgery lasting ≥ 2 hours, with expected hospital stay ≥ 2 days, and receiving general anesthesia were randomly allocated to a Bispectral Index (BIS) or spectral entropy (SE) target of 35 ("low" group) or 50 ("high" group). The primary end point was mean BIS or SE. Secondary end points were postanesthesia care unit length of stay and pain scores, quality of recovery score, hospital length of stay, postoperative complications, and death. A composite end point of postoperative complications (pneumonia, myocardial infarction, stroke, pulmonary embolism, heart failure, and death) was determined at 1 year.

RESULTS: One hundred twenty-five patients were recruited. The mean of the median BIS/SE values for each patient during the maintenance phase of anesthesia in the low and high groups was significantly different: 39 vs 48 (mean difference 8 [95% confidence interval [CI] 95, 6 to 10], P < 0.001). There was also a significant difference in mean volatile anesthetic administration (minimum alveolar concentration): 0.98 vs 0.64 (mean difference 0.35 [CI 95, -0.44 to -0.26], P < 0.001) and target propofol concentrations: 4.0 vs 3.1 µg/mL (mean difference 0.8 [CI 95, -1.2 to -0.3], P = 0.004). Intraoperative mean arterial blood pressures were similar (85 vs 87 mm Hg; mean difference 2 [CI 95, -2 to 6], P = 0.86), and there were no differences in short-term recovery characteristics or hospital length of stay. There was a significant difference in the incidence of wound infection at 30 days (13% vs 3%; risk difference -10% [CI 95, -21 to -0.1], P = 0.04). At 1 year, the composite rates of complications in the low and high groups were 28% and 17% (risk difference -11 [CI 95, -25 to 4], P = 0.15) and mortality rates were 12% and 9%, respectively (risk difference -2 [CI 95, -14 to 9], P = 0.70).

CONCLUSIONS: This pilot study demonstrated that depth of anesthesia targeting with BIS or SE was achievable in a high-risk population with adequate separation of processed electroencephalogram monitor targets. The expected incidence of postoperative complications and mortality occurred. We conclude that a large, multicenter, randomized controlled trial is feasible.

PMID: 24781568 [PubMed - indexed for MEDLINE]
Rationale and Design of the Balanced Anesthesia Study: A Prospective Randomized Clinical Trial of 2 Levels of Anesthetic Depth on Patient Outcome After Major Surgery

SHORT ET AL. ANESTHESIA AND ANALGESIA

MAY 2015 EPUB AHEAD OF PRINT
Rationale and Design of the Balanced Anesthesia Study: A Prospective Randomized Clinical Trial of Two Levels of Anesthetic Depth on Patient Outcome After Major Surgery.

Short TG, Leslie K, Chan MT, Campbell D, Frampton C, Myles P.

Abstract

BACKGROUND: An association between relatively deep anesthesia, as guided by the bispectral index (BIS), and increased postoperative mortality has been demonstrated in 6 of 8 published observational studies, but association does not necessarily mean causality. Small clinical trials of anesthetic depth have demonstrated increased delirium and postoperative cognitive dysfunction in patients who were relatively deeply anesthetized, but have been inadequately powered to study mortality. A large-scale randomized study is required to determine whether causality exists.

METHODS: The primary hypothesis of our study is that "light" anesthesia, defined as a BIS target of 50, will reduce all-cause mortality within 1 year of surgery in comparison with "deep" anesthesia, defined as a BIS target of 35, in patients aged ≥60 years presenting for major surgery under general anesthesia. The trial is an international multicenter, randomized, parallel-group, double-blind (patients and investigators) prospective, intention-to-treat, safety and efficacy study. The relative reduction in mortality in the light anesthesia group is expected to be 20%, giving an absolute risk reduction from 10% to 8%. Power analysis using α = 0.049 and β = 0.2 indicates that 3250 patients are required in each group.

RESULTS: The study is underway, and 1325 patients have been recruited in 40 centers in 5 countries. It is anticipated that the study will be completed in 3 years.

CONCLUSIONS: This randomized controlled trial should definitively answer the question of whether titrating anesthetic depth makes a difference to patient outcome in a vulnerable patient group.

PMID: 25993386 [PubMed - in process]
We ARE asking the right question!

Thank you!

If you do not know how to ask the right question, you discover nothing.

(W. Edwards Deming)

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