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Update on Bispectral Index monitoring☆

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Since 1997, bispectral index (BIS; Aspect Medical Systems Inc., Natick, MA) has been in clinical practice and a wealth of experimental research has accumulated on its use. Originally, the device was approved only for monitoring hypnosis and has now received an indication for reducing the incidence of intraoperative awareness during anesthesia. Numerous studies have documented the ability of BIS to reduce intermediate outcomes such as hypnotic drug administration, extubation time, postoperative nausea and shortened recovery room discharge. Two recent large-scale outcome studies using BIS (one randomized controlled trial and one prospective, nonrandomized historical cohort study) identified an approximately 80% reduction in the incidence of recall after anesthesia. BIS provides clinicians with unique information that can be used to tailor hypnotic drug doses to individual patient requirements. BIS does not predict movement or hemodynamic response to stimulation, nor will it predict the exact moment consciousness returns. This review will also discuss other BIS applications including use in pediatrics, intensive care and for procedural sedation. Some limitations exist to the use of BIS and it is not useful for some individual hypnotic agents (ketamine, dexmedetomidine, nitrous oxide, xenon, opioids). BIS technology is moving out of the operating room and into diverse environments where conscious and deep sedation are provided. Anesthesiologists need to be actively involved in promoting patient safety and helping transition this technology into broader use.

Key words: bispectral index; awareness; recall; technology assessment; sedation.

The release of the bispectral index monitor (BIS, Aspect Medical Systems Inc., Natick, MA) in October 1996 provided anesthesiologists with a reliable brain function monitor that allowed hypnotic titration over the complete range of cortical activity. Numerous comments, editorials, reviews[1–3] and over 550 peer-reviewed publications on BIS have

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appeared over the last 9 years. In January 2004, BIS received an FDA approved indication for reducing the incidence of intraoperative awareness during general anesthesia (510(k), #K030267) Recently, two studies[4,5], prompted the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) to publish a *Sentinel Event Alert* (October 6, 2004) on patient awareness under anesthesia. The American Society of Anesthesiologists (ASA) has responded by convening the **Task Force on Intraoperative Awareness** and is attempting to develop a Practice Advisory on Brain Function Monitoring. Near the end of 2004, approximately 34% of all hospital operating rooms had a BIS monitor, 78% of teaching institutions utilized the monitor and it had a worldwide installation base of over 25 000 units. The purpose of this chapter is to provide some background on BIS and to discuss the clinical implications of recent outcome research and regulatory activity.

BACKGROUND

A link between the measured electrical activity of the cerebral cortex and electroencephalogram (EEG) was first suggested in 1937.[6] Dr Rampil has provided an excellent review and a detailed description of the various approaches to EEG signal processing, including BIS.[7] EEG derivatives such as the power spectral edge, median frequency, zero-crossing frequency, etc. have been extensively investigated and found generally insensitive, nonspecific, or dependent on specific drug combinations and were not monotonically related to drug effect or clinical response.[2,7] Other chapters in this volume discuss other EEG-based brain function monitors such as the Auditory Evoked Potential and Entropy.

Bispectral analysis is a statistical technique that allows study of phenomena with nonlinear character such as surf beats and wave breaking.[8] Bispectral analysis represents a different description of the EEG in that interfrequency phase relationships are measured, i.e. the bispectrum quantifies relationships among the underlying sinusoidal components of the EEG.[7,9] Several variables from the EEG time domain (burst suppression)[10] and frequency domain (power spectrum, bispectrum, beta ratio, SynchFastSlow) are combined into a single index of hypnotic level. The weight factors of the various subparameters were assigned in a multivariate model based on a prospectively collected database of EEG recordings matched to corresponding states of hypnosis and to hypnotic drug levels. The BIS algorithm uses a complex formula with advanced artifact rejection techniques to define a dimensionless BIS value from 0 (isoelectric EEG) to 100 (alert and oriented) that is relatively independent of hypnotic agent (Figure 1). BIS algorithm development has gone through a number of revisions (Table 1). The current version (v4.0 and 4.1) have been designed to use a four-lead proprietary sensor placed on the forehead (Figure 2) that has improved reliability in the sedative range with enhanced artifact recognition/rejection (Table 1). The monitor is available as a stand-alone product with digital signal processing cable (Figure 3) or as an add-on module for most comprehensive patient monitoring systems.

Awake, unpremedicated patients have BIS values at or above 93 (Figure 1). Loss of recall ($<$10%) occurs at BIS values of 75–80.[11] BIS correlates tightly with sedation scales such as the Observer's Assessment of Awareness and Sedation (OAA/S)[12] during midazolam[13], propofol[14,15] or multiple hypnotic agents[16–18] administration. In these studies, loss of response to mild prodding (transition OAA/S 2–1) was defined as loss of consciousness and correlated to BIS values between 68 and 75. BIS values of $\leq$60 have

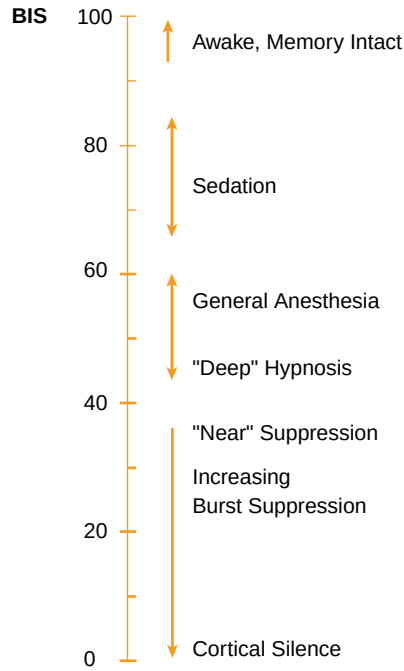

Figure 1. Bispectral index (BIS) scale. Dimensionless scale from 0 (complete cortical EEG suppression) to 100 (awake). BIS values between 65 and 85 have been recommended for sedation while values between 45 and 60 have been recommended for general anesthesia. Below BIS values of 40, cortical suppression becomes discernible in raw EEG as burst suppression pattern.

Table 1. Bispectral index algorithm development.

BIS version	Release date	Clinical endpoint	Comment
1.0	1992	MAC/hemodynamic	Agent-specific, modified by analgesic dose
2.0	1994	Hypnosis/awareness	Reformulation of index, agent-independent
2.5	1995		'Awake' artifact recognition/removal
3.0	1995[a]		Sedation performance enhanced
3.1	1996		EEG burst suppression detection enhanced
3.2	1997		EMG and 'near' suppression handling improved
3.3	1998		EMG detection/removal improved
3.4	1999		15 seconds smoothing, less susceptable to 'arousal delta' patterns on emergence
4.0 (XP)	2001		Resistant to electrocautery, improved performance in sedation range and handling of near-suppression states 4 lead sensor, upgraded DSC, advanced error handling 2nd bipolar EEG rejects eye movement artifact+
4.1	2004[b]		Improved performance in sedation range

MAC, minimum alveolar concentration suppressing movement to surgical incision by 50%; EEG, electroencephalogram; EMG, electromyogram.

[a] FDA (510k) granted 10/96 for monitoring anesthetic effect.

[b] FDA (510k) granted 10/03 for decreasing incidence of recall during general anesthesia in adults.

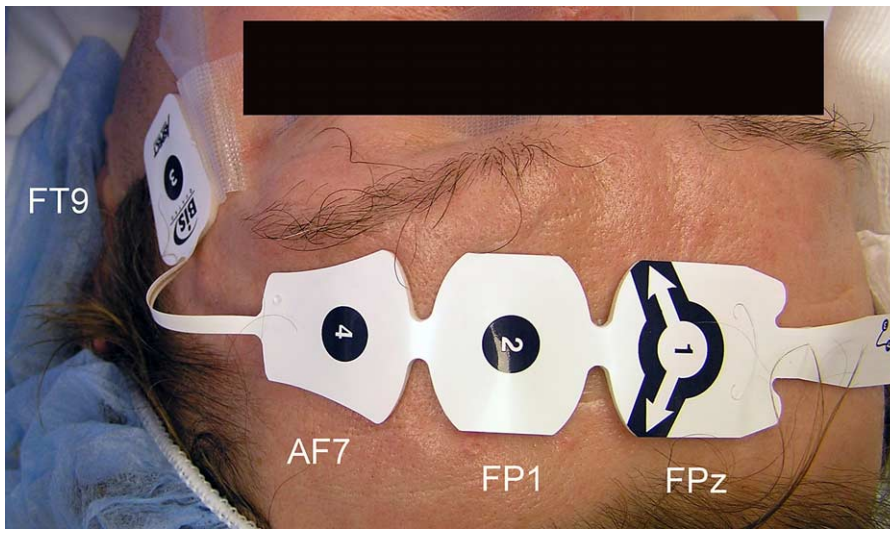

Figure 2. Quattro Sensor for BIS has four self-prepping silver/silver chloride electrodes placed on the forehead corresponding bipolar montage in the international 10–20 system of Fz (Fpz or Afz: lead 1) to F7 (F9 or FT9: lead 3) and F3 (AF3: lead 2) to F7. Lead 4 is the ground electrode and measures electromyography activity of the frontalis muscle below the sensor. Sensor placement requires skin preparation with alcohol, mild debridement with gauze and 2–5 seconds application of digital pressure over sensor lead.

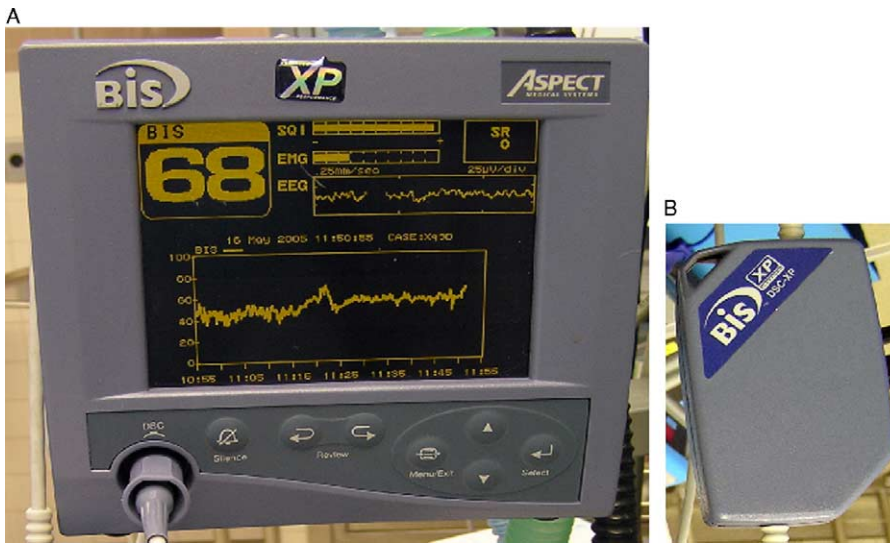

Figure 3. Bispectral index XP monitor (Aspect Medical Systems Inc., Natick, MA). Raw EEG data is converted by the digital signal processing cable or DSC (B) and sent to monitor (A). The patient interface cable that attaches the sensor to DSC is not shown. The trend screen can be reconfigured to review other stored EEG or quality control parameters or to review cases over last 48 hours. The monitor also has long-term memory that can store events over the last 60 days for review of critical incidents.

been associated with a low probability of recall and a high probability of unresponsiveness during surgery under general anesthesia[13,14,19–21] BIS values between 45 and 60 have been recommended for anesthetic maintenance during general anesthesia.[2,22–24] Blinded observation of practitioners attempting a rapid emergence resulted in hypnotic maintenance at BIS values in the high 30 s to low 40 s corresponding to deep sedation and near burst suppression.[4,5,22,25] This range represents a 'comfort zone' for many anesthesiologists corresponding to their routine, unmonitored practice (Figure 5A). As the BIS falls from the mid 30 s to zero, EEG burst suppression increases to cortical silence. BIS responds monotonically to increasing hypnotic drug dose (volatile or intravenous) across the entire spectrum of awareness, independent of agent (exceptions discussed below), and is not significantly influenced by opioids.[2,7,26] BIS does not monitor analgesia and does not predict spinal cord reflexes to painful stimuli such as movement or hemodynamic responses.[2]

HYPNOTIC TITRATION USING BIS

An individual patient's response to sedation and hypnosis is difficult to predict based on a complex interplay of factors including coadministration of multiple synergistic medications and significant individual pharmacokinetic and pharmacodynamic variability. Most anesthesiologists were trained to administer hypnotic anesthetics until both hemodynamic and movement responses were suppressed (Figure 5A) routinely overmedicating their patients. Continuous, real-time measurement of hypnosis using BIS should allow optimization of drug delivery to the individual patient preventing both potential under- and overdosing of anesthetic medications (Figure 5B). The upper limit of hypnotic titration is defined by the absence of awareness and memory. It should also be associated with the minimum, appropriate dose of hypnotic agent. Prevention of relative hypnotic overmedication should theoretically improve morbidity, speed emergence and recovery.

BIS was the first brain function monitor to receive approval (FDA) for hypnotic monitoring based on demonstration of the clinical effectiveness. Briefly, Gan et al demonstrated in a multi-institutional, blinded, randomized controlled clinical trial (propofol/alfentanil/N_2O-based anesthetic comparing standard practice to BIS titration between 40 and 60) modest decrease in propofol dose (23%), decreased time to extubation (35%) and decreased time to discharge from postanesthesia recovery.[22] No change in the incidence of postoperative complications or medication requirements was noted. Song et al found similar results using a sevoflurane based anesthetic in women outpatients presenting for tubal ligation.[25] However, time to orientation, duration of PACU stay, time to oral intake, and time to home-readiness were not affected by BIS monitoring. BIS has also been found useful in predicting fast-track eligibility in ambulatory outpatients using propofol and desflurane.[27] These results have been validated by other investigators[24,28–31], however the cost effectiveness of these modest changes has been debated.[30,32–36] Previous reviews have focused on titration of hypnosis, memory/learning and intermediate outcomes such as time to extubation, time to PACU discharge, postoperative nausea and drug utilization.[2,3,28,37–40]

Clinicians need clear expectations and rational treatment guidelines to utilize BIS measurements to change their practice in a way that leads to improved efficiency, reduces morbidity and may eventually lead to improved patient satisfaction.[41] Johansen et al has described the clinical impact of routine BIS monitoring in a large urban

Table 2. BIS-Guided Hypnosis and Anesthetic Management.

Intraoperative Response	BIS	Treatment
Increase BP, HR, Autonomic or Somatic Response		Increase Hypnotic − ? Increase Analgestic − Identify Strong Stimuli Source
Stable	>65	Rule out Artifact[a], then Increase Hypnotic
Hypotension/unstable		Support BP − Decrease Analgesic − Consider Amnestic
Increased BP, HR, Autonomic or Somatic Response		Increase Analgesic/Maintain Hypnotic − Antihypertensive − add NMB
Stable	50–60	Titration Target − Maintain Vigilance
Hypotension/Unstable		Support BP + Decrease Analgesic
Increased BP, HR, Autonomic or Somatic Response		Decrease Hypnotic + Increase Analgesic +/− Antihypertensive
Stable	<50	Decrease Hypnotic + ?Decrease Analgesic
Hypotension/Unstable		Support BP + Decrease Hypnotic and Analgesic

BP, blood pressure; HR, heart rate; NMB, neuromuscular blocking agent.

[a] Artifact refers to interference from other electrical sources and electromygraphic activity (EMG).

academic/trauma center.[2] The goal of this study was to implement guidelines for anesthetic management (Table 2) that encouraged changes to routine clinical practice. Suggestions for controlling hemodynamic alterations and movement responses were combined with targeted BIS values minimizing both the risk of awareness and of hypnotic overdose. BIS values of 50–65 were suggested during anesthetic maintenance, increasing to a BIS of 75 within the last 15 minutes of the surgical procedure. It was a prospective observational study with a historical control involving approximately 1500 adult surgical patients treated over a 3-month period. Achieving the target BIS maintenance values produced a more rapid extubation time (37%), decreased OR exit time (24%), faster eligibility for phase I PACU discharge (23%) and faster actual PACU discharge time (15 minutes or 7%) for patients extubated in the OR. Improved average extubation time resulted from reduction in patient variability with relatively selective decrease in patients who were slow to emerge. Unexpectedly, adverse perioperative respiratory events decreased significantly from 2.7 to 0.6% (78%), and the frequency of intubated patients arriving in the PACU decreased from 6.9 to 2.6% (62%) with guideline compliance. This study confirmed the utility of BIS monitoring in routine clinical care.

RESEARCH UPDATE: CLINICAL OUTCOME STUDIES

Clinical research can be divided into experimental designs for hypothesis generation (observational and retrospective) or for hypothesis testing such as prospective, randomized (blinded) trials (Type I evidence or 'gold standard'). Goals include characterization of new technology, improvement in clinical outcomes, improvement in patient safety and satisfaction. The real objective of this research into brain function monitoring is to improve recognition of clinical hypnotic states and detection of abnormalities that will lead physicians to alter their behavior and alter patient treatment in ways that improve safety and reduce major negative outcomes. Major outcomes such as mortality and recall during general anesthesia tend to be the most difficult to address due to the extremely low incidence of their occurrence. For example, recall is a relatively rare complication occurring at an incidence of 1–2 cases per thousand.[42,43] Power analysis predicts that to observe a 50% reduction in recall, 41 000 patients would need to be included in a prospective, randomized trial.[44] Modest clinical outcomes, such as decreased drug use and improved anesthetic recovery, are much easier to study and can be adapted to economic analysis (e.g. cost-benefit). Three important papers on BIS monitoring have recently been published and will be briefly discussed.

Currently accepted mortality attributable to anesthesia has been quoted at <1 in 200 000 anesthetics.[45] The influence of anesthetic management and intraoperative events on long-term outcome is of great interest. Monk et al[46] has addressed the relationship of brain function monitoring (BIS) to 1-year mortality after noncardiac surgery. Not surprisingly, they found that patient comorbidity and intraoperative hypotension were predictors of death. However, the study defined a new variable, cumulative deep hypnotic time (BIS <45), which was an independent predictor of mortality. The relative risk was 1.244 per hour for cumulative deep hypnotic time. This is surprising since most BIS studies focus on providing an adequate level of hypnosis (BIS <60) to limit drug dosage and prevent recall, but do not address the consequences of deep hypnosis.[47] In addition, hypnotic agents are commonly overdosed to suppress hemodynamic responses. Although a prospective study, the original design targeted an

extensive evaluation of cognitive function before and after anesthesia and may have introduced some bias into patient selection (cognitive data not reported). Despite the limitations of the study, it reveals an unexpected association of great interest that identifies a new hypothesis requiring validation with a more tightly controlled, prospective randomized trial.

Ekman et al[5] reported a prospective, historical-controlled, cohort trial in consecutive patients ($n = 4945$) undergoing surgery requiring general anesthesia and evaluated them for explicit recall using three structured interviews over 2 weeks following surgery. Compared to a historical control ($n = 7826$) in the same institution using the same definitions of explicit recall, BIS monitoring significantly reduced recall from 0.18 to 0.04% (2 patients, 77% reduction). This study and their previous report[48] defined the necessity for three structured postop interviews to identify explicit recall during anesthesia. Both recall events occurred during induction and intubation with BIS values > 60. In fact, the actual incidence of explicit recall with BIS monitoring is much lower than this value, since if BIS had guided use of hypnotic medication during induction and intubation, these two events would probably not have occurred. Notably, the average BIS recorded during maintenance of anesthesia was 38 ± 8, indicating that patients were routinely placed in the 'deep hypnotic' range as defined by Monk et al[46] described in the preceding paragraph.

The best evidence for reduction in recall after anesthesia comes from the B-Aware trial, a multicenter prospectively randomized study of 2463 high-risk patients (e.g. cardiac surgery, cesarean section, trauma surgery), where BIS was guided in the treatment group to between 40 and 60.[4] Myles et al found an 82% reduction in the incidence of awareness using BIS (2 patients) compared to randomized controls in the routine care group (11 patients). They used three postoperative interviews up to 30 days after surgery. The average BIS during surgery was 44.5 ± 7. One report of awareness in the BIS group occurred at 79–82 during laryngoscopy and the other at 55–59 during use of the sternal saw in off-pump cardiac surgery. The exact sensitivity and specificity of BIS for awareness cannot be defined from this data, but it is clear that the monitor is neither 100% sensitive nor 100% specific.

These three outcome studies, in ascending significance, present the best available data that monitoring in anesthesia changes morbidity and mortality. No other brain function monitor nor other anesthetic monitoring technology has ever been shown to reduce the incidence of adverse outcomes. Even use of pulse oximetry does not reduce the incidence of cardiovascular, respiratory, neurologic or infectious complications following anesthesia.[49] Future analysis of the cost-effectiveness of BIS monitoring should focus on both the costs of awareness reduction and potential for decreased mortality in the first year after surgery with improvements to clinical efficiency and drug utilization.

KNOWN LIMITATIONS OF BIS MONITORING 4.1 SIGNAL QUALITY AND ELECTRICAL INTERFERENCE

Significant EMG (electromyographic) activity may be present in sedated, spontaneously respiring patients, interfering with EEG signal acquisition and contaminating the BIS calculation. Conventionally, EEG signals are considered to exist in the 0.5–30 Hz band and EMG signals in the 30–300 Hz band (although BIS uses EEG signals up to 47 Hz). This separation is not absolute, and low frequency EMG signals can occur in the

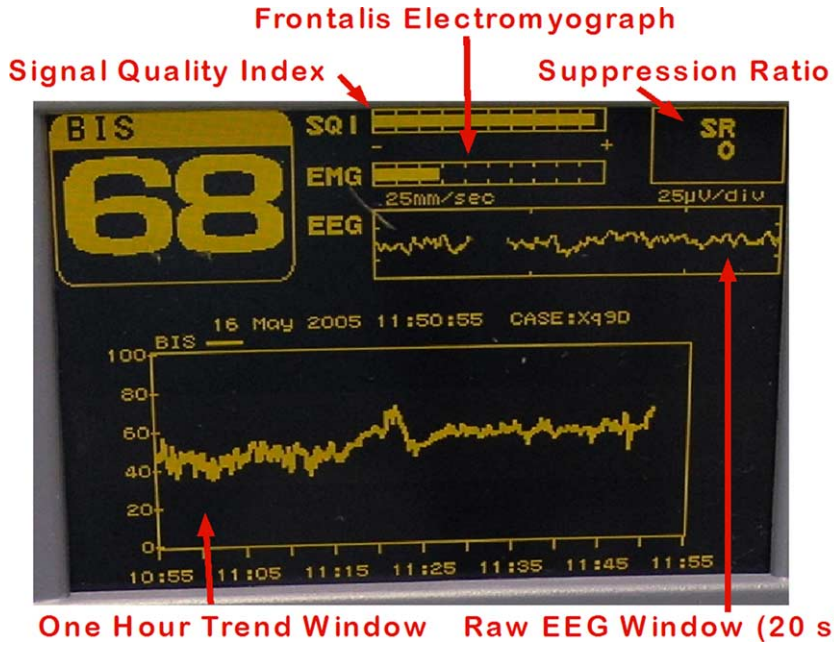

Figure 4. BIS display screen. BIS index (0–100) is shown in upper left. BIS is trended versus time in the lower window. Raw EEG is shown (~20 seondsc) above this. Suppression ratio (SR) represents the cumulative percent of cortical silence over the last 65 seconds. Data reliability may be assessed by evaluating the bar graphs for signal quality index (SQI; global parameter incorporating electrode impedance and artifact detection) and electromyographic activity (EMG) of the frontalis muscle in the 70–110 Hz band (dB). EMG activity over 1/3 of total bar height (30–50 dB) may represent contamination of EMG below 50 Hz and artifactual elevation of BIS value.

conventional EEG band range. This EMG activity may be interpreted as high frequency, low amplitude waves, falsely elevating the BIS. Similarly, falsely elevated BIS values can also occur with high electrode impedances produced by inadequate electrode attachment or misplacement. The A2000XP monitor quantifies and reports high-frequency activity (within the 70–110 Hz frequency range) as an 'EMG' variable and displays this in the upper middle section of the monitor in a bar graph labeled EMG (Figure 4). The bar graph is marked off in decibels which represents the amplitude or power of the signal. Improvements in the BIS algorithm have focused on steadily decreasing the impact of EMG contamination in both anesthetic and sedative ranges (Table 1). There is no simple correlation with EMG in the 70–110 Hz range and artifactual BIS elevation. An alert clinician needs to assess signal quality (SQI, Figure 4), EMG activity and BIS trend with relation to the clinical state of the patient prior to making any treatment decisions.

Hypnotics not effectively monitored by BIS

Inhalation of nitrous oxide up to 50% does not alter BIS, nor does it cause unconsciousness.[50] At 70% nitrous oxide, responsiveness to voice command is lost, but

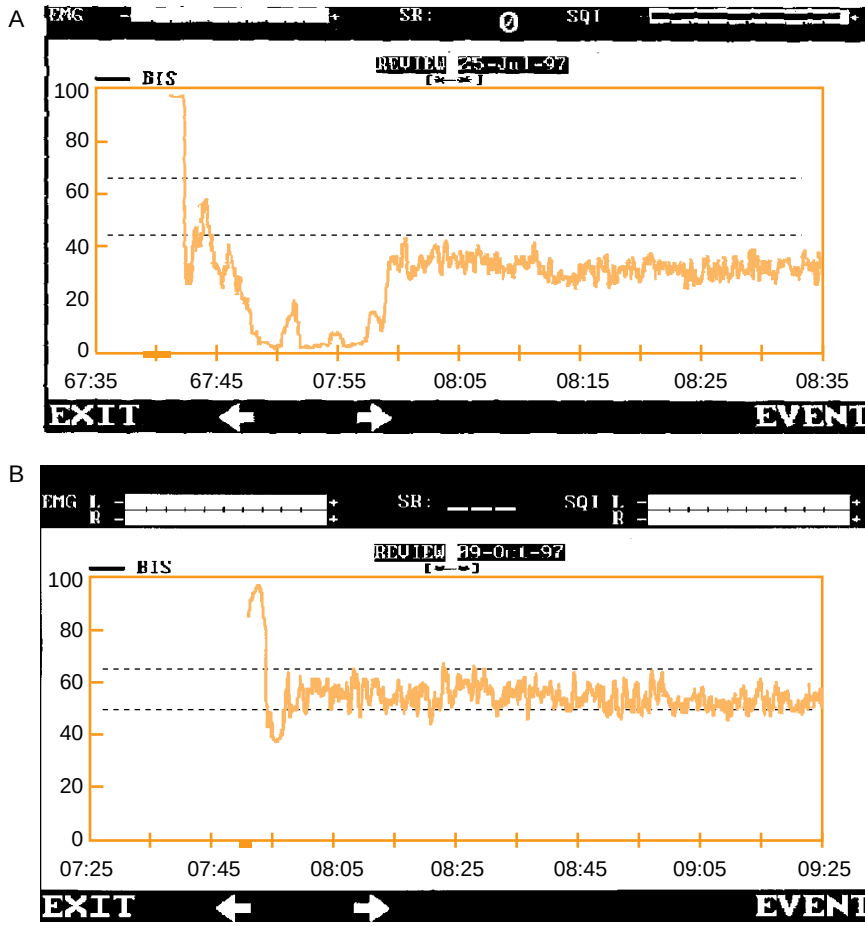

Figure 5. Comparison of anesthetic management during induction and maintenance between standard practice without (A) to goal directed hypnotic titration with BIS (B). Display screen of time course versus BIS value. Blinded provider without training during routine general anesthetic using thiopental/isoflurane and endotracheal intubation. Hypnotic titration for induction and maintenance targeting BIS between 50 and 65 using same anesthetic agents.

BIS does not change.[51] The addition of nitrous oxide to stable plasma concentrations of propofol in volunteers decreased the probability of response to a range of stimuli at any given BIS level.[19] Addition of 55–63% nitrous oxide to a propofol–remifentanil anesthetic did not change BIS but did prevent movement to laryngoscopy and intubation.[52] Based on these results, nitrous oxide appears to add little to hypnotic state and may be functioning predominately as an analgesic.[53] Interestingly, xenon, a noble gas with anesthetic and analgesic properties, appears to potentiate hypnosis by sevoflurane in unstimulated patients and limits BIS response to surgical stimulation (Figures 5 and 6).[54,55]

In contrast to other anesthetic agents, ketamine is a dissociative anesthetic with excitatory effects on the EEG and is thought to produce anesthesia by a unique mechanism.[56] Ketamine doses of 0.25–0.5 mg/kg sufficient to produce unresponsiveness did not reduce BIS.[57–62] When ketamine was used in conjunction with propofol

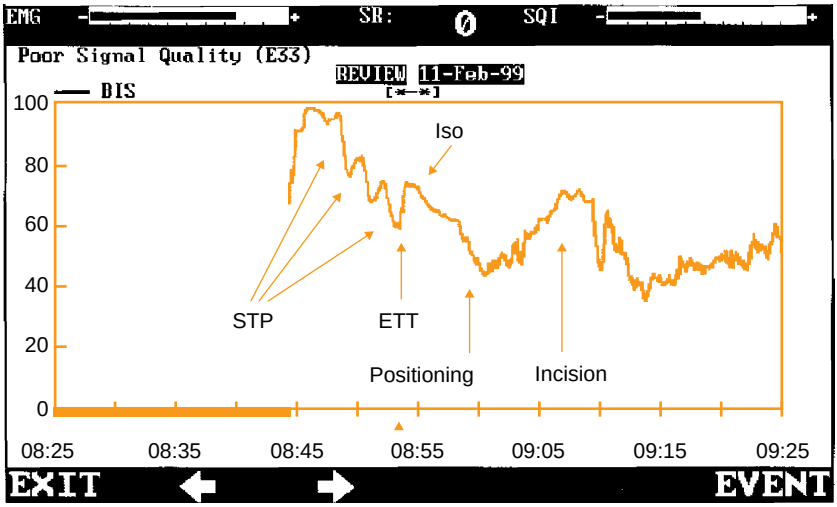

Figure 6. Time course of induction and maintenance for an 85-year-old female undergoing urgent left hip percutaneous pinning and fixation under general anesthesia with thiopental (STP) and isoflurane (ISO). Patient was anticoagulated for chronic atrial fibrillation. STP 25 mg IV given with loss of consciousness, each subsequent dose was given as BIS began to increase. Thirty seconds smoothing rate produced a similar hysteresis between clinical effect and BIS display. After intubation, ISO targeted of 0.6% end-tidal, then lateral positioning. ISO was decreased after positioning to 0.3% and case proceeded. Patient was hemodynamically stable throughout. Fluids were minimized and patient awoke within 2 minutes of surgical completion.

sedation, there was an additive interaction to achieve hypnotic endpoints, yet ketamine did not change BIS values.[60,63] BIS appears to monitor sedation and anesthesia with propofol and low dose ketamine ($<$0.2 mg/kg per hour).[58] It is also unclear if BIS is effective in monitoring sedation produced by dexmedetomidine, an α_2 agonist.[64]

More investigation of BIS changes with opioid dose/response alone and opioid+hypnotics is required. Two basic questions should be addressed. First, can BIS detect an interaction between opioids and hypnotic agents in unstimulated patients under general anesthesia? Preliminary evidence demonstrates that remifentanil, even at large doses, produced no modification of BIS obtained during a constant propofol infusion.[26,65,66] Second, can BIS monitor cortical arousal to surgical stimuli and will opioids modify this response? Guignard et al found that predicted remifentanil serum concentrations above 8 ηg/ml prevented an increase in BIS after laryngoscopy and intubation.[65] Hans et al found that sufentanil plasma concentrations of 0.5 ηg/ml BIS changed 15±8 with incision and at 1.0 ηg/ml BIS changed significantly less (7±6) during propofol general anesthesia.[67] If analgesics modify arousal to painful stimuli, this may explain some initially confusing findings during nitrous oxide and xenon administration (see above).

Disease processes limiting BIS monitoring

Although questions have been raised regarding BIS use in patients with neurological disease, recent publications have been supportive. In the ICU setting, BIS correlates with commonly used sedation scales in neurologically injured patients with and without sedation.[68] Deogaonkar et al suggested that the most recent BIS algorithm function the

best in the ICU. BIS has been found useful in predicting recovery of consciousness from severe brain injury.[69,70] BIS and other electrophysiologic and clinical variables have enabled construction and cross-validation of a model relating BIS(max) to the probability of recovery of consciousness in patients in a coma state due to a severe brain injury.[70] However, one example exists of a patient subsequently found to have genetically determined low-voltage EEG where BIS values were abnormally low (awake baseline $=40$).[71] Major improvements in the current BIS algorithm (v4.0+) should provide a platform for more research into sedation and help define goals, applications and limitations of brain function monitoring in diverse patient populations. The new BIS algorithm should also be cross-validated with older versions.

A prospective, controlled, observational study demonstrated that electroencephalogram slowing associated with dementia changed awake BIS values.[72] Thirty six patients with Alzheimer's disease or multiinfarct dementia and 36 control patients aged >75 years were studied. Both groups were assessed with a Mini-Mental State Test. Baseline BIS in normal, awake controls was 96–99. A significant proportion of patients with dementia had lower than normal 'awake' BIS, which correlated with Mini-Mental State tests. Eighteen of 36 (50%) dementia patients and 8 of 36 (22%) controls had mean awake BIS <93. BIS (v4.0) values were 89.1 (86–92, 95% CI) and 94.7 (93–96), respectively. No significant difference was found in age, sex, activity from the electromyogram, and signal quality index. BIS 4.0 was significantly better at detecting the difference than version 3.4. The utility of the BIS monitor in detecting dementia warrants further investigation.

OTHER APPLICATIONS OF BIS MONITORING

Pediatrics

Children are at higher risk for anesthesia-related morbidity from both over- and undermedication.[73] This is not surprising due to the higher anesthetic requirements and increased incidence of cardiovascular instability observed in infants and young children. A prospective, single institution, cohort study found that intraoperative awareness in 5–12-year-old children may be 8 times higher (0.8%, 0.3–1.7% 95%CI) than adults.[74] This is the first large-scale ($n=864$) study in children using a set of three structured interviews. There is considerable debate regarding identification of intraoperative awareness and its consequences in children. There was no difference in the incidence of postop behavior disturbances in aware (20%) versus nonaware (16%) children. Although several design issues have been raised[75], this study identified intraoperative awareness as an important issue for anesthesiologists. One study has directly measured BIS during planned intraoperative awareness. McCann et al found BIS useful for predicting patient movement to command intraoperative wake-up test during scoliosis surgery.[76]

Will BIS monitoring allow anesthesiologists to navigate between the dangers of excess hypnotics and preventing intraoperative awareness in children? Only adults were used to develop and test BIS. The influence of neuronal and physiological maturation of the brain on BIS, its correlation to drug effects and anesthetic outcome is only just beginning to be investigated. Adult guidelines should not be adopted without validation. Since 2000, a number of excellent studies have examined BIS in children during general anesthesia[77–82], sedation[83–86] and ICU care[87–89]. This is a large topic that deserves its own review.

Sedation: monitored anesthesia care and intensive care

Validated sedation/agitation scales (Observers Assessment of Sedation/Awareness (OAA/S), Richmond Agitation Sedation Scale and Sedation Agitation Scale)[90] have been used to measure the level of alertness/agitation in sedated patients and have improved patient care. The OAA/S was used to develop the BIS algorithm, so it is not surprising that a number of investigators have replicated the tight correlation between the BIS, hypnotic drug concentration and OAA/S for perioperative sedation.[11,14,19,91] These perioperative studies suggest that BIS values ranging between 65 and 80 define an acceptable loss in conscious information processing and recall during sedation/hypnosis. Brain function monitors should provide a unique, objective way to monitor sedation in the intensive care unit (ICU) allowing precise hypnotic titration avoiding both over- and undersedation.

The ICU environment presents unique challenges to brain function monitoring such as long-term sensor application, variety of electrical interference, complex multisystem disease processes, complex pharmacological interactions and tachyphylaxis. The incidence, definition and complications of awareness in the ICU are poorly understood. Goals are poorly defined and have generally focused on providing the nursing staff with an immobile patient. Significant pharmacy costs and other equipment costs are incurred by hospitals using long-term sedation. Oversedation appears to be a common, poorly recognized problem.[92] Difficult questions arise such as: Should continuous, unvarying hypnotic infusions be used; or, should drug-free periods be allowed to provide periods of wakefulness or sleep? BIS decreases markedly in natural sleep, although clear identification of natural sleep using BIS may be problematic.[93–95]

Sedation–agitation scales are not the 'gold standard' of ICU sedation and have significant problems with interindividual application and interpretation. Many investigators investigating BIS in the ICU have made serious methodological errors. First, stimulus–response tests measure a narrow range of sedation focused on responding to voice commands or movement responses to mild or strong stimuli. These tests mix limited tests of cortical function with reflex spinal cord responses. Many investigators and editorialists do not understand this distinction or the limitations of these scales.[96] Second, administration of these tests change the state of the patient, and some investigators have neither defined nor used prestimulus observations in their study designs. Third, sedation scales are ranked, ordinal data (nonparametric) with undefined intervals between each clinical stimulus. A number of investigators have used linear correlation coefficients to compare BIS with sedation scales when nonparametric tests, such as Kendall's tau-b or Spearman's coefficient for simple correlations or Kruskal–Wallis nonparametric ANOVA for more complicated designs, are required.

The utility of BIS in the ICU has been both supported[87,92,97] and questioned.[96,98–100] Significant improvements in the BIS algorithm have addressed a number of problems with monitoring sedation in ICU (Table 1). However, large-scale, well-designed trials are needed to validate these improvements and link sedation monitoring in the ICU to improvements in both intermediate and long-term outcomes.

Conscious sedation

BIS monitoring is moving out of the OR and ICU and into hands of practitioners using conscious sedation in a variety of locations.[101–107] Practitioners accredited for conscious sedation should be trained to avoid crossing over into general anesthesia (BIS

$<$60–65). Preventing oversedation in the emergency room, radiology, endoscopy suites and dental offices would dramatically increase the safety of conscious sedation. Motas et al describe training nonanesthesiologists to provide 'deep sedation' in a children's hospital.[105] This observational study followed personnel administering sedation who were blinded to the BIS score. BIS $<$45 was routinely observed in children ($>$35% procedures) and over 8% had significant episodes of airway compromise and desaturation. BIS monitoring clearly has a function in improving safety during sedation, but anesthesiologists need to be proactive in providing rational guidelines for conscious sedation $\pm$ BIS and improving patient safety.

SUMMARY

Over the last 9 years a large body of experimental research has accumulated on the use of the bispectral index (Aspect Medical Systems Inc., Natick, MA) in monitoring hypnosis during sedation and general anesthesia. The FDA has approved this device for titration of hypnosis and for reducing the incidence of awareness during anesthesia. Numerous studies have documented the ability of BIS to reduce intermediate outcomes such as hypnotic drug administration, extubation time, postoperative nausea, and shorten recovery room discharge. Two recent large-scale outcome studies using BIS (one randomized controlled trial and one prospective, nonrandomized historical cohort study) identified an approximately 80% reduction in the incidence of recall after anesthesia. BIS provides clinicians with unique information that can be used to tailor hypnotic drug dose to individual patient requirements. BIS does not predict movement or hemodynamic response to stimulation, nor will it predict the exact moment consciousness returns. Some limitations exist to the use of BIS and it is not useful for some single agent hypnotic techniques (ketamine, dexmedetomidine, nitrous oxide, xenon, opioids). BIS technology is moving out of the operating room and into diverse environments were conscious and deep sedation are provided. Anesthesiologists need to be actively involved in promoting patient safety and providing guidelines for procedural sedation for other physicians and qualified providers.

Practice points

- a number of technologies have claimed the ability to monitor anesthetic action. To date, only the bispectral index (BIS) has been validated in both controlled, randomized trials and in routine clinical practice as a monitor of anesthetic state providing clinicians with unique information allowing them to minimize the potential for awareness and the consequences of hypnotic overmedication
- BIS is useful for titrating hypnotic drug dose for both anesthetic induction and maintenance. Clinicians need clear expectations and guidelines for implementing BIS monitoring in routine patient care
- practitioners need to understand all the information provided on the BIS monitor to be able to recognized artifact, identify inaccurate BIS readings and rapidly troubleshoot problems

Research agenda

- more prospective, randomized controlled trials of the bispectral index and recall during anesthesia must be completed
- the association of deep hypnotic time and mortality needs validation in a clearly designed prospective observational trial
- application of BIS to unique populations (Pediatrics, Elderly, Neurological dysfunction, Trauma, etc.) should provide more information on important applications and limitations of BIS monitoring
- the incremental improvements in BIS algorithm need better cross-validation. Is the current BIS (4.1) as good as older versions (3.4)? Are there specific applications of different BIS algorithms?
- BIS should provide an important tool for sedation monitoring in ICU and for procedure out of the operating room. Research on appropriate guidelines and training should focus on maintaining BIS in the sedative range. Only qualified and certified providers should be using hypnotics for general anesthesia regardless of the location!

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