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Development and Clinical Application of Electroencephalographic Bispectrum Monitoring

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UNTIL recently, anesthesiologists lacked the ability to monitor the effects of anesthetics on the brain in terms of "depth" or "adequacy" of anesthesia. Typically, surrogate measures of autonomic activity, such as changes in blood pressure and heart rate, have been used to assess the adequacy or inadequacy of anesthesia. Because it is believed that general anesthetics block consciousness by depressing the central nervous system, and electrical activity of the cerebral cortex can be measured using the electroencephalogram (EEG), it is expected that some component of the EEG should relate to adequacy of anesthesia. Such a relation was first suggested in 1937.[1] With the advent of the microcomputer technology, it became possible to reduce the amount of data obtained from an EEG to various processed derivatives.[2] Derivatives such as the power spectral edge, median frequency, and zero-crossing frequency, among others, have been described as potential measures of anesthetic effect on the central nervous system.[3–6] In that these measures were found to depend on specific drug combinations and were not monotonically related to drug effect or clinical response, no gold standard for measuring the entire spectrum of anesthetic effect has been widely accepted.

The first and only technology approved by the U.S. Food and Drug Administration (October 1996) for marketing as an EEG-based monitor of anesthetic effect is the bispectral analysis derivative known as the Bispectral Index Scale (BIS, Aspect Medical Systems, Natick, MA). The purpose of this review is to describe the clinical development of this technology and to assess our current understanding of its utility in clinical practice.

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Bispectral Analysis

Bispectral analysis is a statistical technique that allows study of phenomena with nonlinear character, such as surf beats and wave breaking.[7] Bispectral analysis provides a description to a continuous pseudo–randomly varying signal (*e.g.*, EEG) that is an alternative to other conventional power spectral analysis techniques derived from fast Fourier transformation. The mathematics of bispectral analysis have been described elsewhere.[7–11] The first studies of EEG bispectral analysis were published in 1971.[12] Bispectral analysis is computationally intensive, and it was not until fast microprocessors were developed that online bispectral analysis of the EEG in the operating room became possible.

Conventional analysis of the EEG using fast Fourier transformation produces information regarding the power, frequency, and the phase of the EEG signal. Typical displays, such as the compressed spectral array, graph power and frequency information and discard the phase information.[2] Bispectral analysis represents a different description of the EEG in that interfrequency phase relations are measured, *i.e.*, the bispectrum quantifies relations among the underlying sinusoidal components of the EEG.[2] Additional details regarding the computation of bispectral data can be found in Sigl and Chamoun[13] and in a review by Rampil.[2] The data contained in both the bispectral analysis and conventional frequency–power analyses of the EEG are used to create the proprietary parameter of the bispectral index, or BIS.[2,13] BIS is a dimensionless number scaled from 100–0, with 100 representing an awake EEG and zero representing complete electrical silence (cortical suppression). During development, BIS went through several revisions (table 1) and the currently available versions (versions 3.3 and 3.4) are scaled as shown in figure 1.

The BIS integrates various EEG descriptors into a single variable. The mixture of subparameters of EEG activity was derived empirically from a prospectively collected database of anesthetized volunteers with measures of clinically relevant sedative endpoints and hypnotic drug concentrations.[14] The process by which BIS was derived is shown schematically in figure 2. The EEG was recorded onto a computer and was time-matched with clinical endpoints and, where available, drug concentrations. The raw EEG data were inspected, sections con-

Table 1. Bispectral Index 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*	″	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 s Smoothing, less susceptable to "arousal delta" patterns on emergence

* FDA premarket approval granted October 1996.

BIS = Bispectral Index; MAC = minimum alveolar concentration suppressing movement to surgical incision by 50%; EEG = electroencephalogram; EMG = electromyogram.

taining artifact were rejected, and spectral calculations were then performed to produce both bispectral and power spectral variables. Following statistical ranking, the variables correlating best with the clinical endpoint were chosen. These were then fitted to a multivariate statistical model using the maximum likelihood solution to a logistic regression analysis to produce a continuous series of BIS values. This index was then tested offline in a prospective manner on a new database, and studies evaluated its clinical utility. The parameters used in the current implementations of BIS have been detailed by Rampil.[2]

The BIS monitor represents the successful effort to model EEG *versus* behavioral responses. The BIS algorithm uses various derivatives from conventional EEG power spectral analysis as well as elements of bispectral analysis.

Initial Clinical Studies

In the absence of a gold standard for determining anesthetic depth, initial clinical studies evaluated the predictive power of BIS for clinical endpoints including patient movement to skin incision (similar to the determination of minimum alveolar concentration [MAC]) and autonomic responses to stimulation (hypertension and tachycardia [MAC_{BAR}]). Data from the first two clinical studies were combined to form the database from which BIS version 1.1 was derived.[15,16] BIS was compared with other commonly used power spectral derivatives to predict movement following skin incision in patients receiving thiopental–isoflurane anesthetic.[17] EEG variables 2.0 min before incision were used as individual controls. A statistically significant difference between BIS levels, but not in spectral edge or median frequency, in subjects who moved at skin incision (BIS 65 ± 15, mean ± SD) was noted compared with those who did not move (BIS 40 ± 16). The accuracy (overall accuracy of prediction)‡ was 83%, but the ability to correctly identify nonmovers (specificity) was only 63%. Power spectral derivatives did not predict movement in response to skin incision; this was confirmed in a recent study during thiopental–isoflurane anesthesia.[18]

The BIS version 1.1 was also evaluated for its ability to predict hemodynamic responses (more than 20% increase in blood pressure or heart rate) to laryngoscopy during a thiopental–nitrous oxide–opioid anesthetic technique.[16] A statistically significant difference was found between patients who mounted a hemodynamic response (BIS 67 ± 10) compared with those who did not (BIS 45 ± 14). In this study, power spectral edge and median frequency did not distinguish those subjects who responded from those who did not. However, other researchers have found power spectral edge to be a useful predictor of hemodynamic response to laryngoscopy.[5]

To evaluate the predictive ability of BIS for movement

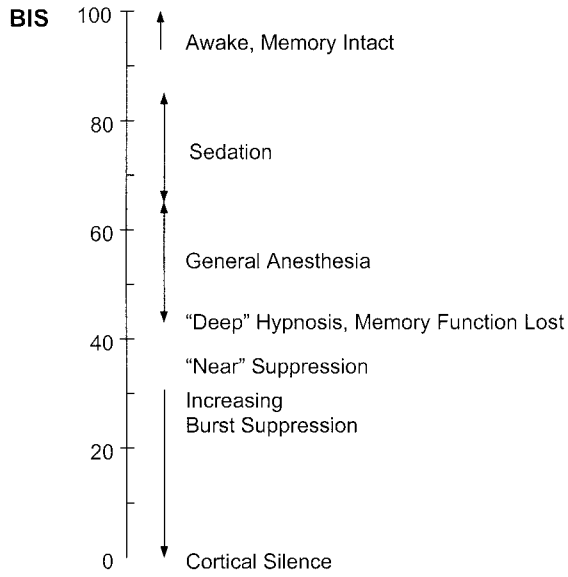

Fig. 1. The Bispectral Index Scale (BIS versions 3.0 and higher) is a dimensionless scale from 0 (complete cortical electroencephalographic [EEG] suppression) to 100 (awake). BIS values of 65–85 have been recommended for sedation, whereas values of 40–65 have been recommended for general anesthesia. At BIS values lower than 40, cortical suppression becomes discernible in raw EEG as a burst suppression pattern.

‡ $\text{Accuracy} = \left(\frac{\text{Total number} - [(\text{False positive}) + (\text{False negative})]}{\text{Total number}}\right) \times 100.$

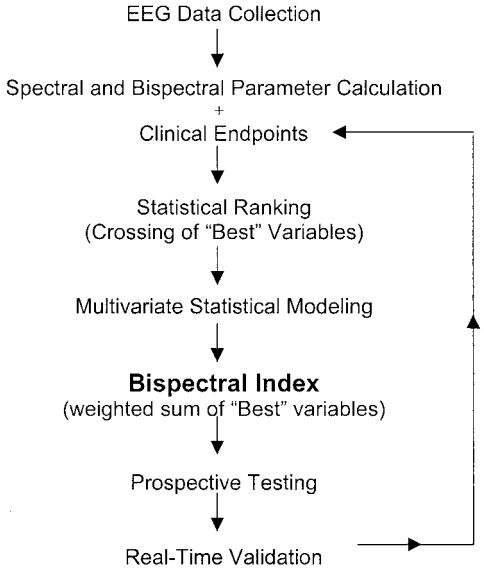

Fig. 2. Bispectral Index Scale (BIS) development process. BIS versions 2.0 and higher were reformulated using hypnosis and awareness as clinical endpoints (see table 1).

using different anesthetic techniques, a prospective comparison was conducted using computer-controlled infusions of propofol (target plasma concentration, 4 μg/ml) plus alfentanil (125 ng/ml) compared with isoflurane (end-tidal concentration, 0.5%) plus alfentanil (125 ng/ml) anesthetics, techniques expected to achieve a 50% movement response to skin incision.[19] In the period before skin incision, BIS was statistically significantly different for those who moved at incision compared with those who did not for each anesthetic technique, whereas other EEG derivatives were not significantly different. However, there was no difference between the patients in the isoflurane–alfentanil group that did not move (BIS 63 ± 10) and those in the propofol–alfentanil group who did move (BIS 63 ± 9). These studies demonstrate that BIS version 1.1 could predict movement response to incision but depended on the anesthetic agents used.

Based on these results, a multicenter study of 300 patients from seven study sites using seven different anesthetic techniques was undertaken.[20] Anesthetic technique was specific to each site and did not vary within each site, although there was significant overlap among drugs used at the various sites. One half of the patients at each site were randomized to receive anesthetic doses in which 50% of patients were expected to move in response to skin incision. The other half was randomized to a treatment group in which the anesthetic drug dose was adjusted to produce a BIS value of less than 60. The percentage of patients who moved in the group where a 50% movement rate was expected was 43% (BIS 66 ± 19 before incision). In the BIS-guided group (in whom anesthetic doses were larger), the movement response rate was significantly lower (13%), as was the BIS (51 ± 19). Overall, as BIS decreased, the probability of a movement response also decreased. At some sites where opioid doses were relatively large, there was no apparent relation between BIS and the probability of movement. Retrospective pharmacodynamic modeling using STANPUMP (Steven Shafer, VA Medical Center, Palo Alto, CA) was performed to estimate the effect-site concentrations of the intravenously administered anesthetics and opioids during balanced anesthesia. Using logistic regression analysis, an interaction model for the effects of the inhalational and intravenous anesthetics and opioids was derived. As the concentration of isoflurane and propofol increased, a decreasing BIS was associated with a decreasing probability of movement. In contrast, increasing opioid dose was associated with a decreased probability of movement without significant changes in BIS. Thus, when large doses of opioids are used, there is a poor association between the probability of remaining immobile after incision and BIS.

Concurrently, several studies furthered our understanding of the anatomic pathways underlying the movement response to surgery. In rats, Rampil *et al.*[21] demonstrated that MAC did not change following removal of the forebrain structures *via* craniotomy. They also demonstrated in the same model that spinal cord transection at C1–C2 level did not alter MAC.[22] Antognini *et al.*[23] separated the systemic and cranial circulations in the goat using bypass circuits to selectively anesthetize either the head or the body (including spinal cord). When the whole animal was anesthetized, MAC of isoflurane was 1.2%. When the cranial circulation alone was anesthetized, MAC was 2.9%. The conclusion from these three studies was that the movement response–reflex to skin incision is mediated primarily at spinal cord level.[24] This anatomic separation of EEG generator sites from the somatic motor control sites in the spinal cord may explain the inability of BIS, which is derived from cortical EEG, to predict reflex movement. Therefore, clinical endpoints used during the development of the BIS version 1.1 were reevaluated.

Reformulation of BIS

These data indicate that the hypnotic component of anesthesia (*i.e.*, "sleep") differs from the analgesic component[25] (fig. 3) and suggest that a satisfactory anesthetic state can be obtained by a balance of hypnotic drugs (*e.g.*, volatile or intravenous anesthetics) and analgesic drugs (*e.g.*, opioids), resulting in unconsciousness and areflexia. Generally, a balance between hypnosis and analgesia is sought. If the dose of hypnotic agent is large, then relatively smaller amounts of analgesic are needed. If analgesic doses are relatively large, then hypnotic medications are decreased to avoid hemodynamic instability. Sedation was selected as the most appropriate clinical endpoint of hypnosis, and BIS was reformulated

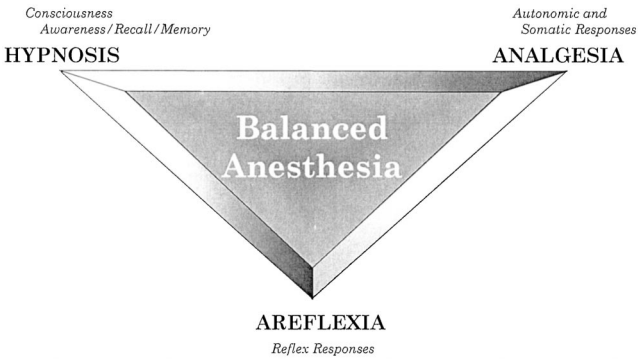

Fig. 3. Components of balanced anesthesia: separation of analgesia, hypnosis, and areflexia (based on Gray's triad).[25]

(version 2.0 and greater) from the existing database[26] (table 1).

A study in 72 volunteers established the relation between BIS, plasma drug concentrations, and level of sedation.[14] These data were also used to develop BIS version 3.0 offline. Steady-state equilibration of plasma drug concentration and effect-site or brain concentration were achieved using computer-controlled, pharmacokinetically driven infusion devices targeted to hold plasma drug concentrations constant for a minimum of 15 min. In these volunteers, the relation between BIS, sedation, and memory function were evaluated using propofol, midazolam, isoflurane (end-tidal concentration held constant) or alfentanil, administered individually. Concentrations of each individual drug were increased in a stepwise fashion after equilibration at each level in a sequence of three to four steps to beyond the level that would normally cause unconsciousness. Subsequently, doses were decreased in a stepwise manner and increased again, and then patients were allowed to recover, so any EEG evidence of acute tolerance could be evaluated. The BIS version 3.0 score ($r = 0.883$) correlated significantly better with the Observer's Assessment of Awareness/Sedation (OAA/S) than did the measured propofol concentration ($r = -0.778$, $P < 0.05$).[27] The correlations between BIS and OAA/S for isoflurane and midazolam were 0.85 and 0.75, respectively; these values were not statistically different from the correlation obtained between measured drug concentrations and OAA/S. BIS values representing unconsciousness (OAA/S = 2) in 50% and 95% of volunteers were 67 and 50, respectively. BIS version 3.0 also had a very high prediction probability (P_K)[28]§§ (0.88–0.98) for correctly identifying loss of consciousness. Alfentanil (50 or 100 ng/ml), alone or in combination with propofol,[29] did not influence this version of BIS. Gajraj *et al.*[30] studied 12 patients with spinal anesthetics (but no surgical stimulation) during repeated transitions from consciousness to unconsciousness following propofol infusions. At a BIS of 55, all patients were unconscious. No data presently exist on the effect of surgical stimulation on the thresholds (BIS) for awareness and memory under general anesthesia.

The BIS version 3.0 was also found to predict responsiveness to verbal command during sedation or hypnosis better than either targeted or measured serum propofol concentration (with or without nitrous oxide).[31] Katoh *et al.*[32] demonstrated the value of this BIS version as a tool for predicting depth of sedation and hypnosis in patients anesthetized with sevoflurane. The P_K[29] for BIS and sevoflurane concentration (0.966) was consistent over the entire sedative range. Both BIS and sevoflurane concentration had a linear relation with OAA/S. Loss of response to mild prodding, defined as a transition from OAA/S score of 2 to 1, occurred at a mean ED_{50} BIS of 66 (95% confidence interval [CI], 64–68; $ED_{95} = 58$). No EEG parameter, including BIS, was a significant predictor of movement in response to skin incision in this study. Other studies confirmed the relation between BIS and level of sedation after midazolam,[33] intraoperative recall after propofol sedation,[34] and suppression of learning after propofol.[35] Taken together, these data suggest that BIS accurately reflects the degree of sedation with volatile and intravenous hypnotic agents, including midazolam. However, reformulation of the BIS decreased the ability to predict movement responses or hemodynamic changes to painful surgical stimulation.[36]

The ED_{50} for unconsciousness (BIS 67) in volunteers[14] was confirmed in paralyzed patients anesthetized with thiopental or propofol.[37] In this study, patients received a single dose of propofol or thiopental and were paralyzed with vecuronium (0.1 mg/kg). The forearm was isolated from the neuromuscular blocking agent by a tourniquet inflated above systolic blood pressure, and return of consciousness was defined as the patient squeezing the investigator's hand twice in response to command. In this study, no patient recovered consciousness with a BIS less than 58, and a BIS of 65 signified a less than 5% probability of return of consciousness within 50 s. BIS did not specifically identify when a particular patient would return to consciousness. This was confirmed by other investigators.[30,38] A limitation of all the "return of consciousness" studies described in this review is that they were conducted in the absence of noxious stimulation. It should also be noted that the definition of "return to consciousness" varies widely across the referenced studies and does not consistently include evaluation of complex command performance (*e.g.*, "move your left hand" or "squeeze my hand twice"). Ethical concerns make it impossible to intentionally provoke return of consciousness during the noxious stimulation of surgery. Thus, there are no data to provide confidence in transferring consciousness thresh-

§§ Prediction probability (P_K) has a value of 1 when the indicator predicts observed anesthetic depth perfectly, and a value of 0.5 when the indicator predicts no better than a 50:50 chance.

olds determined from volunteer studies into the practice of clinical anesthesia.

Pharmacokinetics, Pharmacodynamics, and BIS

Electroencephalographic power spectral parameters display complex relations with hypnotic drug dose that are unique to each class of agents.[39] As mentioned previously, BIS and intravenous or volatile hypnotic dose have been shown to correspond in a statistically significant, linear, monotonic fashion during clinical trials, with BIS decreasing as hypnotic dose increased.[29,32,35,40] When modeling effect-site concentrations of sevoflurane or isoflurane in surgical patients before intubation, BIS had a high predictive power (median coefficients of determination, 0.92 and 0.93, respectively) and displayed some hysteresis (effect site equilibration half time ($t_{1/2}k_{e0}$), 3.5 ± 2.0 min and 3.2 ± 0.7 min, respectively) with end-tidal anesthetic measurements.[40] Quantitative analysis of hysteresis provides information on the speed of onset–uptake and offset–elimination of anesthetic action, whereas monitored or estimated plasma or effect-site drug concentrations does not. The only previous investigation of the dynamic relation between BIS (version 1.1) and end-tidal volatile anesthetic concentration cannot be directly compared because of subsequent reformulation of the BIS.[39]

To date, the most direct evidence linking BIS to brain cellular activity was provided by Alkire, who investigated the correlations between cerebral metabolic rate, sedation, and BIS.[41] With each patient serving as his or her own awake baseline control, regional cerebral metabolic activity was imaged using positron emission tomography under three different conditions: propofol sedation, unconscious propofol, or isoflurane anesthesia. Alkire found that the magnitude of the anesthetic-induced changes in the EEG, evident during sedation and light anesthesia, paralleled the reduction in global cerebral metabolism. Reduction of whole-brain metabolic activity was dose-dependent and decreased in a linear fashion.

The BIS has recently been used as a surrogate measure of anesthetic effect on the brain and employed as the control variable for closed-loop feedback for propofol-based general anesthesia. Mortier *et al.*[42] used effect-site–targeted, computer-controlled propofol infusions continuously adjusted to maintain an average BIS of 65—a BIS value at which patients lost consciousness. This feedback model was able to "clamp" BIS levels by adjusting effect-site propofol concentration to within 10–20% of predicted values despite varying levels of stimulation.

Sedation, Learning, and Memory

There are limited data on the relation between BIS and memory formation under sedation and anesthesia. Liu *et al.*[33,34] demonstrated that BIS correlates well with OAA/S during sedation with both propofol and midazolam during surgery under regional anesthesia. An OAA/S score of 3 or response to a loud voice corresponded to a BIS value of 87 ± 6 and a 40% probability of recall. An OAA/S score of 2 or response to mild prodding corresponded to a BIS value of 81 ± 8 and represented a complete lack of picture recall. In volunteers administered a trivia-type question task, propofol causes a concentration-related impairment of learning.[35] Based on nonlinear regression analysis, learning was suppressed by 50% at a BIS value of 91 ± 1. These findings were validated by Iselin-Chaves *et al.*[29] in volunteers during propofol anesthesia. Recall was impaired at much higher BIS values than response to command with BIS_{50}‖ of 89 (95% CI, 85–93) and BIS_{95} at 79 (95% CI, 70–88) for recall and BIS_{50} of 64 (95% CI, 61–66) and BIS_{95} of 49 (95% CI, 45–54) for consciousness. It should be noted that these studies were conducted in the absence of surgical stimulation.

Lubke *et al.*[43] assessed explicit and implicit memory formation in 96 acute trauma patients across a wide range of BIS values (20–90) during surgery. Memory was tested by stem completion of words presented intraoperatively. No patient had documented "explicit" awareness. However, there was a clear relation between BIS and the ability of patients to complete word stems with words heard during surgery (implicit memory), *i.e.*, at higher BIS levels, patients were more likely to accurately complete word stems than would be expected by chance. Auditory information processing occurred even at BIS levels between 60 and 40. This study demonstrated that memory formation was related to the depth of hypnosis.

Hypnotic titration using BIS has been associated with a reduction in anesthetic agent dosage (see examples in Clinical Utility Trials).[44,45] This reduction in anesthetic dose could theoretically lead to an increase in the incidence of awareness. The incidence of awareness during elective general anesthesia has been reported to be between 0.2% (elective and emergency surgery)[46] and 0.4% (elective surgery).[47] To date, there have been approximately 1,000,000 uses of BIS with an incidence of awareness 0.003% (35 cases) reported to Aspect Medical Systems as of February 2000 (Manberg P, Aspect Medical Systems, Natick, MA, personal communication). BIS was 65 or greater in 17 cases in which BIS trends were available. Eighteen cases were inconclusive because of either a lack of BIS recording (6 cases) or inconsistent descriptions or timing of events (12 cases). Therefore, although the incidence of awareness may be underreported, use of BIS monitoring to guide anesthetic delivery does not appear to increase the likelihood of awareness.

‖ BIS_{50} or BIS_{95} defines the BIS at which 50% or 95% of subjects, respectively, had no response.

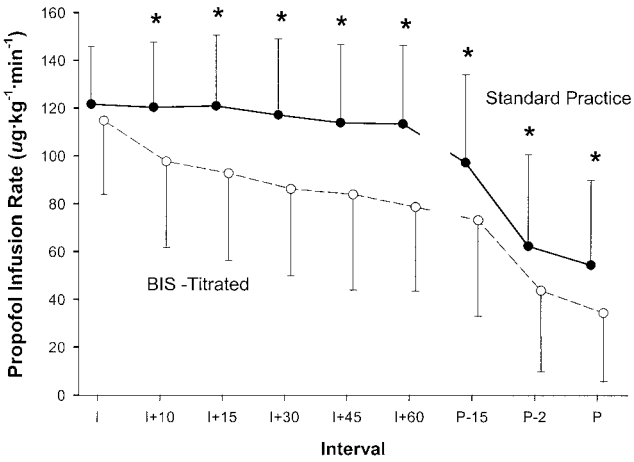

Fig. 4. Plot of propofol infusion rates ($\mu g \cdot kg^{-1} \cdot min^{-1}$, mean ± SD) at various milestones during surgery. The solid line with closed circles indicates the standard practice group, and the dashed line with open circles indicates the Bispectral Index Scale (BIS) group (titration to BIS 45–60). Endpoints are abbreviated as time from procedural start (I) to discontinuing propofol (P). The numbers accompanying these abbreviations refer to minutes before or after the respective endpoint. Statistical significance ($P \leq 0.05$) is indicated with an asterisk. Adapted from Gan *et al.*[44]

Clinical Utility Trials

A patient's response to sedation and hypnosis is difficult to predict because of a complex interplay of factors, including coadministration of multiple synergistic medications and significant individual pharmacokinetic and pharmacodynamic variability. Continuous real-time measurement of anesthetic effect using BIS should allow optimization of drug delivery to each patient, preventing both potential underdosing and overdosing of hypnotic medications. The upper limit of hypnotic titration is defined by the absence of awareness and memory. It should also be associated with the minimum dose of hypnotic agent. Prevention of relative hypnotic overmedication should theoretically speed emergence and recovery.

Gan *et al.*[44] reported a randomized, controlled, blinded, multicenter trial in 302 patients using a standard propofol–alfentanil–nitrous oxide anesthetic technique. Patients were randomized either to a blinded, standard practice group or to standard practice with BIS titration. Propofol infusions were adjusted by clinical observation in the standard practice group and by titration to BIS values of 45–60 during maintenance (60–75 prior to emergence) in the unblinded group. Anesthetic maintenance in the standard practice group typically resulted in average BIS values in the low 40s compared with approximately 50 in the treated group. The propofol infusion rate required for maintenance of anesthesia was decreased in the treated group compared with the standard practice group (fig. 4). Although the total propofol dose used was lower in the BIS group, the total duration of anesthesia was also significantly shorter in this group. Time to extubation was 11.22 min (95% CI, 8.51–13.60 min) in the control group and decreased to 7.27 min (95% CI, 6.23–8.28 min) with BIS titration. In the BIS-monitored group, 43% of patients were fully orientated on arrival in the postanesthesia care unit compared with 23% in the standard practice group. The incidence of postoperative complications did not differ between groups. This study demonstrated that hypnotic titration during anesthetic maintenance can speed emergence and recovery from anesthesia while reducing propofol use.

Song *et al.*[45] studied female outpatients undergoing laparoscopic tubal ligation. Patients were randomly assigned to receive either desflurane or sevoflurane anesthesia, and the anesthesiologist was either unaware of BIS value (blinded) or used BIS (to a value near 60) to titrate volatile anesthetic dose. BIS values in the blinded groups averaged 40 during anesthetic maintenance, whereas those in the titration groups averaged 60. Volatile anesthetic usage decreased significantly by 30–38% compared with blinded controls. Time to extubation decreased from 6.5 ± 4.3 min (mean ± SD) to 3.6 ± 1.5 min (45% decrease) for desflurane and from 7.7 ± 3.5 min to 5.5 ± 2.2 min (29% decrease) for sevoflurane. With BIS monitoring, time to verbal responsiveness decreased from 6.0 ± 3.4 min to 2.8 ± 1.2 min (53%) for desflurane and 7.6 ± 2.7 min to 5.0 ± 2.0 min (34%) for sevoflurane. However, time to orientation, duration of postanesthesia care unit stay, time to oral intake, and time to home-readiness were not affected by BIS monitoring.

Known Limitations of BIS Monitoring

In contrast to other anesthetic agents, ketamine is a dissociative anesthetic with excitatory effects on the EEG. Ketamine doses of 0.25–0.5 mg/kg sufficient to produce unresponsiveness did not reduce BIS.[48,49] When ketamine was used in conjunction with propofol sedation, there was an additive interaction to achieve hypnotic endpoints,[50] yet ketamine did not change BIS values.[50,51] Thus, it appears that BIS cannot be used to monitor hypnosis during ketamine anesthesia.

Inhalation of nitrous oxide at levels of up to 50% does not alter BIS, nor does it cause unconsciousness.[52] At 70% nitrous oxide, responsiveness to voice command is lost, but BIS does not change.[53] Thus, sedative concentrations of nitrous oxide do not appear to affect BIS, which is consistent with its use as a hypnotic index. 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.[31] However, no studies have investigated the effect of the addition of nitrous oxide to a stable general anesthetic during surgical stimulation.

Data are currently lacking regarding opioid dose–responses and interaction of opioids (across a wide spectrum of doses) with hypnotics on BIS. No studies have

evaluated the utility of BIS monitoring in anesthetics based on large doses of opioids.

There is insufficient data to evaluate the use of BIS in patients with neurologic disease. In one subject who was subsequently found to have a genetically determined low-voltage EEG, BIS values were abnormally low (awake baseline = 40).[54] In the intensive care unit (ICU) setting, BIS did not reflect mental status in encephalopathic or neurologically injured patients.[55]

Significant electromyographic (EMG) activity may be present in sedated, spontaneously breathing patients, interfering with EEG signal acquisition and contaminating the BIS calculation. Conventionally, EEG signals are considered to exist in the 0.5- to 30-Hz band and EMG signals exist in the 30- to 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 conventional EEG band range. This EMG activity is 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. Although quantitative EMG activity (decibels) can be displayed on the monitor, there is no simple method to correct the BIS value. Therefore, BIS values that are unexpectedly high based on clinical observation should be interpreted concurrently with the amount of EMG activity.

Other Applications of BIS Monitoring

Pediatrics

Only adults were used to develop and test the BIS. The influence of neuronal and physiologic maturation of the brain on BIS, as well as its correlation to drug effects and anesthetic outcome, is unknown in pediatric patients. Significant barriers exist to defining and testing awareness in the pediatric population, and adult guidelines should not be adopted without validation. Correlation between awareness, level of sedation, and anesthetic outcome with BIS in children have not been published. However, Denman *et al.*[56] reported an approximately linear relation between BIS and end-tidal sevoflurane concentration in infants and children. BIS decreased by 50% in infants younger than 2 yr of age at an end-tidal sevoflurane concentration of 1.55% (95% CI, 1.40–1.70%) compared with 1.25% (95% CI, 1.12–1.37%) in children, consistent with the known increase in MAC in this age group.[57,58] More work is necessary to establish whether BIS provides an age-independent measure of hypnotic drug effect.

Sedation: Monitored Anesthesia Care and Intensive Care

Validated sedation scales, such as the five-point OAA/S,[27] have been used to measure the level of alertness in sedated patients and in the development of the BIS. As described previously, a number of investigators have replicated the high correlation between BIS, hypnotic drug concentration, and OAA/S for perioperative sedation.[29,33–35] It follows that BIS may be effective for defining adequate sedation during monitored anesthesia care, preventing inadvertent and unrecognized oversedation. Iselin-Chaves *et al.*[29] described the BIS_{50} for loss of consciousness as 64–72 and the BIS_{50} for lack of recall as 83–89. BIS correlated more significantly than any other EEG variable with both loss of consciousness and return to consciousness after midazolam[33] and propofol sedation.[34] These studies suggest that BIS values of 65–80 define an acceptable loss in conscious information processing and recall during sedation–hypnosis.[29,31,33,34]

Propofol and midazolam are both used extensively for long-term sedation in ICUs despite poorly defined clinical endpoints and significant pharmacy costs. The influence of multisystem failure on hypnotic pharmacokinetic-pharmacodynamic response is unpredictable in these patients. It would probably benefit patients and speed recovery from long-term sedation to accurately monitor and titrate hypnosis in the ICU. It is not known whether patients should receive continuous, unvarying hypnotic infusions or whether doses should be cycled to allow periods of wakefulness or sleep. Natural sleep can decrease BIS markedly, although clear identification of natural sleep using BIS may be difficult.[59] A direct measure of individual, hypnotic pharmacodynamics would allow adjustment for tachyphylaxis and tolerance during long-term hypnotic infusions. However, future investigations must address the meaning of awareness and recall in the ICU setting. A number of logistical problems must be solved for continuous 24-h recordings of patients in the ICU (*e.g.*, electrodes, montage, EMG activity) The ICU is an electrically hostile environment for recording EEG, and it is unclear how much useful information can be derived in this setting.[55] Evaluating the BIS in the ICU is a fruitful area of research, because preliminary data from the ICU suggest that oversedation is common.[60]

Current Perspective

BIS was developed using clinical endpoints of sedation and relates monotonically to both the hypnotic component of anesthesia and to anesthetic drug concentration. It has been tested and validated in prospective, randomized clinical trials. BIS indicates both the potential for awareness and of "relative" hypnotic overdose but does not predict movement or hemodynamic response to stimulation, neither can it predict the exact moment consciousness returns.

Some limitations exist to the use of BIS. It is not useful during ketamine anesthesia or in patients with neuro-

logic disease. Although advances in sensor technology have produced an easily applied, three-electrode forehead sensor, this sensor will not function beyond the hairline. EMG activity from electrode placement over the frontalis and temporalis muscles can contaminate and falsely elevate the BIS. Anesthesia providers must be trained to detect EMG activity and to be aware of the problems involved in monitor and sensor application. A future version of the BIS, intended to make the index less sensitive to EMG contamination, is being developed (Chamoun N, Aspect Medical Systems Inc., Natick, MA, personal communication).

As we move toward more evidence-based medicine, new technologies will have to be assessed in a manner that demonstrates both their efficacy and utility in clinical practice.[61] Our understanding of the clinical application of this new technology is in its infancy, and its full contribution to the practice of anesthesiology has yet to be determined.

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