

Perioperative monitoring with the electroencephalogram and the bispectral index monitor

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Recent clinical studies using the bispectral index monitor to predict movement, measure the level of consciousness, and reduce the cost of anesthesia have renewed interest in the use of a monitor to assess the effects of anesthetics on the brain. In 1937, Gibbs described electroencephalographic changes during the administration of general anesthetics. Artusio in 1954 used unprocessed electroencephalographic waveform analysis during an ether anesthetic to study the first stage of anesthesia. Some of the first automated electroencephalographic processors used power spectrum analysis for assessment of the patient's brain activity during surgery and anesthesia. The purpose of this article is to provide a historical perspective of the development and use of the processed electroencephalographic monitor. This article also describes studies of clinical usefulness of the bispectral index monitoring device in anesthesia practice today.

Key words: Bispectral index, electroencephalogram power spectrum.

The history of memory formation during general anesthesia

Until the introduction of curare by Griffith and Johnson in 1942, movement during general anesthesia combined with the Guedel stages of anesthesia served as the primary means of detecting light anesthesia. By using curare, anesthesia providers could prevent movement during general anesthesia and not affect the level of consciousness or amnesia.¹ In 1959, Cheek² introduced a hypnotic technique for assessing memory in patients during surgery. Cheek hypnotized 37 subjects who underwent 52 operations with general anesthesia and found that 6 patients ostensibly in a surgical plane of anesthesia heard sounds and conversations.² In another study, Levinson³ simulated a hypoxic anesthesia crisis during the surgical procedures of 10 patients. One month later and under hypnosis, 4 of the 10 subjects reproduced the words spoken by the anesthesia provider during the crisis.³ The patients were anesthetized with oxygen, nitrous oxide, and ether in the third plane of anesthesia verified by an electroencephalogram (EEG).³ Levinson's study showed that subconscious or implicit memory formation can occur in a surgical plane of anesthesia.

Before Levinson demonstrated implicit memory formation, Hutchinson⁴ reported a 1.2% incidence of awareness or explicit memory formation

in a sample population. An analysis of the American Society of Anesthesiologists' closed claims database found the incidence of awareness during general anesthesia was 2%.⁵ Awareness was found to have the same incidence as hepatic dysfunction, myocardial infarction, burns, aspiration pneumonia, and back pain. The patient who experiences awareness can develop a permanent disability due to recurrent nightmares, sleep disturbances, impaired social interactions, difficulties at work, and post-traumatic stress disorder.⁵ The American Society of Anesthesiologists' closed claims analysis identified female sex, gynecological and obstetric procedures, use of muscle relaxants, use of opioids, and not using volatile anesthetics as the major risk factors that increase the claim for awareness during general anesthesia.

While it is difficult to state exactly why awareness during general anesthesia occurs, one explanation is the reality that determining the adequate stage for general anesthesia in surgical patients remains difficult.⁶ The level of anesthetic concentration at which awareness occurs is currently unknown, and a direct method to measure the adequacy of general anesthesia is not available.⁶ In addition, researchers and clinicians still do not know how inhaled anesthetics prevent movement and cause amnesia in the cells of the spinal cord and brain.⁷

Anesthesia providers do not routinely use the EEG to monitor the effect of anesthetics on the brain's electrical activity. The patient's level of anesthesia is determined by observation of physical signs and data from indirect monitors such as the blood pressure, heart rate, and the peripheral nerve simulator, which collectively offer minimal indication of the patient's level of consciousness.

The EEG as an intraoperative monitor

In 1875, a British physiologist reported that electrical currents of varying directions can be detected when electrodes are placed on 2 points of the external surface of the brain or 1 electrode on the gray matter and 1 on the surface of the skull.⁸ Studies with this device, which was called the electroencephalogram, continued on animals until 1929 when Hans Berger described the electroencephalogram of humans.⁸ In 1934 Adrian and Matthews replicated Berger's work.⁸ Studies continued as the EEG became a standard diagnostic tool for the detection and diagnosis of numerous central nervous system diseases. In 1937, the use of the EEG as an intraoperative monitor became a topic of debate and research after Gibbs et al⁹

described EEG changes during the administration of general anesthetics. During World War I, Gudel¹⁰ defined the stages and planes of anesthesia that have become classic indicators of the progressive depression of the central nervous system during inhalation anesthesia.

In 1954, a study by Artusio¹¹ differentiated the first stage of anesthesia from the other stages of anesthesia using an electroencephalographic method. Gudel did not emphasize the first stage as a light plane of anesthesia.¹¹ With an increase in cardiac surgery for the correction of acquired or congenital defects, there was a need to avoid deep planes of anesthesia. The first stage of anesthesia, called analgesia, is the period from the beginning of induction to loss of consciousness. Stage 1 is divided into 3 planes: plane 1 ends with the appearance of partial amnesia, plane 2 ends with the onset of complete analgesia, and plane 3 ends with the loss of consciousness.^{10,11} While changes in conscious activities are progressive throughout the first stage of ether anesthesia, the most pronounced changes in cognitive function were noted during stage 1, plane 3. Artusio¹¹ could not separate the course of events during stage 1 using the unprocessed EEG by itself. The division of the Gudel first stage of anesthesia into 3 planes was accomplished by observation and questioning of patients. Artusio¹¹ reported a specific electroencephalographic pattern for ether analgesia that he called stage 1, plane 3, which was defined by a combination of electroencephalographic waveform analysis and observation of the patient. Artusio's study described the challenge of visual interpretation of the unprocessed EEG and clinical correlation of changes in the patient's level of consciousness.

From the early 1950s until today, the EEG has been used to monitor brain function during high-risk surgical procedures, such as cerebrovascular and cardiopulmonary bypass.¹²⁻¹⁴ However, the unprocessed EEG in the operating room has a number of problems. Observation and interpretation of the subtle changes in an EEG require a trained electroencephalographer.¹⁵ The sensitivity of the conventional 8- to 32-channel EEG strip chart is only as good as the experience and vigilance of the observer. When a standard electroencephalographic machine is used to monitor the brain in the operating room, 15 minutes of continuous monitoring can generate 90 pages of multi-channel electroencephalographic recordings.¹⁶ Even for the experienced observer, visual comparison of previous electroencephalographic segments and detection of changes becomes cumbersome.

Development of the processed EEG

In more recent years, researchers focused on the development of a computer-processed EEG that analyzes and displays information from the EEG in a compact quantitative format. Automated EEG processors that identify changes in anesthetic depth too small to be identified by routine observation techniques used by an electroencephalographer were developed during the 1960s.¹⁷ The early automated processors used power waveform analysis, which is derived from amplification, Fourier analysis, and histogram plotting. The processors amplify and transform the EEG, converting signals from an analog to a digital array of numbers for mathematical analysis. These early EEG processors were based on a linear mathematical model that assumes a stationary Gaussian or bell curve.¹⁸ Early linear processors assumed the statistical properties of the signal do not change, and the amplitudes of the EEG signal are normally distributed.

The most common mathematical technique for statistical analysis of linear EEG signals uses a formula developed by the French mathematician, Jean Baptiste Fourier.¹⁸ Fourier analysis separates the EEG into a number of component sine waves with different amplitudes whose sum is equal to the original waveform. Thus, complex nonstandard waveforms are converted into a number of standard waveforms, and comparisons between the waveforms are simplified.¹⁹ Early in the evolutionary search for a processed EEG, Fourier analysis was applied to EEG signals. Fourier transform analysis is a process that provides information about frequencies that are implicit in the EEG.¹⁹ With the advent of the digital computer in 1965, fast Fourier transform analysis led to a substantial increase in Fourier computation of EEG data. Fourier transform analysis converts a signal from a time domain representation in which amplitude or power is a function of time, to a frequency domain representation in which amplitude or power is a function of frequency.²⁰

The Fourier transform analysis is composed of a series of values at discrete points.¹⁹ The values can be plotted as a histogram with frequency on the horizontal axis and voltage on the vertical axis.¹⁵ The resulting histogram is known as a power spectrum¹⁵ (Figure 1). When fast Fourier transform analysis is completed, data can be displayed in formats known as the compressed spectral array, the density spectral array, or the band spectral array. The compressed spectral array format was developed by Bickford and is a commonly

used display of electroencephalographic power spectral analysis¹⁵ (Figure 2).

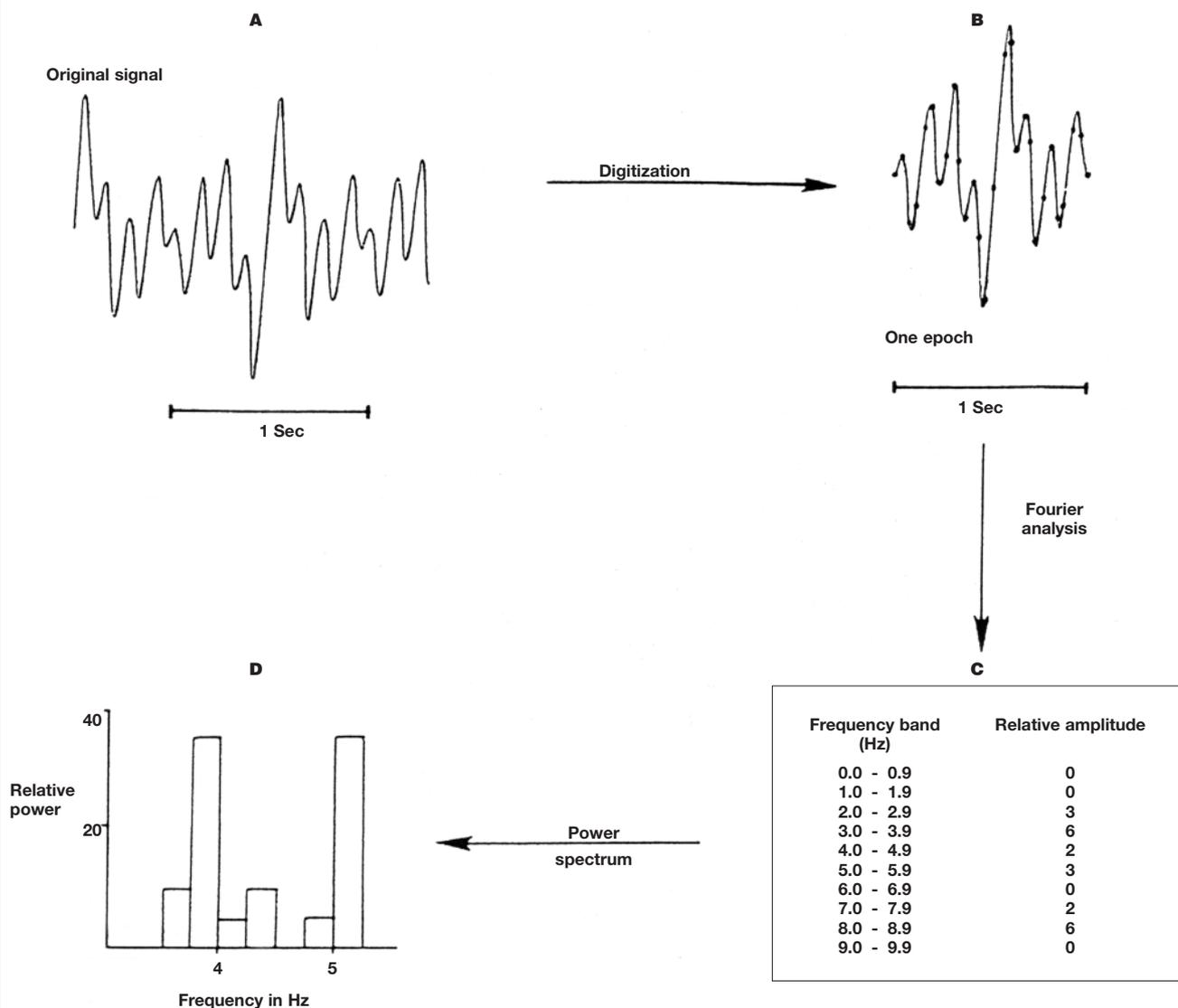
Despite the accurate and useful information obtained with electroencephalographic power spectral analysis, the application of this statistical linear model fails to quantify changes in the EEG that are nonlinear.^{21,22} Power spectral analysis of the EEG provides trend information about changes in the anesthetic depth, but these trends are not sufficiently reliable to be used as an indicator of anesthetic depth or level of consciousness.^{23,24} Power spectral analysis quantifies only the power distribution as a function of frequency, which ignores the phase information in the EEG. The electroencephalographic power spectral analysis also assumes that the statistical properties of the EEG are made by a linear superimposition of statistically independent sinusoid wave components.¹⁹ Biologic systems like the brain exhibit nonlinear nonsinusoidal waveforms that do not conform to the linear assumptions of conventional power spectral analysis.¹⁹

Bispectral analysis explores the phase relations within the EEG that are not analyzed by power spectral analysis. This processing technique analyzes both amplitude and frequency, making bispectral analysis more sensitive.¹⁹ Bispectral analysis further differentiates the EEG signal because it determines the phase relations or inter-frequency coupling among all the component waves of the EEG.^{25,26} Initially used for waveform analysis by geophysicists in the early 1960s, bispectral analysis is a signal processing technique that was used infrequently for decades because of the complex computational requirements. When researchers combined the developments of a high-speed computer microprocessor for fast Fourier transform analysis with bispectral analysis, new interest in the field of electroencephalographic research began.

The bispectral analysis measurement

Bispectral analysis is a processing technique that measures the correlation of phase relationships between different frequency components in the electroencephalographic signals.²⁶ Specifically, this analysis technique quantifies the traditional amplitude and frequency of the EEG with the level of synchronization in the waveforms. It does so by quantifying the phase coupling or synchronization between 2 frequencies and a third frequency resulting in a harmonic.²¹ In 1971, Barnett et al²⁷ identified the measure of cross-coupling or phase between 2 frequencies that they called the *bicoher-*

Figure 1. A schematic representation of the process of power spectrum analysis*



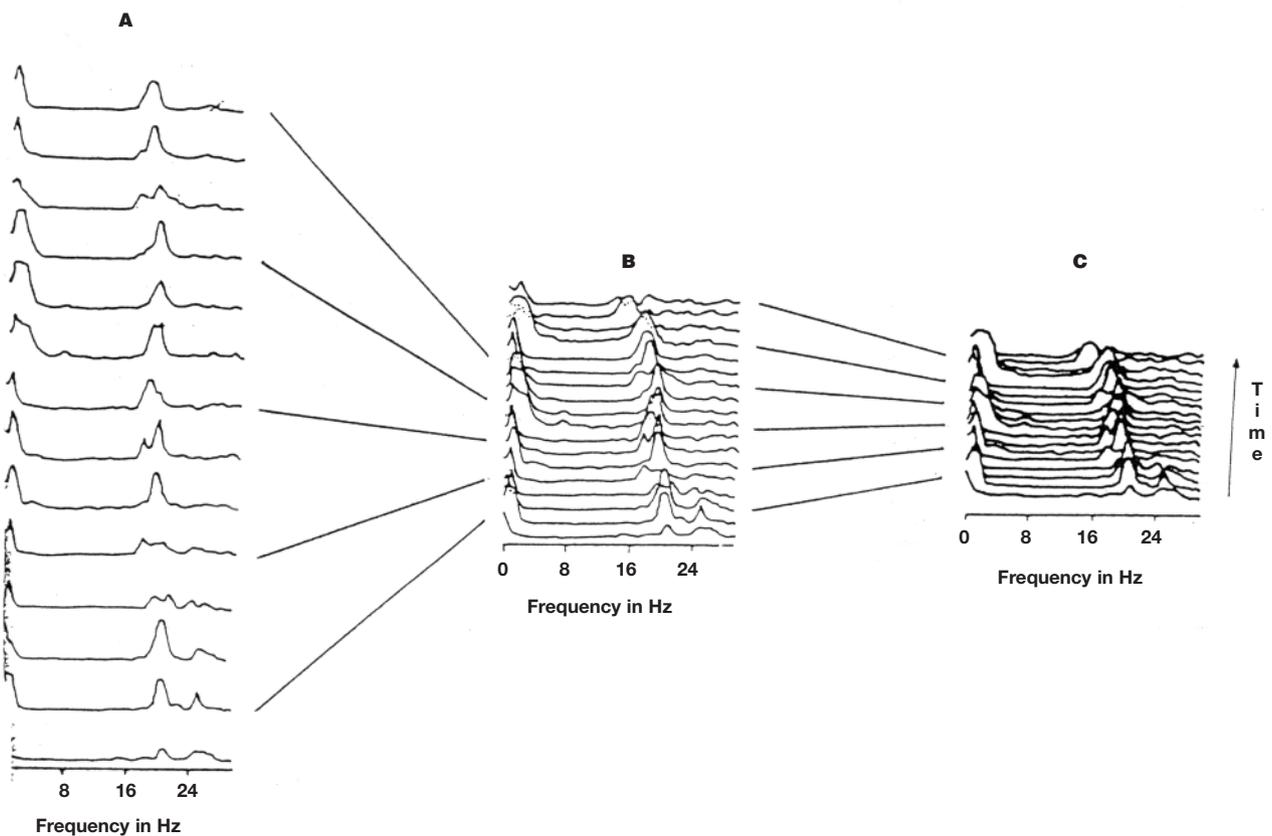
The original continuous waveform (A) is put in digital form by sampling it repeatedly at small intervals, here 1/28th of a second. One epoch of these data (B) is then passed to a computer program to perform a Fourier analysis. The result of this analysis, shown in (C), is a table giving the amplitude of the activity in each frequency band. Finally, the amplitudes are squared (to give power) and plotted as a histogram.

* Reproduced with permission from Levy.¹⁵

ence. Bicoherence is the bispectrum normalized to range from 0% to 100%.¹⁹ The bicoherence or phase coupling between 2 frequencies can vary from 0%, if no harmonic is generated, to 100% if a harmonic is generated.²¹ Bispectral analysis of the phase coupling between 2 frequencies or the bicoherence provides a more comprehensive description of the Fourier transform analysis. The result is a more thorough analysis of the changes in the EEG during sedation and general anesthesia.

The bispectral index (BIS) was derived by identifying characteristic changes in the electroencephalographic bispectrum with periods of altered cerebral function, such as the changes seen with anesthetics. The electroencephalographic changes primarily correlate with the patient's hypnotic state and provide less information about analgesia. The BIS was developed using computerized electroencephalographic signal processing techniques that translate parameters of different

Figure 2. Formation of the compressed spectral array*



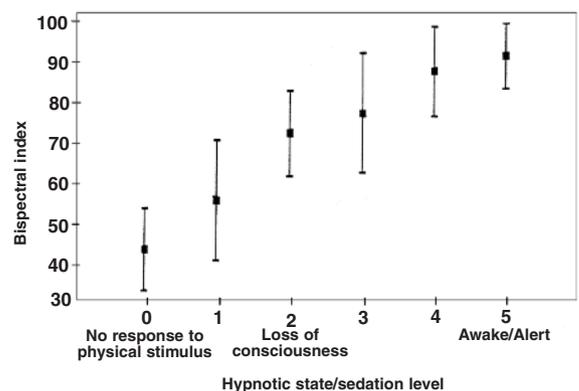
Individual epochs of analysis (A) are plotted closely above one another (B), and a "hill and valley" pattern begins to emerge. This is enhanced by the suppression of lines that would be behind a hill. In the center panel, these lines are dotted, while in the fully compressed picture (C), they have been omitted entirely.

* Reproduced with permission from Levy.¹⁵

cerebral states using bispectral analysis of the EEG.¹⁹ Bloom et al²⁸ studied whether subjects who responded to a mild stimulus showed a greater rise in the BIS value than subjects who did not respond. Subjects who were awake or those deeply asleep showed the least change in the BIS value.²⁸

In a multicenter study in which the BIS was shown to correlate with changes in the level of hypnosis produced by anesthetics and sedatives, a range of values was developed.²⁹ As shown in Figure 3, a BIS in the 85 to 100 range represents a patient who is completely awake, and a BIS in the 35 to 55 range represents a patient who is not responsive to a painful physical stimulus.³⁰ No response to a painful stimulus implies that the patient should not have a cognitive psychomotor response, while blood pressure and heart rate may change.

Figure 3. Level of the bispectral index at each of the sedation levels*



* Values are the means, and error bars indicate the SD. Reproduced with permission from Aspect Medical, Inc.³⁰

Clinical studies to predict movement

Early clinical trials focused on the use of the BIS monitor to predict movement following skin incision during general anesthesia. It is widely known that the minimum alveolar concentration of volatile anesthetic agents is based on the ability of the anesthetic to prevent purposeful movement to painful stimuli in the animal model. Human studies showed that the BIS can better predict movement at the time of incision compared with conventional processed electroencephalographic analysis.^{31,32} A multicenter study showed that the BIS monitor is a useful predictor of response to skin incision during general anesthesia.³³ Kearsse et al³⁴ showed that the BIS monitor is a more accurate predictor of patient movement in response to skin incision during propofol-nitrous oxide anesthesia than power spectrum analysis of the EEG or blood plasma propofol concentrations.

Administering drugs to achieve a state of areflexia, analgesia, and amnesia is one goal of general anesthesia. Areflexia may or may not correlate with the patient's amnesic state or level of consciousness. Compared with intravenous opioids and sedative hypnotics, volatile anesthetic agents have different cellular and molecular mechanisms of action in the brain and spinal cord.

In an animal model, preferentially anesthetizing the brain with a high concentration of isoflurane while administering a very low concentration of isoflurane to the rest of the central nervous system showed that blockade of somatic responsiveness caused by volatile anesthesia occurs below the cerebral cortex.³⁵ In another animal model, Rampil³⁶ showed that inhibition of motor response by isoflurane may be in the spinal cord. Thus, the minimum alveolar concentration required to prevent somatic responsiveness may be independent of the level of consciousness in the brain. A study in humans showed that the type of anesthetic drug affected the accuracy of the BIS for detecting movement.³⁷ Changes in the BIS correlated with the incidence of movement following skin incision. With opioids and low-dose isoflurane and propofol, the correlation of the BIS value and patient movement was lower. This study³⁷ showed that when higher opioid concentrations are present at the time of skin incision, the correlation to patient movement becomes less significant or predictable. Observations using the BIS to predict movement led to research on the use of the BIS monitor to determine the effects of anesthetics on the brain.

The BIS as a monitor of anesthetic effects on the brain

In 1994 researchers presented results of a study evaluating the efficacy of the BIS for pre-

dicting emergence from general anesthesia.³⁸ Sawtelle and Rampil³⁸ showed that an increase in the BIS anticipates, by at least 1 minute, the responsiveness at the end of a general anesthetic. This observation led researchers to the hypothesis that the BIS may be useful for detecting awareness that could occur during lighter planes of anesthesia. In 1995, a study by Kearsse et al³⁹ to correlate changes in BIS with prospectively defined measures of sedation and hypnosis showed that the BIS was a strong predictor of patient response when using propofol for sedation in the presence of nitrous oxide. Based on additional clinical studies of safety and effectiveness, the BIS received marketing clearance from the US Food and Drug Administration as a monitor to measure the effects of anesthetics on the brain in October 1996.⁴⁰

Multicenter studies have shown that the BIS correlates better with responsiveness than the measured propofol concentration and can predict loss of consciousness.⁴¹ In a study to compare the correlation between propofol concentrations with suppression of learning with the 95% spectral edge frequency EEG and the BIS, the BIS value decreased as learning was suppressed, while the 95% spectral edge frequency EEG correlated poorly with suppression of learning.⁴² In studies designed to evaluate awareness and thinking in subjects receiving a hypnotic agent, the examiner must distinguish behavior that can be considered deliberate and willful from behavior that is non-specific and reflexive.⁴³ In a study in which one purpose was to determine whether changes in BIS correlate with subjects' responses to commands during propofol sedation and hypnosis, a strong association between the BIS and the response to commands was shown.⁴³ This study also indicated that the BIS is a better predictor of responsiveness than either targeted or measured serum propofol concentrations. In another study during sevoflurane administration, the BIS monitor was a useful complement to end-tidal sevoflurane to detect inadequate anesthesia during intubation and anesthesia maintenance.⁴⁴

Studies of cost analysis

A study was done to determine whether the addition of the BIS monitor to standard anesthetic care could result in improved patient recovery compared with current practice.⁴⁵ Blinded assessment of patients in the postanesthesia care unit (PACU) showed that with the use of BIS monitoring, patients recovered from general anesthesia faster.⁴⁵ In another study, the use of the BIS moni-

tor improved the accuracy of propofol titration and allowed faster emergence from propofol-alfentanil-nitrous oxide anesthesia.⁴⁶

Glass et al⁴⁷ hypothesized that using a BIS monitor would result in more efficient delivery of propofol compared with standard anesthetic practice. Assuming a propofol cost of \$8.32 for each 200-mg vial, an average of \$13.77 per anesthetic administered was saved using the BIS monitor. In the study by Glass et al,⁴⁷ the anesthetic was adjusted to achieve a target BIS value up to 60 until the last 15 minutes of the anesthetic, when the BIS was allowed to increase to a maximum of 75. Additional research was designed to study adult patients receiving general anesthesia who were extubated according to PACU discharge criteria with no restrictions on the use of hypnotic or analgesic medications. Use of the BIS monitor to guide titration of anesthetic agents resulted in indirect cost savings of \$80 per patient.⁴⁸ The savings resulted from a decrease in extubations in the PACU, time to leave the operating room, and total PACU time.⁴⁸ A study conducted in an ambulatory surgery center using the BIS monitor concluded that anesthesiologists can safely identify, while still in the operating room, the patients who are most suitable for bypass of phase I PACU recovery.⁴⁹ In that study, patients with average maintenance BIS levels of more than 45 were more likely to bypass phase I PACU.

The use of the BIS to predict movement, monitor the effects of anesthetics on the brain, and guide titration of anesthetic agents may lead to better quality and lower costs of anesthesia care. From the early electroencephalographic research of Hans Berger to the BIS clinical trials of today, the use of electroencephalographic monitoring devices to measure the effects of anesthetics on the brain continues.

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