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SPECIAL ARTICLE

Brazilian consensus on anesthetic depth monitoring



Consenso brasileiro sobre monitoração da profundidade anestésica

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Introduction

One of the most important gains in anesthesia was the recent admission that light anesthesia, awakening, intraoperative awareness, and memory are all real problems with deleterious psychological consequences for a significant portion of patients.¹ On the other hand, deep anesthesia appears to be associated with increased morbidity and mortality.²

Maintaining the adequate level of anesthesia depth is critical. Very superficial or deep depth levels can be disastrous in both the short and long run. The patient expects that the procedure be absolutely painless and throughout the surgery he is asleep, without any perception

or memory of what happened during that period. It is important to emphasize that this concept is applied to general anesthesia, and a patient should always be well informed if the anesthetic approach is a regional anesthesia with sedation, a situation that may have awakening episodes not associated with pain or immobility.

Accidental intraoperative awareness (AIA) is the undesirable outcome of insufficient anesthesia. Consciousness research takes into account the ability of an individual to present responses to stimuli and/or commands.

Cerebral monitoring is necessary in current clinical practice of anesthesiology. Avoiding excess anesthetic doses is of great importance, not only because there is the possibility of reducing the immediate adverse effects of anesthetics, such as cardiovascular and respiratory depression, but also to prevent cognitive impairment in patients with low neuronal reserve. AIA is the most feared anesthetic complication regarding the improper administration of anesthetic

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agents. Autonomic signs are not able to guide the adjustment of drugs, as there are many components of the clinical context that interfere with autonomic function.

This paper aims to evaluate concepts related to anesthetic depth monitoring, as well as to show the current evidence and present recommendations for the use of intraoperative monitoring of brain electrical activity. The recommendations may be adopted, modified, or rejected according to clinical needs and possible restrictions.

Concepts

In order to prevent unintentional awakening and deep anesthesia damage, the advancement in the field of brain monitoring and more adequate understanding of the neurobiological processes involving consciousness and memory were necessary. For a proper understanding of this approach, some concepts are important:

- (a) Awareness—a term with broad meaning. For neuroscience, it translates the relationship between the individual and the environment, his responses to external stimuli and self-perception. It has two components: level of consciousness and content of consciousness.³
- (b) Level of consciousness (arousal/wakefulness)—refers to the wakefulness or asleep state. There is an integration of certain nuclei present in brain stem, hypothalamus, and basal ganglia that will inhibit or stimulate the cortex and thalamus, regulating the sleep-wake cycle.⁴
- (c) Content of consciousness (awareness)—refers to the set of information established in functional bases of cortical and thalamic-cortical system. While the subcortical structures interact to keep the cortex awake and stimulated, specific regions of the cortex have a role to process the contents of consciousness.⁵

The level of consciousness may not be related to the content of consciousness. A comatose patient has a reduced level and content of consciousness. Patients in a vegetative state have their sleep-wake cycles intact, but compromised content of consciousness, not being able to interact voluntarily, recognize people, or process information⁶ (Fig. 1).
- (d) Memory—it is the acquisition, development, conservation, and retrieval of information. They are classified according to the duration, function, and content.⁷
- (e) Declarative or explicit memory—refers to information voluntarily or spontaneously redeemed.
- (f) Non-declarative implicit memory—refers to information that is not voluntarily or spontaneously redeemed, able to generate behavioral changes.⁸
- (g) Amnesia—deficit in the formation or retrieval of memories. Anesthetics may affect both explicit and implicit memory, but explicit memory appears to be more susceptible to drug-induced amnesia.⁹

Clinical monitoring of anesthetic depth

Some physiological parameters are used to measure anesthetic depth and guide the anesthetic choice and dose titration. Blood pressure, heart rate, breathing pattern changes, somatic and skeletal motor activities, sweating,

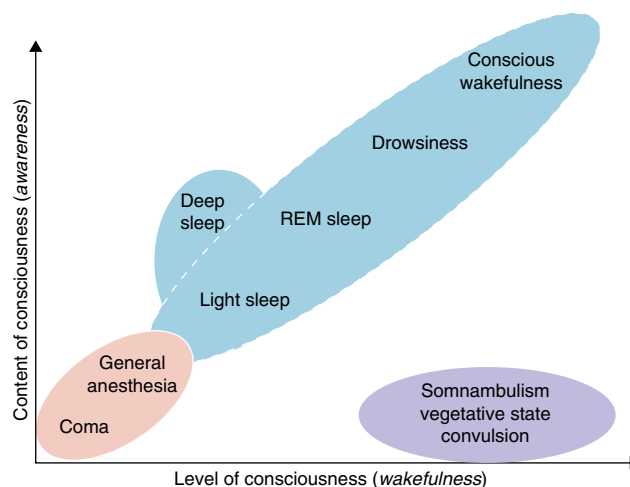


Figure 1 Components of consciousness: level and content of consciousness.

lacrimation, pupil diameter, and vasomotor skin reflexes are used.¹⁰ However, depending on patient's clinical condition and on drugs used, these parameters may have poor representation in assessing anesthetic depth.¹¹

Tachycardia, hypertension, sweating, and lacrimation are usually considered inadequate analgesia signs. However, sympathetic stimulation is not always a result of the painful stimuli perception. There are situations in which the parasympathetic can be predominantly stimulated, such as in the autonomic response due to nociceptive stimuli in the esophagus. In this case, vagal fibers are predominantly involved, triggering a slow heart rate.¹⁰

The presence of movement in response to painful stimuli has been one of the methods for assessing the potency of anesthetic agents. Although the motor response is mediated by spinal reflexes, its presence is an important sign of inadequate anesthesia, which makes the patient susceptible to the risk of intraoperative awakening and awareness.¹⁰

During surgery under general anesthesia, it is the motor response that makes it possible to know whether the patient is able to voluntarily meet the commands and respond to painful stimuli. When a neuromuscular blocking agent is used, it prevents the motor response to voluntarily comply with commands, or the motor reflex response to painful stimuli.

The use of neuromuscular blocker is related to AIA, which rarely occurs when it is not used.¹²

To preserve motor responses of surgical and pharmacologically paralyzed patients, the isolated forearm technique (IFT) is a standard alternative. It consists of the isolation of a forearm with a pneumatic cuff inflated before the intravenous neuromuscular blocker injection, preventing drug action in the temporarily ischemic limb.¹²

The occurrence of motor response with IFT is rated in five levels:

Level 0: No response or spontaneous movement.

Level 1: Random movements unrelated to any stimulation.

Level 2: Movements in response to tactile stimuli, including painful movements (2a: movement not localized, 2b: movement that tracks stimulus).

Level 3: Movement in direct response to verbal command.
 Level 4: Movement in response to questions or response options.
 Level 5: Spontaneous and purposeful movements, showing the patient's intention to communicate.

Although the most frequently found response levels are 0 and 3, it is observed that even if AIA does not occur in level 3, which was demonstrated in a study by Kerssens et al.,¹³ where hemodynamic parameters were not correlated with the presence or absence of response, but the EEG parameters such as BIS and SEF 95%, which showed better integration between their values and the clinical observation by the IFT.¹³

Electrical monitoring of anesthetic depth

Raw electroencephalogram (EEG) has characteristic frequency bands, classified according to fluctuation bands as: *Gamma*, *Beta*, *Alpha*, *Theta*, *Delta* and *Slow* (Fig. 2).^{14,15}

When assessed without processing, they hamper the analysis of intraoperative parameters related to anesthetic depth. With increased anesthetic depth, high amplitude electrical activity is observed at low frequencies and may have surge suppression or no activity (isoelectrical) patterns with higher doses of anesthetics (Fig. 3).¹⁶

The pattern of electrical activity usually shows frequencies up to 70 Hz and amplitudes of $\pm 50 \mu\text{V}$. This activity is superimposed on electromyography, which has amplitudes and similar frequencies but with greater representation in values greater than 50 Hz. However, equipments developed

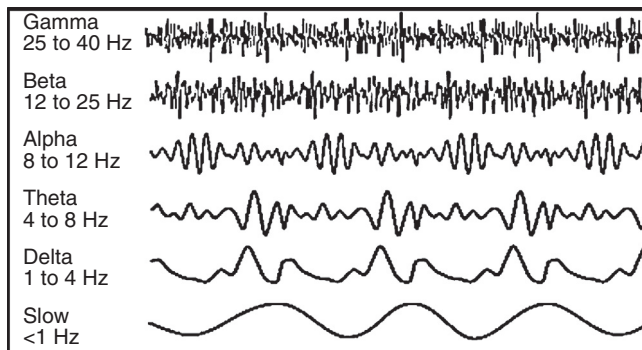


Figure 2 Frequency bands.

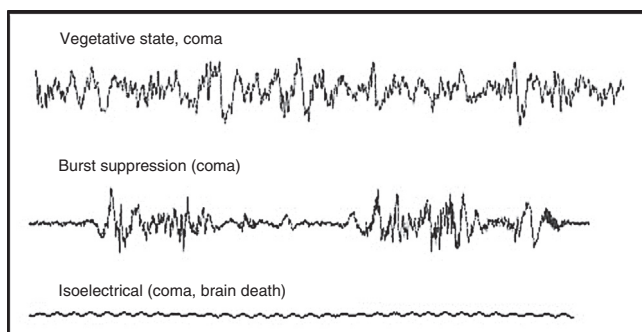


Figure 3 Deep anesthesia standards (isoelectrical or burst suppression).

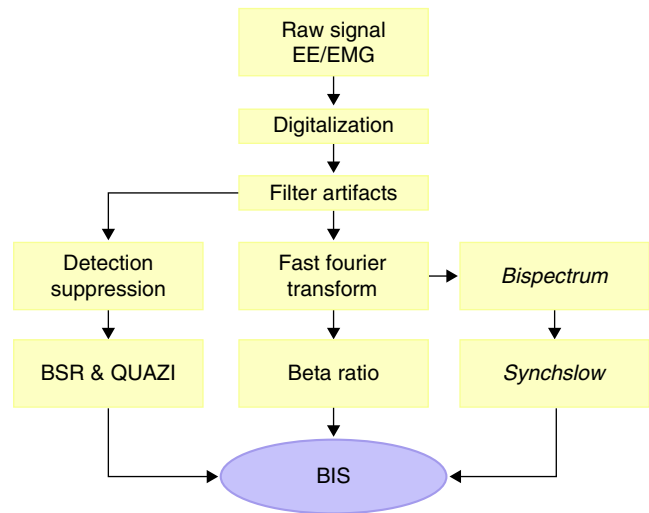


Figure 4 Subparameters generating BIS.

to assess anesthetic depth show, independently, indexes related to electromyography, evaluated in different frequency bands (e.g., BIS: 70–110 Hz and CSM: 75–85 Hz). Each of the anesthetic depth evaluation equipment has its own algorithm with several windows and bands of different analyses.^{17–19}

BIS Vista® (Aspect Medical Systems, Newton, MA)

For the calculation of the indices related to equipment, frequencies up to 47 Hz (nervous system and electromyography) and 70–110 Hz are used for electromyography (EMG), where the signal is picked up at 2-s windows (epochs). The indices are:

(a) Bilateral bispectral

BIS number is obtained from the weighted analysis of 4 subparameters: burst suppression ratio, Quazi suppression, beta relative power, and fast/slow synchronization (Fig. 4), where a multivariate statistical model is applied using a non-linear function. The delay time is 7.5 s and the refresh rate is 1 s.¹⁹

(b) Suppression rate

Burst suppression is defined as intervals greater than 0.5 s, in which the EEG voltage is below $\pm 5 \mu\text{V}$ in the last 60 s. Thus, normal suppression rate is equal to zero.^{14,19}

(c) Electromyographic power

This variable is calculated as the sum of all RMS (root mean square) in the range of 70–110 Hz, normalized to $0.01 \mu\text{VRMS}$ and expressed in decibels (dB). For example, if $\text{RMS} (70-110 \text{ Hz}) = 1 \mu\text{V}$; $\text{pEMG} = 20 \log(1/0.01) = 40 \text{ dB}$. The display range, shown in a bar graph, is between 30 and 55 dB. It is an important parameter, as it measures the electrical activity in the facial nerve nucleus (bulb-pontine region). During general anesthesia, the values are typically below 30 dB. Values above 30 during general anesthesia represent high activity in the facial nerve nucleus¹⁹ (Fig. 5).



Figure 5 Electromyography (EMG) in red.

(d) Asymmetry

It represents power variation between the right and left sides of the brain, with a white spectral signaling the higher power side. In adults, variations up to 20% are considered normal¹⁹ (Fig. 6).

(e) Spectral edge frequency 95% (SEF 95%)

SEF 95% is the frequency below which 95% of the power is in the range up to 30 Hz. However, spectral analysis (spectrogram) has shown to be of great importance for its ability to highlight the alpha-hypersynchronization (thalamocortical) and slow fluctuation (corticocortical) (Fig. 7), characteristics of adequate depth of anesthesia in adults.²⁰

Characteristics of monitoring equipment available in Brazil

The raw signal of electrical activity is picked up by surface electrodes (non-invasive), adapted according to points defined in neurology by the system 10/10 with referential montages (Fig. 8).¹⁵ Table 1 shows the main features of each equipment.^{18,19,21,22}

Description of the evidence collection method

The search strategy used for this recommendation was by research in OvidMedline, Ovid Embase, and Cochrane Library: {Cochrane Database of Systematic Reviews (CDSR); Cochrane Central Register of Controlled Trials (CENTRAL); Database of Abstracts of Reviews of Effects (DARE)}. The

references were crossed with the collected material for identification of items with better methodological design, followed by critical evaluation of its contents and classification according to the strength of the evidence.

The searches were made between June and September 2015. The clinical monitoring survey began in year 1990. For BIS, Entropy, PSA 4000 (Patient State Analyzer), and CSM (Cerebral State Monitor), the survey used was from 2000. The review was limited to prospective studies, preferably systematic reviews with relevance to the topic discussed.

The descriptors used in the search were: *monitoring intraoperative; and/or consciousness monitors/ and or sedation monitor/ and or sedation measurement/and or anesthesia, general/and or anesthesia, intravenous/ and or anesthetics, inhalation/ and or perioperative period/ and or perioperative evaluation/ and or signal processing/ and or computer-assisted/ and or intraoperative complications/ perioperative care/ and or monitoring, physiologic/ and or electroencephalography/ and or mental recall/ and or wakefulness/ and or consciousness/ and or perception/ intraoperative awareness/ or awareness/ and or deep sedation/ and or conscious sedation/ and or depth of anesthesia monitor/ and or postoperative period/ and or EEG or EMG/ and or BIS/ and or Entropy/ and or PSA 4000/CSM.*

The quality of evidence and strength of recommendation adopted for these consensus decisions was from GRADE (Grading of Recommendations, Assessment, Development and Evaluation), according to the following descriptions:

Quality of evidence:

A—High: Level of evidence from well-planned and conducted randomized clinical trials, with parallel groups, adequate controls, adequate data analysis, and consistent findings, targeting the clinical outcome of interest to the physician and the patient.

B—Moderate: Evidence from randomized controlled trials with important problems in conducting, inconsistent results, assessment of a surrogate endpoint rather than an outcome of interest to the physician and patient, assessment imprecision, and publication biases.

C—Low: Results from cohort studies and case control, highly susceptible to bias.

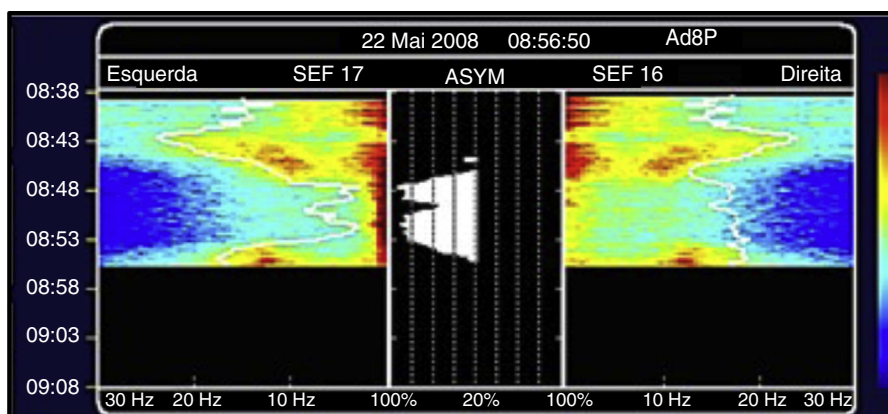


Figure 6 Asymmetry in white, signaling to the left.

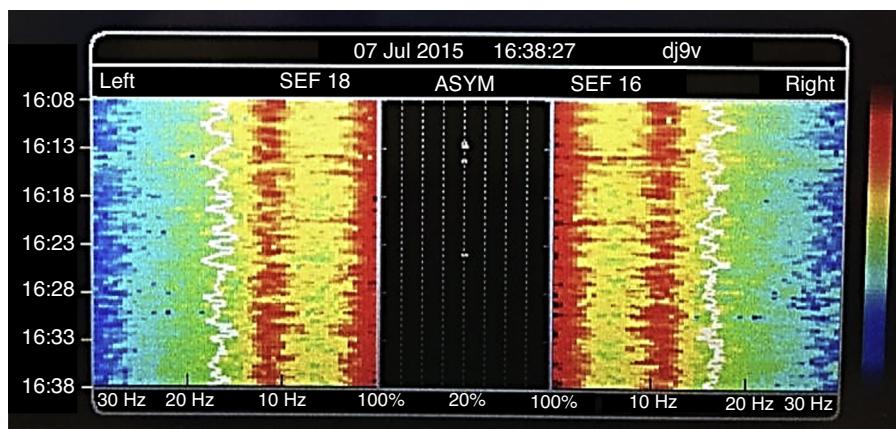


Figure 7 SEF 95% bilateral and bilateral spectrogram with alpha hypersynchronization.

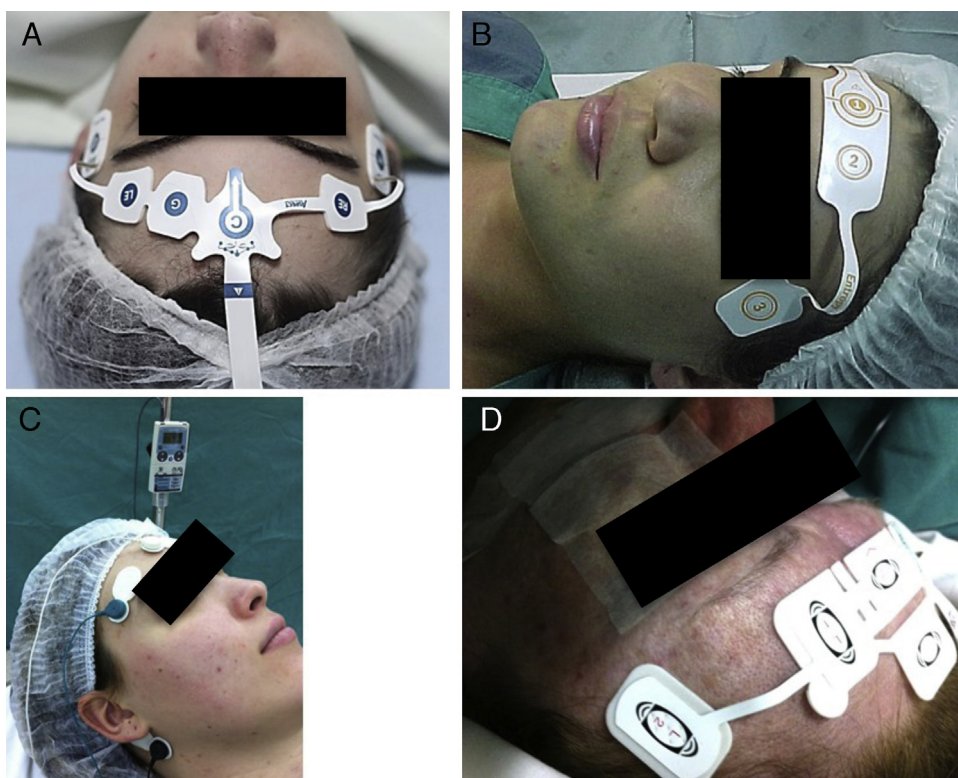


Figure 8 Positioning of the sensors according to the manufacturer: A, BIS; B, Entropy; C, CSM; and D, SEDLine.

Table 1 Main parameters of each equipment.

Equipment	Anesthesia/limits	TS/limits	EMG/limits	Asymmetry	SEF 95%	Spectrogram	Delay time
BIS bilateral view	40–60	±5 μV	70–110 Hz	Yes	Yes	Yes	7.5 s
SEDLine-PSI bilateral	25–50	NA	NA	No	Yes	Yes	6.4 s
Entropy response	40–60	NA	NA	No	No	No	Variable
CSM	40–60	±3.5 μV	75–85 Hz	No	No	No	15 s

NA, not available.

D—Very low: Results from uncontrolled observational studies and unsystematic clinical observations.

Strength of recommendation:

1—Strong: The advantages clearly outweigh the disadvantages; or else, the disadvantages outweigh the advantages.
2—Weak: There is uncertainty between advantages and disadvantage.

Strategies and recommendations

Because the aim of this study was to evaluate the impact of monitoring the brain electrical activity in general anesthesia on different outcomes, we considered the following topics:

Anesthetic consumption

Excessive administration of anesthetic agents is often used unnecessarily. This effect occurs because the depth of anesthesia is usually guided by somatic and autonomic clinical signs. However, these signs do not have reliable measures to ensure unconsciousness.²³ Some studies have shown that proper monitoring of anesthetic depth could reduce excessive administration of anesthetic agents, reducing recovery time from anesthesia, nausea and vomiting, headache, and cognitive dysfunction, especially in the elderly.^{23,24}

The monitoring of anesthetic agent measurements, especially of inhaled gases, has become routine because of the units incorporated into multiparameter monitors. Studies using the quantification of expired gas concentrations showed significant reduction in the total consumption of agents, compared to clinical monitoring.^{25,26} However, it does not guarantee the absence of consciousness and, when compared with the assessment instruments of brain electrical activity, it results in increased anesthetic consumption.^{27–29}

There is a close relationship between inhaled anesthetic agent titration and electrical activity monitoring.^{25,26,30,31} Thus, consciousness monitors began to be used to guide anesthetic administration.

The studies chosen for this evaluation have high scientific consistency; Grades A and B, were selected from among those with low evidence of bias, despite the impossibility of blindness by the professional using the monitor in the study. The inclusion criteria included comparison of anesthetic depth monitoring, such as BIS, Entropia, PSA 4000, and CSM, compared with clinical signs or fractional expired anesthetic gases. Agents used in the studies were propofol, desflurane, sevoflurane or isoflurane.^{25,27–61}

The studies showed that these monitors, especially BIS, when properly used, provide reduction of anesthetic consumption.^{38,39,51,55,62–66}

Recent meta-analysis by Cochrane²³ showed that in 10 studies with intravenous anesthesia involving 672 participants, there was a significant reduction in propofol consumption when the anesthetic depth was guided by the BIS. The mean reduction was $1.32 \text{ mg kg h}^{-1}$ (95% CI -1.91 to -0.73). The same meta-analysis showed that in 14 studies of balanced anesthesia, involving 985 participants, there was a significant reduction in anesthetic consumption with

an average decrease of 0.65 MAC (95% CI -1.01 to -0.28). Regarding analgesic consumption, the studies evaluated fentanyl, remifentanyl, and sufentanil consumptions, showing reduced consumption. Only in the study by Hachero et al.,⁴⁰ a significant increase was found in the use of fentanyl with BIS control. The combining results showed no significant difference in the use of narcotics.

Recommendation

The use of devices to monitor anesthetic depth, such as BIS, Entropia, PSA 4000, and CSM, is associated with reduced inhaled and intravenous anesthetic consumptions, as well as reduced anesthetic recovery time, compared to the method of clinical signs and symptoms monitoring (1A and 1B).

Intraoperative awakening

Studies have shown variability in the incidence of intraoperative awakening due to different survey methods and differences in the studied population. Some studies with populations considered to be at higher risk reported an intraoperative awakening incidence of 1:100, especially when repeated questionnaires are used.⁶⁷ Others reported very low incidence of 1:15,000 when the report is done spontaneously by the patient, as in the project NAP 5.⁶⁸

While it seems reasonable that the monitoring of brain electrical activity can prevent intraoperative awakening, the available evidence shows results that depend on the population, on the anesthetic technique, and on the evaluated monitoring.

It is worth noting the populations that are at increased risk of intraoperative awakening. There are three situations commonly associated with this event: (i) the patient does not tolerate adequate doses of anesthetic (e.g., critical patients); (ii) there is inadequate anesthesia masking signals (use of neuromuscular blockers); (iii) the nature of the operation or the patient's condition requiring different doses.^{67,69}

Other risk factors for intraoperative wake include the ASA status (indicating patients with more comorbidities),^{70,71} use of total intravenous anesthesia, history of depression, absence of premedication, previous history of awakening,⁷² and emergency operation.⁷¹

Some studies have investigated the impact of using BIS in the incidence of intraoperative awakening. Myles et al.,⁷³ showed a significant reduction of the event in a high-risk population (absolute risk reduction of 0.73%) with BIS, compared to standard care. It is noteworthy that the incidence of memory was high in the control group in this study: 0.89%. However, it has not been confirmed in later studies, such as the B-Unaware³⁰ and Bag-Recall.³¹ These studies compared the incidence of intraoperative awakening in high-risk patients randomized into two groups: the use of BIS between 40 and 60 versus MAC maintenance between 0.7 and 1.3. There was no difference between the groups; however, the study power was calculated based on an incidence of 1% and 0.5%, respectively. Zhang et al.⁷⁴ conducted a similar investigation with total intravenous anesthesia, showing that the incidence of explicit memory decreased significantly with BIS monitoring (0.65–0.14%).

B-Unaware³⁰ was the first study to assess the use awareness monitoring to reduce intraoperative awakening. It

surveyed 1941 patients and found an incidence of intraoperative awakening of 0.21% (95% CI, 0.08–0.53) without reducing the event using BIS.

As estimated by the study Bag-Recall,³¹ it would be necessary to study 3333 high-risk patients in order to prevent one episode of awareness using BIS. The results of the Bag-Recall study do not support the superiority of BIS protocol over end-tidal anesthetic-agent concentration protocols to prevent intraoperative awakening even in high-risk patients. This study sought to correct some flaws of the B-Unaware study, such as being multicenter, international, having a larger sample, and discarding low-risk criteria such as factors for inclusion of patients. However, the study had several limitations that may not be ruled out, such as considering the results in patients receiving potent inhalation anesthetic agents, unable to extrapolate them to other agents. Furthermore, the study used only one of the commercially available technologies for monitoring awareness.

Mashour et al.²⁵ evaluated 21,601 patients and did not demonstrate increased efficacy of using monitoring (BIS), compared to the use of anesthetic protocols to reduce the incidence of intraoperative awakening with explicit memory (0.08 vs. 0.12%, $p=0.48$). However, post hoc analysis has demonstrated that the use of BIS may be superior to the absence of monitoring to reduce intraoperative awakening. These data are consistent with those described by the Cochrane systematic review;⁷⁵ however, there was no benefit in anesthesia recovery.

According to the analysis and review of the literature, we observed that the recommendations of the American Society of Anesthesiologists Task Force on intraoperative awakening⁷⁶ corroborate the current studies.

Recommendation

To prevent intraoperative awakening, the use of brain electrical activity monitors is suggested for high-risk patients under balanced general anesthesia (2B). For patients under total intravenous anesthesia, as it is a risk factor for intraoperative awakening, the use of brain electrical activity monitoring is highly recommended (1A).

Morbidity and mortality

If on one hand the maintenance of inadequate anesthesia is associated with intraoperative awakening and its serious consequences, on the other hand, a general anesthesia deeper than necessary to keep the patient unconscious has been considered a marker of severity, especially in elderly and critically ill patients. However, studies evaluating the association between anesthetic depth and mortality are secondary analyses of outcomes designed for another purpose, or are multivariate analysis of institutional databases that, despite having a large observational sample, collide in the weakness of the multivariate model conclusions, which are legitimate proponents of hypotheses, but lack robust prospective studies for causal confirmation of the findings.

The study by Monk et al.⁷⁷ identified the BIS cumulative time < 45 (relative risk = 1.244 h⁻¹; $p=0.0121$) as an independent predictor of mortality in up to one year after the operation. However, it was not confirmed in another study with similar design and presence of cancer as a covariate.⁷⁸

Patients without cancer showed no increased mortality, even with considerably low cumulative levels of BIS.

Secondary analysis of the B-Aware study⁷⁹ evaluating intraoperative awakening showed no difference in mortality between the group undergoing anesthesia guided by BIS and the standard care group. However, in the analysis of the subgroup monitored with BIS, there was higher mortality within four years in the group with deep anesthesia (BIS < 40 for more than 5 min). A similar result was found in the secondary analysis of patients undergoing cardiac surgery in the study B-Unaware.⁸⁰ BIS levels < 45 were associated with higher mortality, along with other severity criteria, such as transfusion, ICU stay, and use of tranexamic acid. The authors hypothesize that low BIS values are an epiphenomenon, that is, they are not responsible for the primary outcome, as in the analysis of patients undergoing non-cardiac surgery in the same study; this association could not be related.⁸¹

Sessler et al.⁸² found that the combination of intraoperative variables, with hypotension, low levels of BIS, and low levels of inhaled anesthetics concentration (Triple Low), is associated with more fragile patients, susceptible to complications. This study linked the association of low MAP (<75 mmHg), low MAC (<0.8), and low levels of BIS (<45) with increased 30-day mortality. The generated hypothesis was that these combined variables are markers of a profile of patients "sensitive" to perioperative stress rather than potential therapeutic targets that may be involved in reducing adverse events. Kertai et al.,⁸³ using the "Triple Low" criteria, found that these variables were not independent predictors when clinical and surgical variables are included in the statistical model.

Evidence of mortality and low levels of BIS association or "Triple low" are conflicting. Nevertheless, they indicate that susceptible patients deserve special care, with the possibility of optimization of results in the short, medium and long run. Willingham et al.,⁸⁴ in a retrospective observational study including 13,198 patients from three clinical trials: B-Unaware, BAG-RECALL and Michigan Awareness Control Study, showed that the risk of mortality at 30 and 90 days postoperatively was increased by approximately 10% for every 15 cumulative minutes in the triple low state, suggesting that this is not an epiphenomenon. Randomized, prospective, controlled studies in progress, such as the Balanced trial (www.anzctr.org.au, ACTRN12612000632897),⁸⁵ comparing the effects of different levels of anesthetic depth in mortality up to one year, probably will clarify the influence of the depth of anesthesia and postoperative mortality.

Recommendation

Electrical nervous activity evaluated mostly by the BIS (disregarding other possible components, such as suppression rate, spectrogram or both), alone or in combination with other variables such as MAP and CAM percentage, has a weak association with mortality (2B).

Postoperative delirium (POD) and postoperative cognitive dysfunction (POCD)

In the elderly population, cognitive changes such as delirium and POCD after anesthetic-surgical procedures have older age as the main risk factor.⁸⁶

POD is an acute onset syndrome characterized by changes in consciousness and floating variation in memory, attention, cognitive, and perceptual disorders.⁸⁷

COPD is a subtle disorder of thought processes that can influence isolated areas of cognition, such as verbal memory, visual memory, language comprehension, visual-spatial abstraction, attention or concentration.⁸⁸

POD is the most important factor for COPD in hospitalized geriatric patients.⁸⁷

The brain of an elderly person requires lower doses of anesthetic agents compared to that of a young person and is more likely to present burst suppression in the EEG.⁸⁹ Brain monitors, such as the BIS, allow adequate anesthetic depth, dose titration, and minimizes the residual effects on cognition.^{76,90-94}

There is correlation between surface anesthesia and post-traumatic stress syndrome and between deep anesthesia and cognitive dysfunction.⁹⁴ Randomized controlled trials show reduced incidence of POD when patients are monitored with BIS.⁹⁰⁻⁹³

Chan et al., in a randomized study with patients aged 60 years or more, comparing patients monitored with BIS or routine care, found that the BIS group (40-60) showed reduced risk of developing delirium in the immediate post-operative period and POCD in the evaluation at three months.⁹¹

Recommendation

Monitoring the depth of anesthesia with BIS monitor facilitates anesthetic titration, decreases brain exposure, especially in the elderly, to high doses of the anesthetic agents, and thus can contribute to reduce POD (1A) and POCD (2A and 2B).

Conflicts of interest

The authors are consultants Medtronic.

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