

NARRATIVE REVIEW

PERIOPERATIVE MEDICINE

Beyond the index of processed electroencephalography: a narrative review

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Abstract

There is a growing interest in monitoring the processed electroencephalography (p-EEG) as a measure of the delivery of anesthetic agent and the depth of the general anesthesia (GA). Each p-EEG monitor constructs an index that is suitable for GA. Although these monitors have become widely used, but it remains controversial whether they can become the gold standard for anesthesia monitoring like pulse oximeter and electrocardiogram. Whether p-EEG-guided anesthesia can affect perioperative outcomes remains unclear. This narrative review describes the relationship between p-EEG monitoring and perioperative outcome such as postoperative neurocognitive function, intraoperative awareness and mortality. Also, this article describes how and what to look beyond the index of processed electroencephalographic monitors.

Abbreviations: GA: General anesthesia; EEG: Electroencephalogram; BIS: Bispectral index; POD: Postoperative delirium; CODA: Cognitive Dysfunction after Anaesthesia; POCD: Postoperative cognitive dysfunction; PACU: Post-anesthetic care unit; POQI-6: Perioperative Quality Initiative-6 Consensus

Key words: Anesthesia; Delirium; Electroencephalography; Intraoperative awareness; Mortality

Citation: Lee KH. Beyond the index of processed electroencephalography: a narrative review. *Anaesth. pain intensive care* 2022;27(1):112–118; DOI: [10.35975/apic.v27i1.2128](https://doi.org/10.35975/apic.v27i1.2128)

Received: April 07, 2022; **Reviewed:** August 16, 2022; **Accepted:** October 20, 2022

1. Introduction

General anesthesia (GA) can be defined as a drug-induced reversible comatose condition, and it is characterized by unconsciousness, amnesia, analgesia, and akinesia.¹ Multiple devices and techniques have been used to investigate the depth of GA. The target organ for GA is the brain, via the generation of loss of responsiveness. Moreover, GA is a continuum of sedation, but there are no direct methods to measure the concentration of anesthetics in the brain. GA makes discrete shapes on the electroencephalogram (EEG), which increases with low-frequency and high-amplitude activity as the level of GA is intensified.¹

It has been emphasized to continuously use the EEG monitor as a way to monitor the depth of GA. However, it is difficult for an anesthesiologist to perform analysis of a raw EEG amid other tasks. Instead of monitoring the EEG, many anesthesiologists prioritize monitoring the cardiovascular system and maintaining intravascular

volume. They are more accustomed to monitor pulse oximetry, heart rate, blood pressure and prevent complications such as cerebral and organ hypo-perfusion, than to read EEGs.

Each processed EEG (p-EEG) monitor uses its own algorithm to generate a target index for the adequate status of GA. For example, Bispectral Index (BIS) is 40–60, Patient State Index is 25–50, and Entropy is 40–60. These are suggested as indices suitable for GA.² Processed EEG monitoring has become accessible during GA, however, whether it should be considered as part of the standard care, like intraoperative electrocardiogram (ECG) monitoring is unclear.³ In addition, whether the monitoring of p-EEG affects the patient's perioperative outcomes also remains ambiguous.

This review article describes the relationship between p-EEG monitoring and perioperative outcome, such as postoperative delirium (POD), intraoperative awareness,

and mortality. In addition, it describes how and what to assess beyond the index of p-EEG during GA.

2. Perioperative Outcome

2.1. Postoperative delirium

Even if a particular anesthesia drug is administered in the equivalent amount to different patients, the effect will differ from patient to patient. For example, in men weighing 70 kg, the muscle mass, fat mass, and the renal clearance will be different at 30 y and 70 y of age. Therefore, if propofol is administered at the same dose of 2 mg/kg, its effect would be different in both cases. POD is more frequent in older adult patients and is associated with deep anesthesia.⁴ POD has become an important postoperative complication and an independent predictor of adverse outcomes.⁵ It would be ideal if p-EEG-guided monitoring could decrease the use of excessive amounts of anesthetics, and preventing deep anesthesia and adverse perioperative outcomes.

Representative randomized controlled trials have compared p-EEG-guided anesthesia and routine care anesthesia in cases of POD and postoperative cognitive dysfunction (POCD). In the 'Cognitive Dysfunction after Anesthesia' (CODA) trial, the primary outcome was the incidence of POCD after three months of surgery. The dosage of anesthetics and the incidence of POCD and POD were decreased in the p-EEG-guided group.⁶ A decreased incidence of POD was also noted in a subsequent study.⁷ Additionally, the incidence of extreme low BIS value (< 20) and burst suppression patterns decreased in the p-EEG-guided group. In BIS or 'Anesthetic Gas to Reduce Explicit Recall' (BAG-RECALL) trial's sub-study, the incidence of POD was meaningfully reduced by 9% in the BIS-guided group when compared with the End-Tidal Anesthetic Concentration (ETAC)-guided group.⁸ However, there was no difference in the incidence of POD between BIS-guided group and the routine care group in the 'Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes' (ENGAGE) trial; 26% in the p-EEG-guided group vs 23% in the routine care group.⁹

In view of the above results (Table 1), there is still lack of evidence to support the use of p-EEG monitoring in older adult patients undergoing GA. Regardless, it is clear that p-EEG monitoring could provide additional data on the conditions of anesthesia. For example, in the ENGAGE trial, anesthesiologists responded on EEG monitoring data by reducing anesthetic administration [a reduction of 0.11 minimum alveolar concentration (MAC)], whereas in the CODA trial, clinicians reduced anesthetic dosage (a reduction of 0.36 MAC).⁹ In the CODA trial, the anesthetic dosage reduction was more

than three times of that in the ENGAGE trial. Because of this difference, the occurrence of POD between the two studies could be different.

2.2. Intraoperative awareness

Intraoperative awareness under GA can be a major concern for the patients as well as the anesthesiologists. Many studies have investigated whether p-EEG monitoring can detect EEG activity associated with consciousness and dismiss the risks of intraoperative awareness (Table 2).

In the multicenter prospective B-AWARE Trial,¹⁰ p-EEG-guided anesthesia was compared to routine anesthetic care in 2,463 patients at high risk for intraoperative awareness using either a total intravenous anesthesia (TIVA) or an inhaled agent technique. They found that the number of patients who reported awareness was smaller in the p-EEG group than in the routine anesthesia care group (0.17% vs 0.91%) and estimated that the p-EEG-guided anesthesia reduced the risk of awareness by 82%.

In the single-center prospective B-UNAWARE trial,¹¹ p-EEG-guided anesthesia was compared to ETAC-guided anesthesia in 1,941 patients at high risk for awareness using an inhaled agent technique. They found that the number of patients who reported definite awareness was low in both groups. The authors stated that their findings did not support the use of routine p-EEG monitoring to avoid intraoperative awareness.

In the multicenter prospective BAG-RECALL trial,¹² p-EEG-guided anesthesia delivery was compared to ETAC-guided anesthesia delivery in 5,713 patients at high risk for intraoperative awareness using an inhaled agent technique. They found that 5 of 9 with definite awareness and 6 of 18 with possible awareness did not have either a BIS > 60 or an ETAC less than 0.7 age-adjusted MAC. The authors concluded that p-EEG-guided anesthesia is not superior to ETAC-guided anesthesia.

In the multicenter prospective Michigan Awareness Control Study,¹³ p-EEG-guided anesthesia delivery was compared to ETAC-guided anesthesia delivery in 21,601 patients undergoing GA using an inhaled agent technique. In an interim analysis, they stated no significant difference in the incidence of definite awareness among p-EEG-guided anesthesia and ETAC-monitored anesthesia (0.08% and 0.12% respectively). However, in a post hoc analysis, they estimated that a p-EEG-guided anesthetic technique would lead to a 4.7-fold reduction in definite or possible intraoperative awareness compared with routine care.

Table 1: Randomized controlled trials and observational studies about relationships between processed electroencephalogram-guided anesthesia and postoperative delirium and postoperative cognitive dysfunction

Author, Year	Population of trial	Primary outcome or hypothesis	Conclusion
Chan et al. ⁶ 2013	age ≥ 60 y, n = 921, noncardiac surgery, Inhalation (89%), ASA ≥3 (16%)	POCD at three months after surgery	BIS (40–60) vs Routine care. Average BIS; 53.2 ± 8.9 vs 38.6 ± 6.5 (p < 0.001). 8.5% significant reduction in POD in the BIS-guided group.
Radtke et al. ⁷ 2013	age ≥ 60 y, n = 1277, noncardiac surgery, Inhalation (65%), ASA ≥3 (48%)	POD from postoperative day 1 to postoperative day 7	BIS (40–60) vs Routine care. 4.7% significant reduction in POD in the BIS-guided group. SR or deep anesthesia (BIS <20) is reduced in BIS-guided group.
Whitlock et al. ⁸ 2014	age > 60 y, n = 310, cardiothoracic surgery, Inhalation (100%), ASA ≥3 (100%)	POD in intensive care unit	BIS (40–60) vs ETAC (0.7–1.3 age-adjusted MAC) guided anesthesia, 9.2% non-significant reduction in POD in the BIS-guided group.
Soehle et al. ²³ 2015	age > 60yrs, n = 81, Cardiac surgery, Inhalation (100%)	Patients with postoperative delirium will spend more time in burst suppression than non-delirious patients.	Delirious patients remained significantly longer in the intraoperative burst suppression state (107 minutes vs 44 minutes, p = 0.018) than non-delirious patients.
Fritz et al. ³¹ 2016	age ≥18 y, n = 727, cardiac/noncardiac surgery, Inhalation (100%), ASA ≥3 (97%)	Whether the duration of intraoperative EEG suppression is independently associated with POD.	Patient with more suppression were more likely to experience POD (p < 0.0001). Predictors of EEG suppression included higher end-tidal volatile anesthetic concentration and lower intraoperative opioid dose.
Hesse et al. ²⁹ 2019	age ≥18 y, n = 626, noncardiac surgery, Inhalation (98%), ASA ≥3 (48%)	Patients with emergence trajectories that contain sdSWA will have lower incidence of PACU delirium.	Specific EEG patterns (intraoperative burst suppression and emergence trajectory such as sdSWA) were associated with PACU delirium.
Shortal et al. ²³ 2019	age (22–39.5 y), n = 27, 1.3 MAC isoflurane anesthesia	Greater duration of EEG suppression during anesthesia would be associated with increased time to emergence.	EEG suppression is not an important determinant of recovery time or the degree of cognitive impairment upon emergence from anesthesia in healthy adults.

BIS; bispectral index, EEG; electroencephalography, ETAC; end-tidal anesthetic concentration, MAC; minimum alveolar concentration, PACU; post-anesthetic care unit, POCD; postoperative cognitive dysfunction, POD; postoperative delirium, sdSWA; spindle domain slow wave, SR; suppression ratio.

In these studies, the incidence of awareness was reported differently according to the methods used to detect and report the intraoperative awareness, which could

confound the results. In 2014, the fifth National Audit Project (NAP5) consisted of a retrospective observational study that reviewed over 2.8 million

Table 2: Processed electroencephalogram-guided anesthesia and intraoperative awareness

Author, Year	Population of trial	Diagnostic methods or awareness	Incidence or awareness	EEG-guided group vs Control group	Conclusion
Myles et al, 2004	≥18 y, n = 2463, female (38%), TIVA (42%) and inhalation (58%)	Brice questionnaire, Three times (2–6 h, 24–36 after surgery, POD 30), By one reviewer.	Confirmed awareness (0.1% vs 0.8%)	BIS-guided (40–60) vs Routine care	82% reduction in the incidence of awareness in the BIS-guided group.
Avidan et al, 2008	≥18 y, n = 1941, female (47%), Inhalation (100%) with ETAC monitoring	Brice questionnaire, Three times (0–24 h, 24–72 h after surgery, POD 30), By three reviewers.	Definite intraoperative awareness (0.002% vs 0.002%)	BIS-guided (40–60) vs ETAC guided (0.7–1.3 MAC)	The use of the BIS protocol was no reduction of awareness, the amount of anesthetics, and postoperative mortality.
Avidan et al, 2011	≥18 y, n = 5713, female (42%), Inhalation (100%) with ETAC monitoring	Modified Brice interview, Two times (0–72 h after surgery, POD 30), By three reviewers	Definite intraoperative awareness (0.24% vs 0.07%) Definite or possible intraoperative awareness (0.66% vs 0.28%)	BIS-guided (40–60) vs ETAC guided (0.7–1.3)	BIS is not superior to a protocol of ETAC monitoring with alarm.
Mashour et al, 2012	≥18 y, n = 18836, female (55%), Inhalation with ETAC monitoring	Modified Brice interview, One time (POD 28 to 30), By three reviewers	Explicit recall (0.08% vs 0.12% with ETAC monitoring)	BIS-guided (<60) vs ETAC-guided care (age-adjusted MAC < 0.5)	No significant difference in the incidence of definite awareness between BIS guided and ETAC monitoring.

BIS; bispectral index, ETAC; end-tidal anesthetic concentration, MAC; minimum alveolar concentration, POD; postoperative day, TIVA; total intravenous anesthesia.

patients records during a 12-month period.¹⁴ The incidence of accidental awareness was 1:19,000 (95% confidence interval [CI] of 1:16,700–1:23,450).¹⁴ This rate is very low (less than 0.0005%). However, Errando et al.¹⁵ reported a much higher rate of awareness. They reported an overall incidence of awareness of 1% and an incidence of 0.6% in elective procedures.

The available evidence supporting the use of p-EEG monitoring to minimize awareness is inconclusive.¹⁶ The ‘Perioperative Quality Initiative-6’ (POQI-6) consensus recommended the use of alarmed ETAC monitoring or p-EEG monitoring to decrease the risk of intraoperative awareness, especially with TIVA with neuromuscular blocking agents.¹⁷

2.3. Mortality

Most studies that assessed long term mortality aim at

assessing intraoperative awareness and cognitive function. A long-term follow up study of the B-AWARE trial showed no differences in myocardial infarction, stroke or death.¹⁸ Patients who received BIS monitoring with a BIS < 40 for > 5 min showed significantly higher mortality than those who did not. In another study, there was a significant association between deep anesthesia (BIS < 45) and long-term mortality (3-year survival) in patients undergoing cardiac surgery in the B-UNAWARE trial.¹⁹ However, there was no association (adjusted HR [95% CI] 1.03 [0.93-1.14]) between deep anesthesia and mortality in patients undergoing non-cardiac surgery in the B-UNAWARE trial.²⁰

The results of studies on mortality are inconsistent. The CODA trial reported a 3-month mortality, with higher mortality in patients receiving BIS monitoring than in those receiving routine care (7.8% vs 6.1%).⁶ In addition,

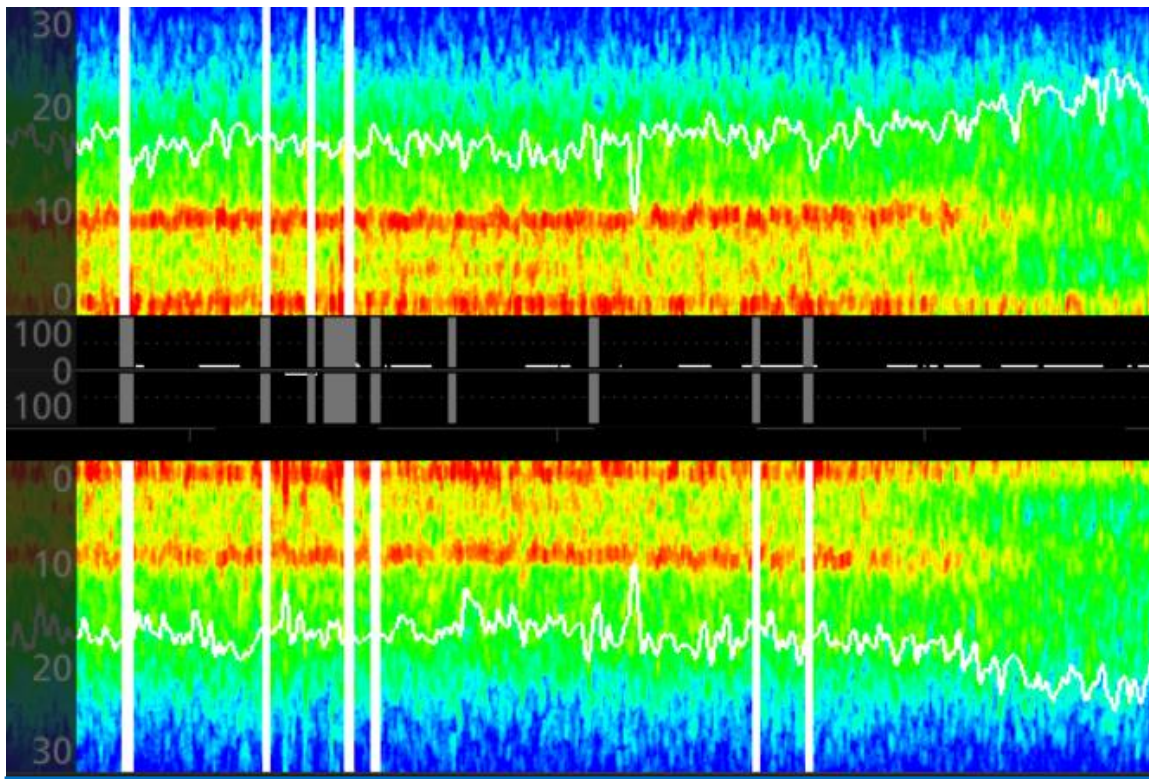


Figure 1: Pattern of zipper opening on density spectral array screen

12-month mortality after deep (BIS 35) or light (BIS 55) anesthesia did not significantly differ, at 11% and 12%, respectively.²¹ This study was prematurely terminated due to futility. Although avoiding EEG suppression had no effect on the rate of POD in ENGAGE trial, p-EEG-guided anesthesia reduced the 30-day mortality rate by 4.6-fold, when compared to routine care.⁹

The mortality rates seem to be more affected by known vital factors, such as comorbidities, than by the depth of anesthesia. This effect was explained by Lindholm et al.²², who found that “low BIS” was no longer a statistically significant variable after malignancy was included as covariate in their mortality model.

3. Beyond the index

The parachute does not prevent all deaths caused by jumping off planes, as the speedometer does not prevent all car accidents.³ The same can be applied for p-EEG. Processed EEG-guided anesthesia did not affect the prognosis of healthy young patients.²³ These monitors have some limitations of their own. After the analog EEG signals received from the surface of the forehead are converted to digital signals, there is loss of signal fidelity since what is shown is the recently calculated past event, and not current event.² Processed EEG is highly sensitive to electrical interference and artifacts

because the signals received at the surface of the skin are approximately 100 times smaller than the ECG signal.² Clinicians often see a discordance between the p-EEG index and the raw EEG waveform. Processed EEG indices can be affected by hypothermia, hypoglycemia, acid-base abnormalities and aging.^{24,25}

Just like anesthesiologists received interpretation of ECG training, they also need to have EEG training. It has been reported that anesthesiologists who have not previously received EEG training can be trained to read EEG waves and help reduce complications associated with insufficient or excessive anesthesia.²⁶ In a study, 40 anesthesiologists could distinguish anesthetic-related EEG changes after a short training session.²⁷ Likewise, participants in a session of intermediate length were able to interpret the EEG and calculate a BIS index that was similar to the index generated by the EEG monitor.²⁸ Hesse et al.²⁹ reported that the episodes of EEG suppression during GA were associated with delirium in the post-anesthetic care unit (PACU). If the Spindle Domain Slow Wave (sdSWA) appeared during the emergence period, the rate of PACU delirium was relatively low.²⁹ Therefore, more information can be obtained and applied to GA if anesthesiologists can interpret EEG waveform.

Hence, anesthesiologists should be able to analyze more

than just looking at the numbers on p-EEG monitors. Examples include burst suppression/suppression ratio, spectral array and EEG wave morphology shown on the density spectral array (DSA) screen.³⁰ DSA results are easy to interpret and have a high-resolution spectrographic display of bi-hemispheric activity. The burst suppression (BS) ratio represents the time spent with an EEG activity below 5.0 mV longer than 0.5 sec as a fraction of total recorded time.³⁰ The BS ratio has been associated with negative outcomes such as POD.^{4,29,31} Previous studies have suggested that the longer EEG suppression, the higher is the occurrence of POD.^{29,31,32} Spectral edge frequency (SEF) is a white line superimposed on the graph, where 95% of the total power lies on one side of the line (toward the inside of the graph) and 5% lies on the other side.³⁰ The spectrogram is plotted in two dimensions by arranging the time on the x-axis, frequency on the y-axis, and power through color coding on the z-axis. Spectral analysis makes it easier to visualize frequency content, especially the oscillation of EEG waveform, and to identify fine changes in the frequency arrangement.²⁴ For example, the appearance of theta oscillations (4 to 8 Hz) indicates a more intense state of GA with sevoflurane.^{33,34} Similarly, anesthetic concentrations decreased below MAC when theta oscillation disappeared, and emergence could be predicted by a “zipper opening” pattern (Figure 1).

4. Conclusion

No anesthesia monitor is perfect. It is not yet known whether processed electroencephalography (p-EEG)-guided monitoring has a positive effect on perioperative outcomes, or whether it should be routinely used. However, the role of EEG in providing information about the brain for intraoperative anesthesia management is well-understood. Therefore, it is important for anesthesiologists to receive training on p-EEG interpretation, including density spectral array (DSA) screen, Spectral edge frequency (SEF), burst suppression (BS) ratio, and four channel raw EEG tracing. In the studies reviewed, monitoring alone did not change the patient’s perioperative outcomes. The anesthesiologist’s monitoring skills, decisions and actions are the key factors that affect the patient’s outcome.

5. Financial support and sponsorship

No financial support was involved in the completion of this review.

6. Conflicts of interest

The author declares that there was no conflict of interest involved.

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