This article has been accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination, and proofreading processes, which may lead to differences between this version and the version of record.

Please cite this article as https://doi.org/10.4097/kja.21349
Title: The raw and processed electroencephalogram in modern anesthesia practice: a brief primer on select clinical applications

Ki Hwa Lee, MD, PhD¹, Talmage D Egan, MD², Ken B Johnson, MD³

¹ Associate Professor, Department of Anesthesiology and Pain Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea
² Professor, Department of Anesthesiology, University of Utah, Salt Lake City, UT, USA
³ Professor and Vice chair for research, Department of Anesthesiology, University of Utah, Salt Lake City, UT, USA

Running title: A primer on processed EEG monitoring

Corresponding author: Ki Hwa Lee, MD, PhD
Department of Anesthesiology and Pain Medicine, Haeundae Paik Hospital, Inje University College of Medicine, 875, Haeundae ro, Haeundae gu, Busan, Republic of Korea
+82-51-797-0421, tedy333@paik.ac.kr

Previous presentation in conferences: Not applicable
Conflict of interest: The researcher claims no conflicts of interest.
Funding: KHL has no funding. TDE and KBJ have received research funding from Medtronic.
Acknowledgments: Not applicable
IRB number: Not applicable
Clinical trial registration number: Not applicable
The raw and processed electroencephalogram in modern anesthesia practice: a brief primer on select clinical applications

Running title: A primer on processed EEG monitoring
Abstract

The evidence supporting intraoperative use of processed electroencephalography monitoring to guide anesthetic delivery is rapidly maturing. This article reviews key features of electroencephalography waveforms and their clinical implications in selected patient populations and anesthetic techniques. The first patient topic reviewed is the vulnerable brain. This phrase has emerged as a description of patients who may exhibit increased sensitivity to anesthetics and/or may develop adverse neurocognitive effects following an anesthetic. Processed electroencephalography monitoring of patients with a known or suspected vulnerable brain with focused attention on the suppression ratio, alpha band power, and processed electroencephalography indices may prove useful. Second, processed electroencephalography monitoring along with vigilant attention to anesthetic delivery may minimize the risk of intraoperative awareness when providing a total intravenous anesthetic in combination with neuromuscular blockade. Third, we suggest that processed electroencephalography monitoring has a role in anesthetic and resuscitative management when faced with adverse changes in blood pressure. Fourth, processed electroencephalography monitoring can better identify anesthetic requirements and guide anesthetic titration in patients with known or suspected substance use.

Keywords: Alpha rhythm; Anesthesia; Brain waves; Electroencephalography; Hemodynamic; Intraoperative awareness; Substance use disorders; Vulnerable population.
Introduction

Because the target organ of many anesthetic drugs is the brain, clinical investigators have been interested in the development of brain function monitors. An ideal monitor would reliably measure anesthetic drug effects. Several electroencephalography (EEG) monitoring devices have been introduced that measure frontal electrical cortical activity and process the EEG signal to generate indices of brain electrical activity that closely correlate with hypnotic effects of anesthetics [1–3]. These brain function monitors are designed to complement other measures of the adequacy of anesthesia, including expired anesthetic gas concentrations, hemodynamic and respiratory variables, and clinical assessments such as patient movement.

Although processed EEG (pEEG) monitors have been available for decades, they have not enjoyed widespread clinical use in some practices. Without adequate training, the clinical utility of the raw EEG waveform, indices of hypnosis, burst suppression ratio, the spectral edge, and various graphical displays of the EEG information is not obvious. Furthermore, in contrast to standard, deterministic monitors like the electrocardiogram, the pEEG is a stochastic measure that must typically be interpreted probabilistically; it is therefore inherently less robust than routine clinical monitoring systems. In addition, as a clinical state monitor that requires 15–30 seconds of raw EEG waveform to compute, the pEEG indices reflect brain activity from the very recent past; it is therefore not quite real time compared to standard deterministic monitoring variables such as the electrocardiogram [4].

Despite these limitations, the role of pEEG monitoring in anesthesia patient care has matured. With advances in understanding and interpreting the raw EEG waveform, processed EEG parameters, and graphical EEG displays such as the spectrogram, the technology has emerged as an important tool in optimizing anesthetic delivery. This review briefly outlines clinical rationale underpinning the application of pEEG monitoring in modern anesthesia practice.
The Raw and Processed EEG: Key features

To set the stage, a brief review of basic features of the EEG waveform and how the raw waveform can be processed into various parameters and graphical displays provides a framework for interpreting the EEG in the clinical setting and considering the data supporting the application of the pEEG to improve anesthesia care. Key elements to understand include raw EEG waveform morphology, spectral analysis, burst suppression, and alpha power.

EEG Waveform Morphology: The raw EEG waveform, plotted in microvolts versus time, is characterized in terms of frequency and amplitude and continually cycles around electrical zero. Frequencies are arbitrarily described using five bands measured in cycles per second or Hertz (Hz): delta (up to 4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (14–32 Hz), and gamma (> 32 Hz). Amplitudes are described using power, defined as the amplitude squared (so that the amplitude is always a positive number) and reported in decibels (dB), a logarithmic scale that provides a convention to visualize a wide range of amplitudes. Changes in amplitude are referred to as oscillations. Given that available commercial pEEG monitors require sensors be placed over the forehead, waveform frequency and amplitude signals reflect electrical activity largely from the frontal cortex.

Spectral analysis: Spectral analysis is perhaps the most important of the EEG processing methods in clinical anesthesia because most inhaled and intravenous general anesthetics result in a generalized “slowing” of the raw EEG waveform, wherein the waveform exhibits increased power in lower frequency bands. This slowing of the raw EEG waveform can be characterized using spectral analysis. Applying Fourier’s Theorem using a Fast Fourier Transform, spectral analysis is a mathematical technique to separate a complex sine wave (like the raw EEG) into its component sign waves, thereby generating a power versus frequency histogram. General anesthetics such as
isoflurane or propofol characteristically produce a leftward shift in the power versus frequency histogram. This leftward shift is reflected in a lower median frequency (i.e., frequency in the power versus frequency histogram in which 50% of the power is lower and 50% is higher) and a lower spectral edge frequency (frequency below which 95% percent of the power in the power versus frequency histogram is found).

Spectrogram: In addition to numerical parameters like the median frequency and the spectral edge frequency, the results of spectral analysis can also be visualized in the form of a spectrogram. A spectrogram plots the power across a spectrum of frequencies as they change over time [5]. Time is displayed along one axis and frequency and power along the opposite axis (some commercial devices plot time on the horizontal axis, others plot time on the vertical axis). Frequency is typically presented from 0 to 30 Hz. Applying a “heat map” approach, power is presented using color from blue (-40 dB) to red (15 dB). The “warmer” the color, the greater the power (e.g., blue represents lower power, red represents higher power). The spectrogram is intended to reduce the cognitive workload in interpreting the EEG, making it easier to visualize where most of the power in the EEG signal resides [6]. Fig. 1 presents differences in alpha band power between two patients.

Burst Suppression: When select anesthetic concentrations (e.g., halogenated agents, propofol, etomidate, thiopental, among others) reach sufficiently high levels, periods of isoelectricity are generated in the raw EEG. These periods of isoelectricity are typically interspersed with “bursts” of EEG activity. Still higher anesthetic concentrations can result in complete burst suppression, wherein the EEG is completely isoelectric. Computed as part of a signal processing technique known as aperiodic analysis, the burst suppression ratio is the proportion of time in which the EEG is isoelectric over a specified length of time (usually 15–60 seconds). Other conditions can also result in burst suppression or isoelectricity, including hypothermia and cerebral ischemia, among
others. Advanced age is associated with burst suppression at lower anesthetic concentrations.

Alpha power: The alpha band is of particular interest in that it changes with general anesthesia and declines with age more so than other frequency bands [7]. It is thought to originate from thalamocortical electrical activity which plays a role in integrating sensory information and synchronizing different cortical regions of the brain with one another [8]. As such, alpha band power has been the subject of several studies exploring how it can be used as a potential biomarker of brain health in the perioperative period [9].

The Vulnerable Brain

The phrase vulnerable brain has emerged as a description of patients who may exhibit increased sensitivity to anesthetics and/or may develop adverse neurocognitive effects following an anesthetic. Patients with advanced age, neurovascular disease, intracranial pathology, traumatic brain injury, or an overwhelming infectious or metabolic derangement are examples of patients who may have a vulnerable brain.

Neuroscientists suggest neurons in a vulnerable brain have diminished mitochondrial production of energy substrates that reduce neuronal electrical activity and synaptic neurotransmission [10]. Anesthetizing a vulnerable brain may further reduce aerobic metabolism reducing production of energy sources to sustain neuronal electrical activity and connectivity. Significant cerebral ischemia or hypoperfusion during anesthesia can be detected by changes in the EEG. Particularly during stable anesthesia, a sudden alteration in the EEG (i.e., shift in power to lower frequency ranges, decrease in amplitude, periods of burst suppression, isoelectricity and/or a drop in a pEEG index) may indicate incidental cerebral ischemia.

A large body of work has explored pEEG guided anesthetic titration to improve clinical outcomes associated with the vulnerable brain, including post-operative delirium (POD), post-operative
cognitive dysfunction (POCD), and mortality, among others. Table 1 presents a summary of results from four randomized controlled trials (RCTs) exploring the use of pEEG guided anesthetic delivery on the incidence of POD and POCD. Although compelling, results are varied making it difficult to distil out clinical directives that have a consistent impact on these outcomes. For example, in patients over the age of 60 years, some trials reported pEEG guided anesthetic titration reduced the incidence of POD while others did not. Only one found that pEEG guided anesthesia decreases the incidence of POCD.

In a recently published large RCT, the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) trial [11], the authors compared pEEG guided (target Bispectral Index [BIS] value ≥ 40) with routine anesthesia delivery. The main finding was that pEEG guided anesthesia did not decrease the incidence of POD, despite a modest reduction in anesthetic exposure (a decrease in the median end tidal anesthetic concentration from 0.8 to 0.7 minimum alveolar concentration [MAC]) and a reduction in the duration of EEG suppression (a decrease in the median duration of time with the BIS value less than 40 from 60 to 32 minutes). See Table 1 for details.

In an independent analysis of the ENGAGES trial data, Ackland and Pryor [12] identified an important issue with the reported burst suppression. They pointed out that prior retrospective observational studies have established that EEG suppression in the presence of low anesthetic concentrations has a higher incidence of POD [13]. They also pointed out that the published threshold for increased risk of POD is a duration of burst suppression of 4 or more minutes. In the ENGAGES trial, the median duration of EEG burst suppression was 7 and 13 minutes in the pEEG guided and the control groups, respectively. The duration for both groups exceeded the threshold for an increased risk of delirium. They suggest that with the duration of burst suppression above the threshold for POD, it is difficult to draw any conclusions about the utility of pEEG guided
anesthetic delivery on reducing the incidence of POD.

To synthesize a consensus from this body of work, meta-analyses have systematically assessed potential benefits of pEEG guided anesthesia in reducing the incidence of POD and POCD. Yodying et al. [14] analyzed data from three RCTs exploring the incidence of POD in a combined cohort of 2529 patients and three RCTs exploring the incidence of POCD in a combined cohort of 2051 patients. They reported a reduction in the incidence of POD in patients over the age of 60 years undergoing non-cardiac and non-neurosurgical procedures from 21% without to 15% with pEEG monitoring. They also reported a small reduction in the incidence of POCD at three months after surgery from 9% without to 6% with pEEG monitoring [14]. In another meta-analysis that analyzed five RCTs with data from 2654 patients, MacKenzie et al. [15] determined that the use of pEEG monitor was associated with a 38% reduction in the odds of developing POD and that data were insufficient to assess the relationship between pEEG and POCD.

Expanding this line of investigation, researchers have identified selected measures in neuronal electrical activity, burst suppression and changes in alpha band that may serve as an electrophysiologic phenotype of a vulnerable brain [9]. Both are available with newer conventional pEEG monitors but do require some expertise to properly interpret at the point of care.

Many studies suggest that anesthesia induced burst suppression is a risk factor for POD [7,16–19]. As an example, Purdon et al. [7] studied EEG changes in patients from ages 18–90 years receiving either propofol or sevoflurane as a maintenance anesthetic. They found decreased power in all EEG frequency bands with increasing age. Alpha power decreased more than other frequency bands and burst suppression was more evident in elderly patients.

In an observational cohort analysis, Fritz et al. [18] enrolled 619 patients to undergo general anesthesia with a planned intensive care unit (ICU) admission after surgery. They assessed delirium using the Confusion Assessment Method for the ICU and measured burst suppression.
They found that 162 patients developed POD and that patients with more burst suppression were more likely to develop delirium. Approximately 15% of patients that developed POD had no burst suppression but rose to 35% in patients with 18 or more minutes of burst suppression. They reported a similar finding with a BIS value less than 20. In their analysis, they also found that patients that received less intraoperative opioid were likely to experience more burst suppression.

Similar findings have been reported in patients following cardiac surgery [19]. In a retrospective analysis of the same patient cohort, Fritz et al. [16] explored patient sensitivity to inhaled anesthetics. They found that those patients that experienced burst suppression at lower inhaled anesthetic concentrations had a higher incidence of POD. They concluded that burst suppression in the presence of low inhaled anesthetic concentrations may serve as a phenotype of anesthetic sensitivity that puts them at risk for poor cognitive outcomes.

Giattino et al. [20] studied 15 patients where they conducted a preoperative neurocognitive assessment and then measured alpha power among other EEG metrics during anesthesia and surgery. They found a correlation between frontal alpha-band activity and preoperative cognitive function that was not present in other EEG frequency bands such as delta, theta, or beta bands [20]. The authors suggested that lower intraoperative frontal alpha power may identify patients with poor cognitive function not well appreciated before surgery and who may benefit from practices that minimize or prevent POD and POCD.

In a large multicenter trial, Hesse et al. [17] studied EEG changes during emergence from anesthesia and the development of delirium in the post-anesthesia care unit (PACU). They characterized a set of 7 different EEG patterns during emergence from anesthesia defined as emergence trajectories. Emergence trajectories made comparisons between the power in alpha and other EEG frequency bands. Those patients that did not develop oscillations in alpha power in the various emergence trajectories were at higher risk for POD in the PACU [17]. Of note, this
phenomenon was more pronounced in patients that received ketamine or nitrous oxide.

Taking this concept one step further, Shao et al. [9] demonstrated an important relationship between changes in the alpha band power and burst suppression. They analyzed EEG data for the presence of burst suppression and diminished alpha band power in patients maintained with either propofol or sevoflurane. They characterized the relationship between burst suppression and alpha power using logistic regression and found that for each decibel decrease in frontal alpha power, the odds of experiencing burst suppression increased by 1.33-fold. From their analysis, they propose these findings represent an EEG phenotype of a vulnerable brain.

Although these measures may allow early detection of patients who are vulnerable to adverse neurocognitive outcomes, their clinical value merits further investigation and will likely be part of a comprehensive approach to brain health in the perioperative period. In addition to monitoring EEG values, anesthesia care providers will likely have to utilize more refined approaches to anesthetic titration, implement tools to assess cognitive function throughout the perioperative period, and implement post-operative patient care pathways that minimize adverse outcomes [21,22].

Implementing these patient care adjuncts will likely unveil gaps in anesthesia care providers experience in conducting a preoperative cognitive assessment and awareness of the adverse consequences of their anesthetic technique on long term brain health because of limited to no follow up with their patients over a period where neurocognitive deficits may appear after surgery.

Recent consensus guidelines from the Perioperative Quality Initiative (POQI) report insufficient evidence to recommend the use of pEEG monitoring to minimize the risk of POD and POCD in older high-risk patients undergoing general anesthesia [23]. It is important to emphasize, however, that the POQI group of experts noted that three large, randomized trials demonstrated a decrease of POD with EEG-guided general anesthesia; only the ENGAGES trial showed no effect. We anticipate future work will explore the use of pEEG monitoring to “detect unintended burst...
suppression” to include recommendations that clinicians become facile at interpreting spectral displays and alpha band power to guide anesthetic delivery in the vulnerable brain population.

In summary, when providing an anesthetic approach for a patient with a known or suspected vulnerable brain, EEG monitoring with focused attention on the suppression ratio, alpha band power, and pEEG indices may prove useful, along with other measures in minimizing post-operative neurocognitive decline. Avoiding excessive anesthesia, anesthetics known to increase POD, and providing prompt treatment of physiologic and metabolic derangements (e.g., low hematocrit, hyponatremia, acidosis, etc.) are also likely important factors in minimizing POD.

**Reducing Awareness During Total Intravenous Anesthesia**

When administering a total intravenous anesthetic (TIVA) technique, there are no available monitors to measure exhaled drug concentrations. TIVA commonly consists of a continuous infusion of propofol in combination with bolus administration or a continuous infusion of an opioid. Anesthesia care providers rely on clinical signs of an adequate depth of anesthesia and ensure continuous delivery of intravenous drugs. This is in stark contrast to using potent inhaled agents, where continuous monitoring of exhaled drug concentrations is routine. The presence of exhaled drug concentrations affirms delivery of anesthetic drugs. One sign of inadequate anesthesia is patient movement. When neuromuscular blockade is used, taking away patient movement as a sign of inadequate anesthesia, the risk of awareness with TIVA rises.

Investigators have explored the incidence of awareness with varied results. In a retrospective observational study that reviewed over 2.8 million patient records during a 12-month period, the 5th National Audit Project (NAP5) explored incidence of accidental awareness as spontaneously reported by patients during general anesthesia [24]. They reported that 147 patients experienced accidental awareness with an overall incidence of 1:19000 or 0.005%. The incidence of awareness,
however, varied with anesthetic technique. Twenty-eight patients undergoing a TIVA reported awareness. TIVA was found to have a higher incidence of 1:14000 or 0.007%. The incidence increased to 1:8333 or 0.012% with TIVA in combination with neuromuscular blockade. The NAP5 report went on to emphasize that compared to other anesthetic techniques, awareness with TIVA was largely avoidable and likely related to inadequacies of drug delivery. In the absence of monitoring to confirm propofol concentrations, NAP5 authors suggested the use of pEEG monitors may help prevent awareness when using TIVA in combination with neuromuscular blockade. This recommendation is especially important when considering propofol as a maintenance anesthetic. Variability in propofol effects is substantial and requires careful titration to achieve desired effects yet avoid adverse effects. For example, recommended target concentrations range from 3 to 6 μg/ml when using target-controlled infusions and can vary further depending on the co-administration of opioids, and patient traits such as an anxious or frail elderly patient [25].

Exploring a similar question, Errando et al. [26] conducted a prospective single center observational study investigating the incidence of awareness using a structured interview in the PACU. Investigators, blinded to anesthetic technique, interviewed 4001 patients that received anesthetics from 42 different anesthesia care providers. Of those, over 1200 patients received a TIVA. They reported an overall incidence of awareness of 1:100 or 1%. By anesthetic technique, the incidence with potent inhaled agents was 1:167 or 0.6% and with TIVA was 1:91 or 1.1%. The authors pointed out that the incidence was higher in younger patients, emergency procedures, and anesthetics delivered at night and that the incidence was lower in patients that were premedicated with a benzodiazepine.

The large difference in the incidence of awareness reported in these two studies is likely because of differences in how awareness was detected. The NAP5 study relied on patients self-reporting awareness and followed by documentation that could be identified in their retrospective analysis.
In the prospective observational study, all patients were interviewed about awareness in the PACU and those that reported events consistent with awareness had follow up interviews 7 and 30 days later. As such, the methodology used to report awareness played a significant role in the reported rates. With larger the patient population it is more difficult to employ thorough reporting methods.

Many investigators have explored whether pEEG monitoring can detect brain electrical activity associated with awareness [27–29]. Although laudable, this effort is hampered by studying an adverse event that rarely occurs using a monitor that characterizes brain electrical activity but is not a direct measure of patient responsiveness or consciousness. As such, the notion that pEEG monitors are a reliable awareness monitor remains somewhat controversial. Nevertheless, consensus experts have recommended “the use of end-tidal anesthesia gas monitoring with alarms or processed EEG to reduce the risk of awareness with recall in patients receiving general anesthesia” [23].

In summary, when providing an anesthetic for patients who may benefit from a TIVA and require moderate to deep neuromuscular blockade, such as patients with a history of severe post-operative nausea and vomiting undergoing a laparoscope procedure, pEEG monitoring, along with vigilant attention to intravenous drug administration may minimize the risk of awareness.

**Anesthetic Titration in Patients with Hemodynamic Instability**

Discovering the optimal approach to managing intraoperative hemodynamic instability can be difficult. For example, initial treatment of high or low blood pressure may be best with adjustments in anesthetic dose, administration of a vasoactive agent, or both. The most prudent choice is not always readily evident. As suggested by Fehr et al [30], pEEG monitors may offer information that suggest which treatment is best. Although plausible, there is a paucity of research exploring their benefit in this setting. Researchers, however, have explored how pEEG indices in
combination with hemodynamic and anesthetic dosing levels may predict adverse outcomes and
mortality with varied results [31–34].

As an example, in a large retrospective single center analysis by Sessler et al. [35], the authors
described a triple low phenomenon that consisted of a mean blood pressure less than 80 mmHg, a
BIS value below 40 and minimal alveolar concentration of less than 0.8 that served as a strong
predictor of 30-day mortality. The authors concluded that the triple low was a promising triad of
findings, but additional study was warranted to validate it as a predictor of perioperative mortality.
Follow up prospective validation work compared mortality between two patient groups exhibiting
triple low physiology. In one group, anesthesia care providers were advised via the electronic
anesthetic record to “consider hemodynamic support” whereas in the control group no advisory was
offered. An effective response to the advisory was administration of a vasoactive agent within 5
minutes of the alert or decreasing the end tidal anesthetic by more than 20%. They found that the
advisory did not change 90-day mortality. The authors point out that anesthesia care providers
ignored the advisory approximately half the time. This finding was unanticipated. They
anticipated more anesthesia care providers in the advisory group would respond more frequently
and fewer would respond in the non-advisory group. They suggested their data were inadequate to
properly explore whether a triple low advisory would improve outcomes [36].

We suggest that this unanticipated finding may represent an education gap among anesthesia care
providers. Specifically, anesthesia care providers may lack understanding of how pEEG indices in
combination with other physiologic measures can be used to improve outcomes and address
hemodynamic perturbations. We propose that pEEG monitoring can contribute to discriminating
between the need for a vasoactive agent, volume resuscitation, or adjusting the anesthetic in a
variety of clinical scenarios. As an example, consider the hemodynamic-pEEG profiles that
inform intraoperative management presented in Fig. 2. The figure presents options for normal,
low, and high blood pressure conditions versus normal, low, and high pEEG indices.

As an example, if a patient exhibits high blood pressure but has a low pEEG index (e.g., a BIS value ≤ 40), increasing the anesthetic, although likely effective at lowering the blood pressure, may lead to excessive anesthesia and prolonged emergence. An antihypertensive may be more appropriate. In this scenario, a likely source of high blood pressure is essential hypertension and not from inadequate anesthesia. This approach of considering hypertension in the context of pEEG values is useful when caring for patients where unnecessary administration of anesthetics may increase the risk of worrisome postoperative adverse events [30].

Under selected conditions of mild to moderate low blood pressure, in addition to administering vasopressors, inotropic agents, and intravenous fluids, pEEG monitoring may inform whether it is appropriate to adjust the anesthetic. For example, if a patient exhibits mild hypotension and low pEEG indices, corrective actions include reducing the anesthetic and administering vasoactive drugs and intravenous fluids. Although less likely, if a patient exhibits hypotension and high pEEG indices, it may be prudent to restore the blood pressure with vasoactive agents and intravenous fluids before reducing the anesthetic.

In instances of severe hypotension from blood loss, pEEG monitoring may be especially helpful. Hemorrhagic shock results in an increase in intravenous anesthetic concentrations because of altered distribution and metabolism. The increased drug levels produce more pronounced anesthetic effect that is reflected in lower processed EEG indices, providing a rational basis for anesthetic administration [37]. Cardiac output is reduced altering the pharmacokinetics of anesthetic drugs. As the volume of distribution contracts, conventional dosing can lead to elevated blood and effect site drug concentrations with pronounced drug effects. When managing an anesthetic under these conditions, anesthesia providers often decrease drug delivery.

An example of this phenomenon presents the blood pressure and BIS values from a case report
describing significant blood loss in a 70-yr-old woman had undergoing repair of an abdominal aneurysm [38]. She was anesthetized with a propofol-alfentanil TIVA. Of note the hemorrhage associated drop in blood pressure was preceded by a drop in the BIS. The authors suggested that pEEG values may serve as an early warning to altered drug pharmacokinetics from severe blood loss.

In summary, we suggest that pEEG monitoring has a role in anesthetic and resuscitative management when faced with adverse changes in blood pressure. We also suggest that addressing education gaps that exist in clinician understanding of how pEEG monitoring in combination with conventional physiological monitors may be used to improve intraoperative and long-term patient outcomes.

Patients with a History of Substance Abuse

Patients with a history of substance abuse present challenges when formulating the appropriate anesthetic dose to achieve the desired level of sedation, analgesia, and immobility. Prolonged exposure to opioids, alcohol, stimulants, among others or use of drugs to treat opioid use disorder may make finding the appropriate anesthetic dose difficult. Among several concerns, perhaps chief among them, is the risk of unintended awareness during general anesthesia [39]. Prior work exploring the scientific foundation behind this concern is limited, but that which exists is interesting and perhaps unexpected. Selected substances are briefly discussed below.

Researchers have studied how painful stimuli processing are altered in chronic pain. Chronic opioid use differentially affects the level of consciousness and spinal cord responses to surgical stimulation. As an example, Oh et al. [40] measured end tidal sevoflurane concentrations needed to maintain a BIS value less than 50 (SEVOBIS50) in chronic opioid using and opioid naïve patients. They defined chronic opioid users who received a stable dose of oral morphine of at least 60 mg per
day daily for at least 4 weeks. SEVO$_{\text{BIS}50}$ was determined using Dixon’s up-down method and probit analysis. The predetermined consistent end tidal sevoflurane concentration was confirmed and maintained for 15 minutes to ensure equilibrium end tidal and effect site concentrations. Subsequently, BIS values were obtained for 1 minute at 10-second intervals in the absence of a surgical stimulus. If the average of the 5 values was < 50, the authors decreased the sevoflurane by 0.2% for the next patient, and if the average was > 50, the authors increased the sevoflurane by 0.2% for the next patient. They reported a modest decrease in the SEVO$_{\text{BIS}50}$ levels for chronic opioid use when compared to opioid naïve patients of 0.84 (95% confidence interval, 0.58–1.11) and 1.18% (95% confidence interval, 0.96–1.40). Although not intuitive, patients that chronically consume opioids may require less maintenance anesthetic.

The mechanism behind this observation is not well elucidated but thought to be a function of how the data were collected and how the results were interpreted. SEVO$_{\text{BIS}50}$ is not defined in the same manner as MAC. MAC is defined as the concentration needed to blunt a response to a standard stimulus such as surgical incision in 50% of patients whereas the BIS is a pEEG index of brain electrical activity suppression. Although this study did not explore changes in sevoflurane MAC because of chronic opioid use, it did evaluate how chronic opioid use influenced brain electrical activity under general anesthesia. A limitation of this approach was that the SEVO$_{\text{BIS}50}$ was not evaluated in the presence of a nociceptive stimulus. Unlike MAC studies, the impact of sevoflurane on spinal cord transmission from nociceptive stimuli was not determined.

As with the vulnerable brain, chronic pain patients exhibit unique characteristics in the spectral display. Specifically, chronic pain patients exhibit changes in the theta frequency band (3–8 Hz) not otherwise observed in opioid naïve patients [41]. The clinical implications of these changes have yet to be elucidated. Future work is warranted to explore how theta frequency band changes can be used to titrate anesthetic delivery to this patient group.
In response to the opioid epidemic, buprenorphine has been used to manage patients with opioid use disorder and chronic pain. It is a partial opioid mu receptor agonist and an opioid kappa and delta receptor antagonist. It has a much higher affinity for mu receptors than several commonly used opioids such as fentanyl, hydrocodone, oxycodone, and morphine but has a similar affinity to hydromorphone [42]. With a higher affinity, it displaces opioid agonists and competitively occupies up to 80–95% of receptors at clinical doses. As a partial agonist, it is considered safer as it has a ceiling effect on ventilatory depression although analgesia may be less pronounced [43]. Conflicting concerns have emerged regarding its use during the perioperative period. There is a concern for inadequate acute pain control because buprenorphine will occupy mu receptors displacing pure opioid agonists. Conversely, cessation of buprenorphine increases the risk for opioid use disorder relapse, and it associated adverse outcomes.

Recent recommendations propose maintaining buprenorphine at preoperative doses throughout the perioperative period [43,44]. Under selected conditions, reducing buprenorphine doses may be considered with procedures with associated with significant pain. This is done to allow for more receptors to be occupied by full opioid agonists.

Although these guidelines focus anesthesia care providers on the challenges of providing adequate and safe perioperative care, they are based on lower levels of evidence, such as case series, case reports, observational studies, studies without control groups, and expert consensus. Future work is warranted to establish evidence on how to best manage buprenorphine administration during perioperative care. As such, when formulating an appropriate anesthetic for patients treated with buprenorphine, anesthetic choice and dose require individualization and timely adjustment to achieve desired effects. Opioid analgesic efficacy and interactions with sedatives and potent inhaled agents are likely altered making conventional approaches to dosing challenging and even inadequate. Using pEEG indices and end tidal inhaled agent concentrations may prove useful in
titrating anesthetic delivery in this patient group.

Alcoholics can have varied anesthetic requirements based on their state of inebriation. If acutely intoxicated they require less anesthesia and if sober, they can have increased anesthetic requirements. Acute alcohol intoxication slows the EEG and may influence BIS values. Gerstman et al. [45] found a moderate correlation between BIS values and venous blood alcohol concentration (r = −0.49, P = 0.029) in healthy young adults. In their study, 21 participants consumed a median of 90 g of alcohol over a 3-hour period. The authors concluded that BIS values may be decreased in the presence of alcohol.

Fassoulaki et al. [46] compared induction and maintenance propofol dose requirements in alcoholics and non-alcoholics. They defined chronic alcoholics as consuming an average of 40 g per day of ethanol for at least 2 years. They defined non-alcoholics as consuming alcohol only occasionally or not at all. They found that with induction, the mean propofol dose required for loss of responsiveness was modestly increased in alcoholics compared to non-alcoholics (2.7 ± 0.4 versus 2.2 ± 0.4 mg/kg, respectively). Similarly, if using propofol as a maintenance anesthetic, the total amount was increased in alcoholics compared to non-alcoholics (4.2 ± 1.0 versus 3.2 ± 0.8 mg/kg, respectively) [46].

In summary, providing an anesthetic to patients with known or suspected substance use can be difficult. Patients can have unanticipated enhanced or diminished anesthetic requirements. pEEG monitoring with attentive hemodynamic monitoring can better identify patient anesthetic requirements and guide anesthetic titration to avoid excessive or inadequate anesthesia.
Conclusions

Advances in understanding nuances to intraoperative EEG monitoring applicable at the point of care are emerging as tools to better guide anesthetic delivery in selected patient populations. In this article, we reviewed well described but perhaps poorly appreciated key features of EEG waveforms and their clinical implications. They included EEG waveform morphology, spectral analysis, burst suppression, and alpha power. We endorse education that raises awareness among anesthesia providers as to their clinical utility at the point of care. This review article also posits that in selected patient groups and anesthetic techniques, EEG monitors have a place and can improve patient outcomes and minimize adverse events.
References


9. Yu Raymond Shao, Pegah Kahali, Timothy T Houle, Hao Deng, Christopher Colvin,


Table 1. Selected Randomized Controlled Trials Comparing Processed Electroencephalography Guided to Routine or End Tidal Anesthetic Gas Guided Anesthetic Delivery on Postoperative Delirium and Postoperative Cognitive Dysfunction

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Experimental Design</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
</table>

This article is protected by copyright of Korean Journal of Anesthesiology. All rights reserved.
<table>
<thead>
<tr>
<th>Study</th>
<th>Demographics</th>
<th>Anesthetic Technique</th>
<th>Primary Outcome</th>
<th>Secondary Outcome</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Dysfunction after Anaesthesia Chan et al. 2013 [47]</td>
<td>Demographics: age ≥ 60, ASA ≥3 (16%), Male (61%)</td>
<td>Non-cardiac and non-neuro surgical</td>
<td>Median BIS values in the pEEG guided and routine care group were 53 and 36 respectively</td>
<td>pEEG guided anaesthesia reduced the amount of propofol and inhaled anesthetics by 21% and 30% respectively.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anesthetic technique: TIVA (11%) &amp; inhalational agents (89%)</td>
<td>Primary outcome: At three months after surgery, there was a 4.5% reduction in the incidence of POCD in the pEEG guided group compared to the routine care group.</td>
<td>Secondary outcome: No difference in the incidence of POCD, but a 8.5% decrease in the incidence of POD one week after surgery.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pEEG guided group: Target BIS 40-60 in 462 patients</td>
<td>Routine care in 459 patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary outcome: incidence of POCD 3 months after surgery.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secondary outcome: incidence of POCD and POD one week after surgery.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring depth of anaesthesia decreases the rate of POD but not POCD Radtke et al. 2013 [48]</td>
<td>Demographics: age ≥ 60, ASA ≥3 (48%), Male (54%)</td>
<td>Non-cardiac surgery</td>
<td>Median BIS values in the pEEG guided and routine care group were 53 and 36 respectively</td>
<td>Intraoperative pEEG monitoring may provide anesthesia care providers a tool to influence one of many factors that lead to POD.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anesthetic technique: TIVA (35%) or inhalational agents (65%)</td>
<td>Primary outcome: POD was 16.7% in the BIS guided group and 21.4% in the routine care group. No difference in POCD between groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>pEEG guided group: Target BIS 40-60 in 575 patients</td>
<td>Routine care in 580 patients</td>
<td>pEEG-guided anesthesia reduced the occurrence of extremely low BIS values (&lt;20) and burst suppression and that this may have decreased the incidence of POD.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary outcome: POD &amp; POCD at baseline, 1 week, and 3 months after operation.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative Delirium in a Substudy of Cardiotoracic Surgical Patients in the BAG-RECALL Clinical Trial Whitlock et al. 2014 [13]</td>
<td>Demographics: age ≥ 60, ASA ≥3 (100%), Male (63%)</td>
<td>Cardiothoracic surgery</td>
<td>Primary outcome: 19% in the BIS group and 28% in the end-tidal guided group developed POD - a 9% non-significant reduction in the BIS guided group.</td>
<td>A larger RCT is warranted to further explore the role of pEEG guided versus end-tidal guided anesthetic delivery on POD after cardiothoracic surgery.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anesthetic technique: Inhalation agents</td>
<td>Independent predictors of POD included low anesthetic dose, intraoperative transfusion, &amp; ASA physical status.</td>
<td>Patients in poor health may be more sensitive to anesthetics and have a higher risk of POD.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pEEG guided group: Target BIS 40-60 in 149 patients</td>
<td>End-tidal guided group: Target between 0.7 and 1.3 MAC in 161 patients</td>
<td></td>
<td>Given the association between POD and poor patient outcomes, development of methods to minimize POD should be prioritized.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients screened twice a day for POD using the CAM-ICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary outcome: Incidence of POD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BIS: Bispectral index, TIVA: Total intravenous anesthesia, pEEG: Processed Electroencephalography,

POCD: Postoperative cognitive dysfunction. Assessed using selected tools. Some examples include cognitive failure questionnaire to indicate potential subjective problems with perception, memory, and motor function, neuropsychological tests such as the verbal fluency test, verbal learning test, and color trail making test. POD: Postoperative delirium. Assessed using selected tools. An example includes the CAM-ICU, BAG-RECALL: BIS or Anesthesia Gas to Reduce Explicit Recall. It is a prospective, multi-center, randomized, controlled trial to determine whether a bispectral index-guided protocol is superior to an anesthesia gas-guided protocol in reducing intraoperative awareness with explicit recall in high-risk surgical patients, RCT: Randomized Clinical Trial, MAC: Minimum alveolar concentration, CAM-ICU: Confusion Assessment Method for the intensive care unit, ENGAGES: Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes, SR: Suppression ratio, MABP: Mean arterial blood pressure.
Fig. 1. Examples of high (Panel A) and low (Panel B) alpha power within a left frontal spectral display. The left vertical axis is frequency (Hz). The right vertical axis is power (dB). Cooler and warmer colors represent low and high power. The horizontal axis is time (minutes). The dark blue horizontal lines present the alpha band range (8–12 Hz).
Fig. 2. Intraoperative hemodynamic-processed electroencephalography decision matrix for choice of altering anesthetic depth versus administering vasoactive agents and fluid administration.