American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on the Role of Neuromonitoring in Perioperative Outcomes: Electroencephalography

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Electroencephalographic (EEG) monitoring to indicate brain state during anesthesia has become widely available. It remains unclear whether EEG-guided anesthesia influences perioperative outcomes. The sixth Perioperative Quality Initiative (POQI-6) brought together an international team of multidisciplinary experts from anesthesiology, biomedical engineering, neurology, and surgery to review the current literature and to develop consensus recommendations on the utility of EEG monitoring during anesthesia. We retrieved a total of 1023 articles addressing the use of EEG monitoring during anesthesia and conducted meta-analyses from 15 trials to determine the effect of EEG-guided anesthesia on the rate of unintentional awareness, postoperative delirium, neurocognitive disorder, and long-term mortality after surgery. After considering current evidence, the working group recommends that EEG monitoring should be considered as part of the vital organ monitors to guide anesthetic management. In addition, we encourage anesthesiologists to be knowledgeable in basic EEG interpretation, such as raw waveform, spectrogram, and processed indices, when using these devices. Current evidence suggests that EEG-guided anesthesia reduces the rate of awareness during total intravenous anesthesia and has similar efficacy in preventing awareness as compared with end-tidal anesthetic gas monitoring. There is, however, insufficient evidence to recommend the use of EEG monitoring for preventing postoperative delirium, neurocognitive disorder, or postoperative mortality. (Anesth Analg XXX;XXX:00–00)

GLOSSARY

BAG-RECALL = BIS or Anesthetic Gas to Reduce Explicit Recall trial; **BIS** = bispectral index; **CODA** = Cognitive Dysfunction after Anaesthesia; **CI** = confidence interval; **DeLiT** = Dexamethasone, Light anaesthesia, and Tight glucose control; **EEG** = electroencephalogram; **ENGAGES** = Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes; **ETAG** = end-tidal anesthetic gas; **GRADE** = Grading of Recommendations Assessment, Development and Evaluation; **MAC** = minimum alveolar concentration; **MACS** = Michigan Awareness Control Study; **OR** = odds ratio; **POQI** = Perioperative Quality Initiative; **RR** = relative risk; **STRIDE** = A Strategy to Reduce the Incidence of Postoperative Delirum in Elderly Patients

General anesthesia is a reversible state of drug-induced loss of consciousness.[1] Traditionally, anesthesiologists are trained to deliver sufficient anesthetic, using population-based dosing guidelines, to ensure unconsciousness in every patient. Anesthetic doses are then adjusted to avoid autonomic and somatic responses to surgical

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stimulations. The anesthetic state is, therefore, conceptualized as a reversible coma consisting of 3 clinical deliverables, namely unconsciousness, immobility, and control of autonomic responses to nociception.[2] This approach is generally effective and safe in the majority of patients. However, in patients with exceptional anesthetic requirements, routine doses may result in unintentional awareness during anesthesia. On the contrary, in patients who are especially sensitive to anesthetics, the same dose may become excessive, resulting in cardiovascular, respiratory, and possibly neurological side effects. In this respect, tracking anesthetic response based on autonomic changes (eg, heart rate and blood pressure) could be misleading.[3,4] It should be noted that autonomic responses emanate from primarily subcortical and spinal reflexes, thus indicating the antinociceptive state rather than the conscious state, although noxious stimuli may also activate neurons in the thalamus and cortex.[5–8]

Because anesthetics work primarily on the brain to produce loss of consciousness, there is growing interest in monitoring the electroencephalogram (EEG) as a measure of anesthetic effect, particularly as it relates to the delivery of unconsciousness. In general, as the dose of anesthetic is increased, one can observe a progressive slowing of the EEG. Typically, this is associated with increasing amplitude and the occurrence of spindles in the frontal electrodes.[9–11] When further doses of anesthetic are administered, EEG burst suppression and isoelectricity can be observed.[12–14]

Interpretation of raw EEG signals in the operating rooms could be challenging to the anesthesiologists. As such, a large number of processing algorithms have been developed to facilitate real-time analysis. Using fast Fourier transformation, spectral (frequency) data are extracted from epochs of raw EEG signals and are displayed as overlapping spectrograms to indicate the relative contributions of various frequency bands.[14,15] There are also higher-order processing techniques. The bispectral analysis determines the phase shift between adjacent EEG waves,[16,17] entropy quantifies the regularity (or synchrony) of the signals,[18,19] wavelet analysis measures the temporal and spectral relationship of EEG waves,[20] and other methods describe the topographic changes of EEG during anesthesia.[21] In addition, complex algorithms, including the symbolic dynamic method[22] and the adaptive neuro-fuzzy inference system,[23,24] have been developed to determine the association between spectral frequencies and anesthetic effect. Supplemental Digital Content, Table S1, http://links.lww.com/AA/C956, shows the characteristics of currently available EEG monitors in the operating room. To simplify interpretation of EEG signals, a common feature of all monitors is to scale the output to produce a univariate index for describing the clinical state of the patients during anesthesia.[16,18–26] These indices generally range from 0 (isoelectricity) to 100 (awake), and an optimal range for anesthesia is between 40 and 60.

Based on the processed EEG index value, anesthesiologists may therefore adjust anesthetic administration to target a desired effect in the brain. This may avoid overdose of anesthetics. In this respect, large doses of anesthetics may provoke systemic inflammatory response,[27,28] increase deposition of Alzheimer proteins,[29–33] and have been shown to prolong cognitive recovery in animal models.[34,35] There is also neuronal apoptosis with EEG burst suppression.[36,37] As a consequence of cardiovascular or neuronal depression, there are also indirect physiological effects that may lead to hypoperfusion and tissue hypoxia.[38–40]

In an updated meta-analysis of 36 studies, EEG-guided anesthesia decreased anesthetic requirements, reduced emergence time, and expedited discharge from the postanesthetic recovery unit.[41] However, it remains unclear whether these changes in anesthetic delivery affect other postoperative outcomes. The purpose of this expert group meeting was to summarize the current literature and to develop consensus statements on the clinical utility of processed EEG monitoring. Specifically, we addressed the questions whether anesthetic administration guided by processed EEG would reduce the rate of (1) unintentional awareness with recall during anesthesia; (2) postoperative delirium; (3) postoperative neurocognitive disorder; and (4) long-term mortality after surgery.

METHODS

The Perioperative Quality Initiative (POQI) is an international, multidisciplinary, nonprofit organization that organizes conferences to develop consensus-based recommendations on perioperative care.[42] The sixth consensus conference (POQI-6) was convened between November 29 and December 1, 2018 in Dallas, Texas, to address issues on postoperative delirium and issues on clinical utility of neuromonitoring. This report focuses on the association between intraoperative processed EEG monitoring and postoperative outcomes.

Systematic Review

Before the meeting, systematic reviews and meta-analyses were conducted to assess the impact of processed EEG monitoring on awareness with recall during general anesthesia, postoperative delirium, neurocognitive disorder, and long-term mortality after surgery. We only included randomized controlled trials in the systematic reviews. Trials were eligible if they studied patients having surgery with general anesthesia using one of the recognized EEG devices (Supplemental Digital Content, Table S1, http://links.lww.com/AA/C956) for monitoring during general anesthesia. Trials were included regardless of language, publication types (abstract or full articles), or primary objectives of the study. We excluded trials that primarily evaluated the use of EEG monitoring for brain mapping or detection of cerebral ischemia and convulsion. Observational studies and trials that did not report methodology used to identify the outcomes of interest were also excluded.

We identified trials by searching 4 major databases, including the Ovid version of MEDLINE (Ovid MEDLINE [Ovid Technologies, Norwood, MA] In-Process and other Non-Indexed Citations and Ovid MEDLINE, 2000 to October 1, 2018), EMBASE (2000–2018), the Cochrane Central Register of Controlled Trials (third quarter 2018), and the Cochrane Database of Systematic Reviews (second quarter 2018). PubMed search using the feature of "related articles" and search of the Web of Science for cited references of key publications were also performed. Supplemental Digital Content, Table S2, http://links.lww.com/AA/C956, summarizes the search strategies for each of the outcomes.

Two reviewers evaluated the title and abstract of each of the citations identified during the search process. Potential

citations that fulfill the eligibility criteria were shortlisted for full-text review. The same reviewers then evaluated the eligibility of the articles independently. Final inclusion of a citation was determined by a consensus process.

In each of the included trials, we extracted data on patient population and demographic characteristics, treatment allocation (EEG monitoring versus standard care or active controls), concealment of randomization, blinding of the trial, and methods of outcome assessment. The relative risk (RR) and associated 95% confidence intervals (CIs) were calculated for each of the trials included. Data on RR were then pooled together using DerSimonian and Laird random effects model.[43] Heterogeneity between trials was determined by the calculation of I^2 value. Heterogeneity was considered as substantial if I^2 was >75%, and low heterogeneity was defined when I^2 value was <25%.

Modified Delphi Process

During the course of the consensus conference, the literature was reviewed in a series of breakout and plenary sessions to formulate consensus statements and recommendations for current practice and future research. The strength of the evidence was rated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Supplemental Digital Content, Table S3, http://links.lww.com/AA/C956).[44] In the last session of the POQI-6 conference, all members of the working group voted to indicate whether they agreed with the statements and recommendations or not, dissenting votes and comments were also recorded.

Shortly after the meeting, the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) Trial was published.[45] ENGAGES compared the effect of EEG-guided anesthesia to avoid burst suppression and bispectral index (BIS) <40 with routine care on postoperative delirium and 30-day morbidity and mortality. The results were incorporated in our meta-analyses, and updated statements were sent to POQI-6 members for revoting in March–April 2019. The updated recommendations were shown in the Table.

RESULTS

Supplemental Digital Content, Figures S1–S4, http://links.lww.com/AA/C956, shows the flowcharts for the literature search in each of the specified outcomes. Overall, we retrieved a total of 1023 articles in our literature review. After screening the titles and abstracts, we studied the full texts for 133 articles in detail. Only 22 articles, derived from 15 trials (n = 41,509), fulfilled the eligibility criteria for inclusion in our meta-analyses. Among these articles, 7 studied the effect of EEG monitoring on awareness with recall,[46–52] 6 evaluated postoperative delirium,[45,53–57] and only 3 measured postoperative neurocognitive disorder.[53,54,58] Ten articles investigated the effects of EEG monitoring on long-term mortality.[53,59–66] All the included trials used the BIS monitor. In one pilot study, assessing the influence of anesthetic depth on 12-month mortality, some of the EEG recordings was measured by state entropy (55). Therefore, much of the results are only applicable to BIS monitoring.

Awareness With Recall

Seven trials, involving a total of 34,544 patients, were included in this meta-analysis. The median sample size was 2463 patients per trial. Supplemental Digital Content, Tables S4–S5, http://links.lww.com/AA/C956, summarizes the characteristics and quality measures of the included trials.

Table. Perioperative Quality Initiative-6 Consensus Statement Regarding the Use of Electroencephalography to Guide Administration of General Anesthesia

	Statement	Strength	Level of Evidence	For	Against
#1	We recommend that clinicians consider using EEG monitoring to inform anesthetic management	Weak	D	21	1[a]
#2	We recommend clinicians be knowledgeable in EEG interpretation (raw waveform, spectrogram, and processed indices) when using these technologies in anesthetic management	Strong	C	22	0
#3	We recommend 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	Strong	C	21	1[b]
#4	We recommend the use of processed EEG monitoring to reduce the risk of awareness with recall in patients receiving total intravenous anesthesia during general anesthesia.	Strong	C	22	0
#5	There is insufficient evidence to recommend using processed EEG monitoring in older high-risk surgical patients undergoing general anesthesia to reduce the risk of postoperative delirium.	N/A	N/A	16	6[c]
#6	We recommend clinicians consider using EEG monitoring to detect unintended burst suppression during general anesthesia.	Weak	C	18	4[d]
#7	There is insufficient evidence to make a recommendation on the use of process to decrease the risk of postoperative neurocognitive disorder in older patients having major noncardiac surgery.	N/A	N/A	21	1[e]

Abbreviations: BIS, bispectral index; EEG, electroencephalogram; ENGAGES, Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes; N/A, not appropriate; POQI, Perioperative Quality Initiative.

[a]L.A.F. concerned that this is a future goal and not practical in current practice.

[b]J.M.L. believed recommendation should be weak.

[c]Six POQI participants (P.S.G., S.K., M.A.R., M.D.M., P.L.P., and M.H.) voted against this statement and desired to express a dissenting view: (1) Three large randomized trials have demonstrated a decrease of postoperative delirium with EEG-guided general anesthesia; only the ENGAGES trial showed no effect. (2) ENGAGES trial failed to modify anesthetic exposure in ENGAGES trial. (3) EEG suppression and duration of BIS <40 were significantly longer in patients with delirium compared with those without in previous trials (including the ENGAGES trial).

[d]L.A.F., J.M.L., D.L.M., and C.B. believed the current data did not support the statement.

[e]T.L.H. advised a weak recommendation for the use of EEG.

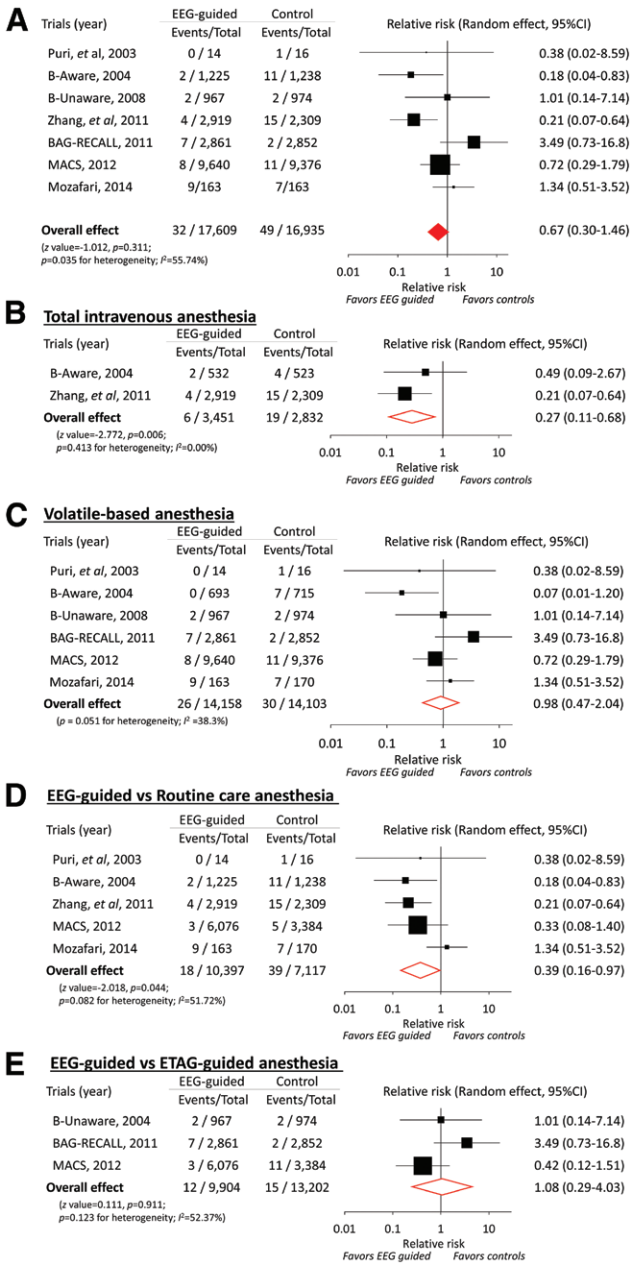

Figure 1. A, Pooled estimate for intraoperative awareness in patients receiving EEG-guided or routine care anesthesia. Sensitivity analyses showing the pooled estimates for intraoperative awareness in patients receiving total intravenous (B), volatile anesthesia (C), EEG guided with routine care (D), or ETAG-guided anesthesia (E). Figure reused with the permission of the POQI. For permission requests, contact info@poqi.org. BAG-RECALL indicates BIS or Anesthetic Gas to Reduce Explicit Recall trial; CI, confidence interval; EEG, electroencephalogram; ETAG, end-tidal anesthetic agent; MACS, Michigan Awareness Control Study; POQI, Perioperative Quality Initiative.

The median (range) follow-up rate was 98.3% (87.2%–100%). The B-Aware trial, B-Unaware trial, BIS or Anesthetic Gas to Reduce Explicit Recall (BAG-RECALL) trial, and the trials by Puri and Murthy[47] and Zhang et al[50] studied high-risk patients for awareness.[48,51,52] The Michigan Awareness Control Study (MACS) recruited unselected patients.[49] Mozafari et al[46] included patients having abdominal surgery with unknown risk, but the rate of awareness in this study was reported as 12.0%. Four trials evaluated BIS monitoring with routine care.[46–48,50] B-Unaware, BAG-RECALL, and MACS included active controls so that the non-BIS monitoring group received end-tidal anesthetic gas (ETAG)-guided care (with low ETAG alarm activated), aiming to deliver inhaled anesthetics between 0.7 and 1.3 age-adjusted minimum alveolar concentration (MAC).[49,51,52] B-Aware trial and the study by Zhang et al[50] also included patients receiving total intravenous anesthesia.[48]

The MACS trial deserves further discussion because it was stopped early for futility.[49] In an interim analysis of the first 18,836 patients, the incidence of awareness in the BIS group was 0.08% and that for ETAG group was 0.12% (P = .48). In a post hoc analysis, it was found that 36% of patients in the BIS group did not have BIS recorded and anesthetics were managed according to clinical signs (ie, routine care). The rate of awareness in this group of patients was significantly higher than those who actually had BIS monitored (0.05% vs 0.15%; P = .006, Fisher exact test).

Overall, the incidence of awareness was low (0.23%, 81 events). Figure 1A shows the RR of awareness in all included trials. The pooled analysis showed that BIS-guided anesthesia did not reduce the risk of awareness (RR [95% CI], 0.67 [0.30–1.46]). Because there was substantial heterogeneity (I^2 = 55.7%), we conducted 2 subgroup analyses. In patients receiving total intravenous anesthesia (n = 6283), a pooled analysis showed that BIS-guided anesthesia significantly reduced the risk of awareness (RR [95% CI], 0.27 [0.11–0.68]; I^2 = 0.0%; Figure 1B).[48,50] In contrast, BIS monitoring did not demonstrate benefit in those who received volatile-based anesthesia (n = 28,261; RR [95% CI], 0.98 [0.47–2.04]; I^2 = 38.3%)[46–49,51,52] (Figure 1C).

In trials that compared BIS-guided anesthesia with routine care as the control group (n = 17,514),[46–50] the risk of awareness was reduced with BIS monitoring (RR [95% CI], 0.39 [0.16–0.97], I^2 = 49.8%; Figure 1D). By restricting trials that recruited patients at high risk for awareness,[47,48,50] the benefit of BIS monitoring was more significant (RR [95% CI], 0.23 [0.11–0.49], I^2 = 0.0%). However, BIS-guided anesthesia has no effect on awareness when an active control group was used (ie, ETAG guided)[49,51,52] (RR [95% CI], 1.08 [0.29–4.03]; I^2 = 52.3%; Figure 1E).

Postoperative Delirium

We initially identified 5 trials investigating the effect of BIS monitoring on the occurrence of postoperative delirium.[53–57] The ENGAGES trial was recently published, and this was subsequently included in our meta-analysis.[45]

All the included trials aimed to test whether an optimized anesthetic administration with EEG monitoring would reduce anesthetic exposure and would consequently decrease the risk of postoperative delirium. The 2 trials by Sieber et al[55,56] studied the use of BIS monitoring to guide sedation for hip fracture fixation with spinal anesthesia. The trial by Radtke et al[54] and the Cognitive Dysfunction after Anaesthesia (CODA) trial compared BIS monitoring with routine care in general anesthesia.[53] The BAG-RECALL substudy compared BIS-guided anesthesia with ETAG-guided care with alarm in a selected group of patients having cardiac or thoracic surgery that were admitted to the intensive care unit.[57] Finally, the recently published ENGAGES Trial

compared EEG-guided anesthesia to avoid burst suppression and BIS <40 with routine care.[45]

The overall incidence of postoperative delirium in these trials was 22.5% (875/3891). EEG (or BIS) monitoring reduced the risk of delirium (RR [95% CI], 0.78 [0.61–0.98]), but there was substantial heterogeneity (I^2 = 70.8%; Figure 2). The effect of BIS monitoring disappeared after excluding trials on sedation alone (RR [95% CI], 0.80 [0.60–1.07]; I^2 = 78.2%).[45,53,54,57]

Three observational cohorts[67–69] have also reported the association between EEG burst suppression and postoperative delirium. In a substudy of the Systematic Assessment and Targeted Improvement of Services Following Yearlong Surgical Outcomes Surveys (n = 619), Fritz et al[67] showed a higher risk of postoperative delirium in patients with EEG burst suppression during surgery compared with those who did not (adjusted odds ratio [OR] [95% CI], 1.29 [1.10–1.50]). Similarly, Soehle et al[69] reported a 2.5-fold increase in the duration of intraoperative burst suppression among cardiac surgical patients suffering postoperative delirium (n = 26) compared with those who did not (n = 55). Finally, the occurrence of EEG burst suppression during maintenance of anesthesia was associated with delirium in the postanesthetic care unit (OR [95% CI], 1.86 [1.13–3.05]).[68]

Postoperative Neurocognitive Disorder

Three trials have reported the effect of BIS monitoring on postoperative neurocognitive disorders in noncardiac surgery.[53,54,58] Ballard et al[58] used both EEG and cerebral oximetry to guide anesthesia, with BIS targeted at 40–60, and an algorithm to maintain regional cerebral oxygen saturation ≥50%. Compared with routine care, EEG and cerebral oximetry monitoring reduced the rate of mild neurocognitive disorder at 3 months after surgery, defined as a decline in performance in ≥1 neuropsychology test. There was no observable effect on moderate or severe postoperative neurocognitive disorder. The CODA trial randomly assigned 921 patients having major noncardiac surgery to receive EEG-guided anesthesia, aiming at BIS of 40–60 or routine care.[53] At 3 months after surgery, patients in the BIS group had a lower rate of neurocognitive disorder than controls (10.2% vs 14.7%). There was no effect on subjective cognitive decline as measured by the cognitive failure questionnaire. It should be noted that BIS-guided anesthesia did not affect early neurocognitive performance at 1 week after surgery, and the results may be obscured by early surgical recovery. The higher rate of neurocognitive disorder in the control group was associated with lower BIS, longer duration of BIS <40, and higher anesthetic dose administered. Finally, Radtke et al[54] studied 1155 patients having elective noncardiac surgery. Patients were randomly assigned to have BIS (targeted between 40 and 60) monitoring or routine care. The primary outcome was postoperative delirium; neurocognitive performance was also measured using computerized neuropsychological tests. Although the rate of delirium was reduced with BIS-guided anesthesia, it did not affect neurocognitive disorder. In contrast to CODA, EEG recorded in the trial by Radtke et al[54] was similar in the BIS and control groups. It should be emphasized that patients with mild cognitive impairment during the preoperative assessment (mini-mental state examination score <24) were typically excluded from these trials. Therefore, the effect of BIS monitoring in high-risk patients has not been studied.

Overall, 7.9% (161/2041) of patients tested positive for neurocognitive disorder at ≥12 weeks after noncardiac surgery. Our pooled analysis showed a significant decrease in the risk of developing postoperative neurocognitive disorder with BIS monitoring (RR [95% CI], 0.69 [0.51–0.94]; I^2 = 0.0%; Figure 3).

Long-term Mortality

The effect of BIS monitoring on long-term mortality was studied in 9 trials (n = 4267), resulting in a total of 10 published articles.[45,53,54,59–64,66] The majority of studies were designed to evaluate awareness and cognitive performance.[51–54,60,63,66] Long-term mortality was therefore a secondary goal and may lower the validity of the data.[70] The long-term follow-up study of the B-Aware trial showed no difference in myocardial infarction, stroke, or death.[63] However, in patients receiving BIS monitoring, those who have BIS <40 for >55 minutes had a

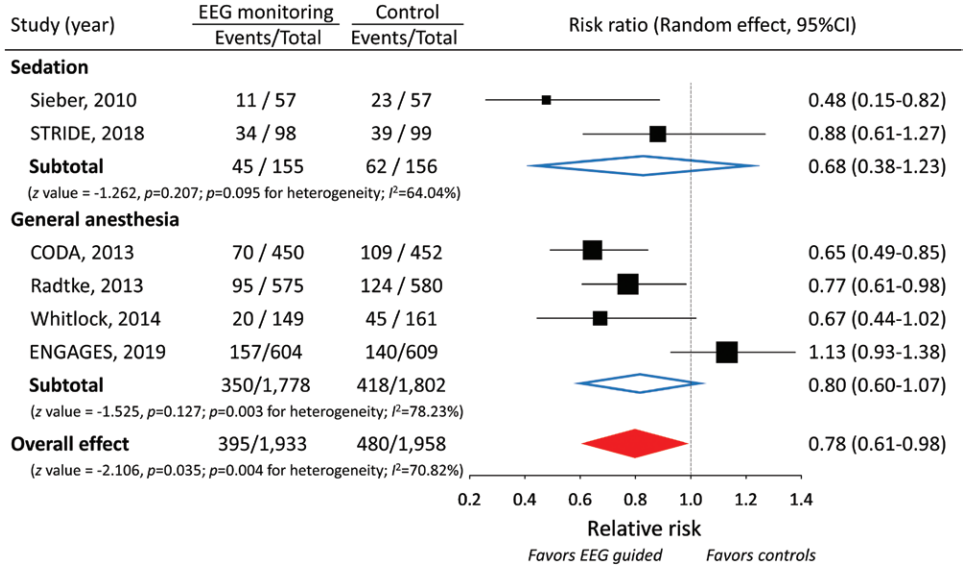

Figure 2. Forest plots of trials comparing the risk for postoperative delirium in patients receiving EEG monitoring or routine care anesthesia. Figure reused with the permission of the POQI. For permission requests, contact info@poqi.org. CI indicates confidence interval; CODA, Cognitive Dysfunction after Anaesthesia; EEG, electroencephalogram; ENGAGES, Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes; POQI, Perioperative Quality Initiative; STRIDE, A Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients.

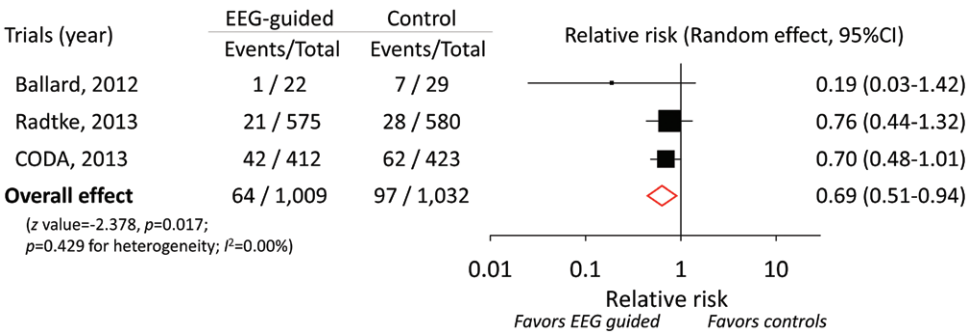

Figure 3. Forest plots of trials comparing the risk for postoperative neurocognitive disorders in patients receiving EEG monitoring or routine care anesthesia. Figure reused with the permission of the POQI. For permission requests, contact info@poqi.org. CI indicates confidence interval; CODA, Cognitive Dysfunction after Anaesthesia; EEG, electroencephalogram; POQI, Perioperative Quality Initiative.

significantly higher mortality than those who did not (the propensity score adjusted hazard ratio [HR] [95% CI], 1.41 [1.02–1.95]). Kertai et al[61] analyzed the 3-year survival status for the B-Unaware trial patients. In patients having cardiac surgery, there was a significant association between deep anesthesia (BIS <45) and long-term mortality (adjusted HR [95% CI], 1.29 [1.12–1.49]).[61] However, there was no observable association between deep anesthesia and mortality in noncardiac surgery adjusted HR (95% CI), 1.03 (0.93–1.14).[62] The CODA trial reported 3-month mortality, and this was higher in patients having BIS monitoring (7.8%) compared with those in the routine care group (6.1%).[53] Brown et al[60] studied the long-term mortality of patients in the original sedation trial for hip fracture fixation.[56] Among the 114 patients who were recruited to the trial, BIS-guided light sedation (BIS >80) reduced 12-month mortality compared with deep sedation (BIS, 50), 22.2% vs 43.6%, in patients with higher Charlson comorbidity score >4.[60] However, the findings could not be reproduced in a subsequent trial by the same group with larger sample size (n = 200). The 12-month mortality was 14% in both the light and heavy sedation group.[66]

Two trials were specifically designed to investigate the influence of BIS monitoring on long-term mortality. The Dexamethasone, Light anaesthesia, and Tight glucose control (DeLiT) trial was a 3 × 2 factorial trial.[59] Patients having major noncardiac surgery were randomly assigned to receive anesthesia aiming at BIS of 55 (light anesthesia) or 35 (deep anesthesia). The trial was stopped early (n = 381; 39.3% of planned sample size) because of futility. Along with other interventions, deep or light anesthesia had no effect on 12-month mortality, 11% vs 12%, respectively. The Balanced pilot trial studied 125 patients to test the feasibility to maintain target BIS values. At 12 months after surgery, major vascular events, infective complication, and death were 17% in the light anesthesia (BIS, 50) and 28% in the deep anesthesia group (P = .15). Although the rate of delirium was not affected by avoiding EEG suppression, ENGAGES reported a 4.6-fold decrease in 30-day mortality among patients with EEG-guided anesthesia compared with routine care (0.65% vs 3.07%; HR [95% CI], 4.8 [2.1–10.8]).[45] Overall, light versus deep anesthesia, guided by EEG monitoring, has no effect on long-term mortality (RR [95% CI], 0.95 [0.80–1.12]), and there was substantial heterogeneity (I^2 = 38.4%; Figure 4).

A few studies have also reported the association between deep anesthesia and long-term mortality. The first observational cohort study by Monk et al[71] showed an increased risk of 12-month mortality with deep anesthesia (BIS, <45) in 1064 patients having major noncardiac surgery (OR [95% CI], 1.24 [1.06–1.44]) per hour of deep anesthesia. The finding was consistent with another cohort study showing an increased 2-year mortality in patients with intraoperative BIS <45, but this was heavily influenced by preexisting malignant disease[72] (HR [95% CI], 1.18 [1.08–1.29] per hour of deep anesthesia). The association was no longer significant in an analysis restricted to patients with cancer.[73]

Others have analyzed large databases to study the link between long-term mortality and EEG suppression. Sessler et al[74] reported an increase in hospital death and mortality in 24,120 noncardiac surgical patients when a state of "triple low (low BIS, low anesthetic dose, and low arterial pressure)" occurred. In a retrospective analysis of B-Unaware, BAG-RECALL, and MACS trials, 90-day mortality was increased by 9% for every 15 cumulative minutes in triple low state. However, the same association could not be replicated in another cohort of 16,263 patients.[75,76]

Finally, Willingham et al[65] reported the association between intraoperative EEG suppression (>5 minutes) and 12-month mortality data from selected patients in the B-Unaware and BAG-RECALL trials. The propensity score adjusted mortality was not significant in patients with or without burst suppression during anesthesia (OR [95% CI], 0.83 [0.55–1.25]). However, coincident EEG burst suppression and hypotension with mean arterial pressure <55 mm Hg increased the risk of 12-month mortality by almost 3-fold (OR [95% CI], 2.96 [1.34–6.52]).

Based on this literature, the working group analyzed the summary data and developed 7 consensus statements (Table; Figure 5).

DISCUSSION

1. We recommend that clinicians consider using EEG monitoring to inform anesthetic management. (*Weak recommendation, Grade D evidence*)

Rationale for Recommendation: Despite being a surrogate marker for consciousness during anesthesia, the EEG acts as a sensitive and real-time measure of cerebral responsiveness to anesthetic administration. There is now consistent evidence to suggest that EEG-guided anesthesia reduces anesthetic exposure and decreases early recovery time.[41] However, the reduction in anesthetic exposure did not

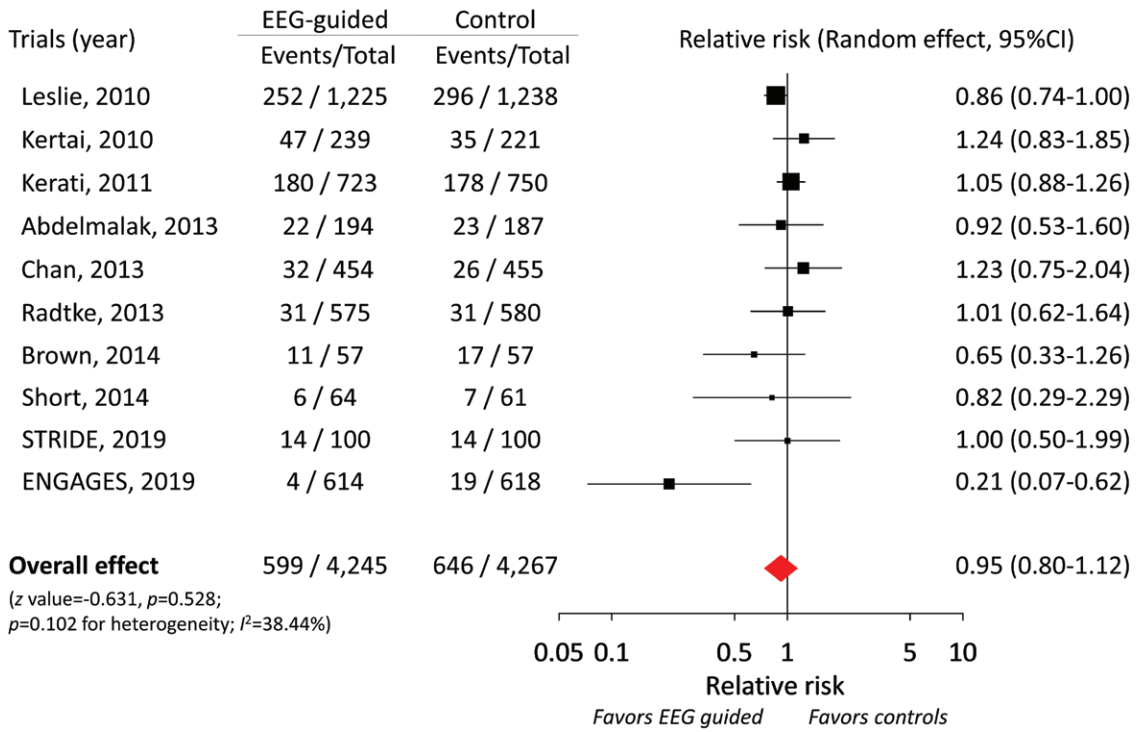

Figure 4. Forest plots of trials comparing the risk for long-term mortality after surgery in patients receiving EEG monitoring or routine care anesthesia. Figure reused with the permission of the POQI. For permission requests, contact info@poqi.org. CI indicates confidence interval; EEG, electroencephalogram; ENGAGES, Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes; POQI, Perioperative Quality Initiative; STRIDE, A Strategy to Reduce the Incidence of Postoperative Delirum in Elderly Patients.

translate to better outcome. In our meta-analysis of randomized controlled trials, long-term mortality was not improved with EEG monitoring compared with routine anesthetic care (Figure 4). Similarly, results from observational cohorts[71–73] and large database analysis were conflicting.[74,75,77] It should be noted that another trial of 6500 high-risk patients has recently completed long-term follow-up.[78] The Balanced Anesthesia Trial (Australian New Zealand Clinical Trials Registry No: ACTRN12612000632897) was designed to evaluate whether light anesthesia (BIS, 50) would improve all-cause mortality compared with deep anesthesia (BIS, 35) at 12 months after major surgery. The results of this trial would likely influence our conclusions regarding the utility of EEG monitoring on long-term outcome. Regardless of the trial results, it can be argued that EEG monitoring can provide additional information on the anesthetized state and what intervention may be appropriate. In particular, the processed EEG provides a relatively specific signal regarding the adequacy of hypnosis, such that, when movement or hemodynamic perturbations are observed, the clinician can more intelligently decide on the intervention required (eg, additional hypnotic or opioid).

In considering the potential benefits of EEG monitoring, the workgroup recognized that there are additional costs to implement EEG monitoring. This includes the acquisition costs for EEG monitors as well as costs required for the sensor electrodes. Because EEG monitors are increasingly available, we believe anesthesiologists should consider including EEG as part of the vital organ monitors to guide anesthetic management.

2. We recommend clinicians be knowledgeable in EEG interpretation (raw waveform, spectrogram, and processed indices) when using these technologies in anesthetic management. (*Strong recommendation, Grade C evidence*)

Rationale for Recommendation: Because of its complexity, the raw EEG signal is typically digitized and processed by proprietary algorithms into various parameters that can be empirically linked to the clinical state (Table). There are limitations to the processed indices. The administration of nitrous oxide and ketamine can activate the EEG, maintaining EEG indices indicative of the awake state despite clinically evident sedation.[79] In addition, EEG recordings are small-amplitude signals and may be overwhelmed by high-frequency noises, such as electrical mains, electromyogram, electrocardiogram, and electrocautery. Current devices are generally equipped with hardware and software to filter and reject artifacts. However, as artifacts are removed from the incoming signals, the amount of EEG recording available for processing per unit time will be reduced. Consequently, signal processing may stretch for a longer period of time before an updated value is obtained. Therefore, the prevailing index number may not represent the current state of consciousness.[80] The indices are, therefore, best viewed as "state monitors," meaning that they reflect the state of the brain in the recent past rather than the current or future condition.

To avoid misinterpretation, the working group believes that it is important to display raw EEG signals on the screen and that anesthesiologists should be trained to read raw

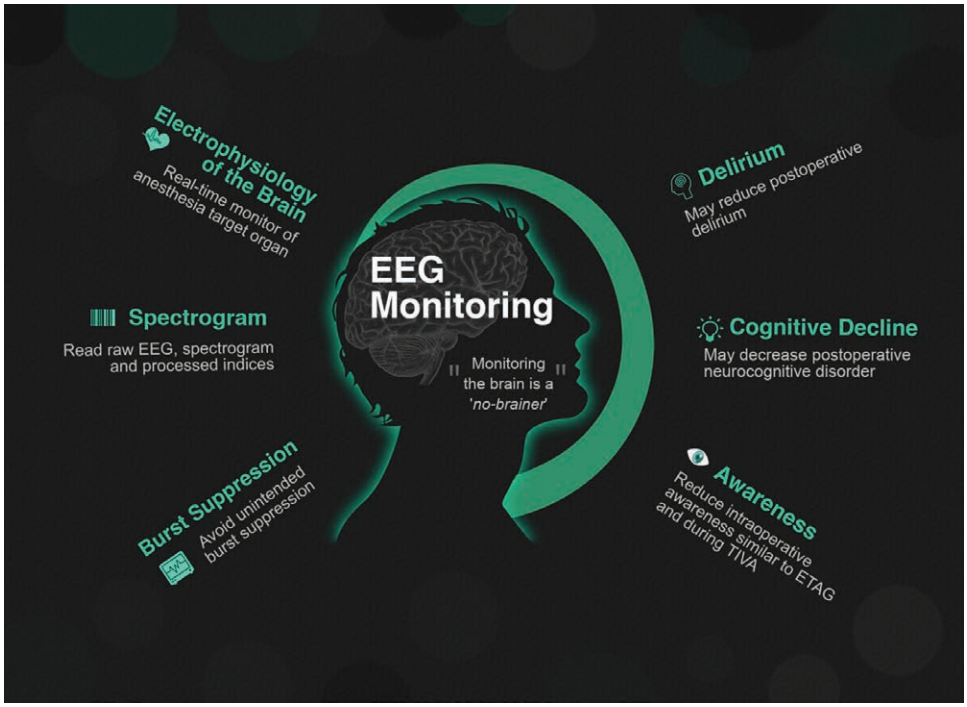

Figure 5. Schematic diagram (infographic) illustrating the clinical utility of intraoperative electroencephalographic monitoring. Figure reused with the permission of the POQI. For permission requests, contact info@poqi.org. EEG indicates electroencephalogram; ETAG, end-tidal anesthetic agent; POQI, Perioperative Quality Initiative; TIVA, total intravenous anesthesia.

EEG waveforms. While expert analysis of the EEG requires substantial expertise, there are certain elements in the raw waveform, such as the spectral changes and burst suppression, that can be readily recognized and serve as the basis for clinical inference. In a study of 40 anesthesiologists, the majority were able to recognize anesthetic-related EEG changes after a 15-minute tutorial.[81] Similarly, individuals with 45-minute training were able to read EEG and derived a BIS score that was similar to the value generated by the machine.[82] Currently, a large amount of educational material is available online. The websites www.AnesthesiaEEG.com and www.icetap.org provide interactive tutorials for self-learning.

3. We recommend 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. (*Strong recommendation, Grade C evidence*)
4. We recommend the use of processed EEG monitoring to reduce the risk of awareness with recall in patients receiving total intravenous anesthesia during general anesthesia. (*Strong recommendation, Grade C evidence*)

Rationale for Recommendation: A major impetus for the development of processed EEG is to prevent awareness. The current literature, however, does not demonstrate benefit of EEG monitoring compared with ETAG-guided anesthesia (Figure 1). Our subgroup analyses showed that ETAG-guided anesthesia with alarms produced similar efficacy for preventing awareness compared with BIS monitoring (Figure 3). However, ETAG monitoring can only be applied to volatile-based anesthesia. In this regard, an analysis restricted to patients receiving total intravenous anesthesia demonstrated substantial benefit with BIS monitoring (Figure 2).[48,50] However, the current data were limited to 2 studies with few events (0.4%, 25/6283); future trials are required to confirm this finding. Nevertheless, in critical incidents reporting, EEG monitoring may reduce awareness by 51.9% (42/51 awareness cases),[83] and that monitoring may be most useful in patients receiving total intravenous anesthesia and neuromuscular block.[84] In common to any monitoring device, alarm with appropriate limits should be set for EEG and ETAG monitors, so that anesthesiologists can be alerted in a timely fashion for impending situations.

5. There is insufficient evidence to recommend using processed EEG monitoring in older high-risk surgical patients undergoing general anesthesia to reduce the risk of postoperative delirium.

Rationale for Recommendation: Anesthesia has been implicated in the pathogenesis of postoperative delirium.[85] It has been postulated that EEG-guided anesthesia, by reducing anesthetic exposure, may reduce the incidence of delirium. Our meta-analysis of 6 trials demonstrated a 22% reduction in postoperative delirium with BIS monitoring, but there was substantial heterogeneity (Figure 4). In a subgroup analysis that excluded trials on EEG-guided sedation, the benefit of BIS monitoring was no longer significant. Currently, there is insufficient evidence to recommend the use of EEG monitoring to reduce the risk of postoperative delirium. Nevertheless, 6 of the POQI-6 participants were concerned with the recommendations. They have highlighted that the ENGAGES trial[45] did not provide comparable evidence as for the previous trials.[53,54] In particular, ENGAGES failed to modify anesthetic exposure in a clinically meaningful manner. Anesthetic concentrations were reduced by 0.11 MAC in the EEG-guided group compared with usual care, a difference that is unlikely to be clinically significant. In contrast to the CODA trial, anesthetic concentrations were reduced

by 0.36 MAC in the EEG-guided group.[53] All patients in the ENGAGES trial tended to spend a large proportion of time with BIS <40. There was also large variability, even in the EEG-guided group, suggesting that EEG guidance was inadequately performed (Supplemental Digital Content, Figure S5, http://links.lww.com/AA/C956). It would appear that the ineffective EEG-guided anesthesia may contribute to the lack of reduction in postoperative delirium. There are other concerns of the ENGAGES trial. First, duration of EEG suppression and BIS <40 were longer in patients with delirium compared with those without. Second, confusion assessment method testing was not started within 24 hours after surgery and was only performed once daily. It should be noted that delirium typically follows a fluctuating time course.[68,86] It is, therefore, not surprising that postoperative delirium may have been missed with the current assessment. Overall, the dissenters are very concerned that the tremendous benefits of intraoperative EEG guidance in elderly patients would not be valued sufficiently, especially the avoidance of burst suppression to reduce the risk for postoperative delirium. It should be noted that a postoperative delirium substudy of the Balanced Anesthesia trial has completed recruitment.[78] The results of this substudy will further define the role of EEG monitoring for the prevention of delirium.

6. We recommend clinicians consider using EEG monitoring to detect unintended burst suppression during general anesthesia. (*Strong recommendation, Grade C evidence*)

Rationale for Recommendation: A number of observational studies have highlighted the association between EEG burst suppression and postoperative delirium.[67–69] Given that delirium is a serious and potentially lethal complication, it would be reasonable to avoid burst suppression during anesthesia. However, the hypothesis was not supported by a recent randomized trial.[45] In ENGAGES trial, patients were randomly assigned to receive EEG-guided anesthesia, designed to avoid burst suppression or routine care. The primary outcome was rate of delirium within the first 5 days after surgery, and this did not differ between groups, but there are important limitations of the trial. Furthermore, 30-day mortality rate as an exploratory outcome was significantly lower in the EEG-guided group compared with controls (HR [95% CI], 0.21 [0.09–0.48]). It is likely that forthcoming trials, such as ENGAGES-Canada (ClinicalTrials.gov Identifier: NCT02692300) and the Balanced Anesthesia Trial, will reform the role of EEG monitoring in the near future. Although there may not be obvious harm with EEG burst suppression, the associated large doses of anesthetics will delay emergence[41]; it is, therefore, advisable to avoid unintended burst suppression during anesthesia.

7. There is insufficient evidence to make a recommendation on the use of processed EEG to decrease the risk of postoperative neurocognitive disorder in older patients having major noncardiac surgery.

Rationale for Recommendation: Three trials have investigated the effect of EEG monitoring on postoperative neurocognitive disorder.[53,54,58] Although our meta-analysis showed that BIS-guided anesthesia reduced neurocognitive disorder, the effect size was small and the result was dominated by one trial. Until further data are available, there remains insufficient evidence to recommend the routine use of EEG monitoring for the prevention of neurocognitive disorder.

Limitations

Our review had a number of limitations. First, all the included studies used the BIS monitor for EEG monitoring. This is likely because the BIS was the first monitor introduced to the market. Inevitably more experimental data, particularly those drawn from human studies, are available for BIS. Although most EEG monitors use the same scale, the signal-processing algorithms are different and it remains uncertain if the findings in BIS monitoring can be extrapolated to other devices. This is a very important limitation of our recommendations and highlights the need for anesthesiologists to be trained in reading EEG waveforms and other nonproprietary parameters (eg, spectrogram) when using other EEG monitors to guide anesthetic management. Future outcome studies should focus on other monitors. Second, we focus on EEG as a measure of the anesthetic effect on the brain. It should be noted that auditory-evoked potential can also be used to indicate patient responsiveness during anesthesia. There are, however, long delays in evoked potential signal acquisition and the devices are generally less commonly available.[87,88] Third, we did not include observational data in our meta-analysis. In general, these studies support the use of EEG monitoring; however, there are selection biases that may influence the results. Finally, because the results from large randomized trials become available, our consensus statements may need to be reviewed and updated.

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