Prevention of Intraoperative Awareness with Explicit Recall

Making Sense of the Evidence

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UNINTENDED intraoperative awareness with subsequent explicit recall (AWR) is a major concern for patients undergoing general anesthesia and has persisted as a complication despite modern anesthetic techniques. In order to eliminate this complication, it would be helpful if anesthesia practitioners could determine reliably and accurately when patients were unaware. Although voluntary patient movement in response to commands reliably reflects awareness, the absence of such movement does not guarantee unawareness. Patients might have received paralytic agents or anesthetic agents that lead to unresponsiveness but not unconsciousness.1 There is ongoing debate whether the prevention of all intraoperative awareness episodes, even those without explicit recall, should be a therapeutic goal for anesthesiologists.1,2 In this clinical commentary, we are not addressing this controversy, but are restricting the discussion to the prevention of AWR.

Potent inhaled anesthetic agents are commonly administered, and the routine availability of agent analyzers to measure exhaled or end tidal anesthetic concentration (ETAC) of these drugs was an important development. First, they enabled practicing clinicians to determine whether patients were receiving anesthetic concentrations typically associated with unawareness. Second, they allowed practitioners to set alarms to alert them to concentrations deemed insufficient or excessive. However, there is interpatient variability in response to anesthetic drugs and it is currently impossible to measure the anesthetic concentration at the target site. As such, measurement of ETAC is, on several levels, a surrogate measure of the pharmacodynamic effects of general anesthesia. Furthermore, intravenous anesthetics such as propofol have a wider variability in dosing (as judged by the larger standard deviation of CP0.5, the intravenous equivalent of minimum alveolar concentration)3 and currently lack a metric for real-time monitoring. A brain monitor that could provide more direct and potentially reliable surrogacy for unawareness would therefore be an advance for anesthesia professionals.

As far back as 1937, Gibbs, Gibbs and Lennox suggested, “The anesthetist and surgeon could have before them on tape or screen a continuous record of the electric activity of both heart and brain.”4 Characteristic electroencephalographic changes associated with general anesthesia were appreciated and described more than 75 yr ago. However, the use of electroencephalography in the operating room was not always considered practical and the interpretation of potentially complex waveforms was challenging. Furthermore, a multitasking practitioner might not have the time to scrutinize the electroencephalogram waveform continuously. Also, subtle electroencephalographic changes occurring with fluctuations of anesthetic depth, such as shifts from lower to higher frequencies, could easily be missed with the naked eye. The development of quantitative indices based on computer processing of the electroencephalogram had important
implications for the practicing clinician. First, processing provided a numerical index, which was intended to indicate whether a patient was likely to be awake, sedated, unaware, or deeply anaesthetized. Second, quantitative indices allowed practitioners to set alarms based on statistically determined thresholds, which could alert them to the possibility that a patient was receiving either inadequate or excessive anesthetic concentrations. In 1996, the bispectral index (BIS®) monitor (Covidien, Boulder, CO) received approval from the Food and Drug Administration in the United States as a monitor with the potential to decrease the incidence of intraoperative awareness. The objectives of this article are 1) to review the incidence and consequences of AWR, 2) to review the major randomized controlled trials investigating the use of structured protocols in the prevention of AWR, 3) to reconcile apparent disparities across the trials in order to provide evidence-based recommendations for the prevention of AWR, 4) to appraise the evidence that BIS use prevents excessive anesthetic administration, and 5) briefly discuss brain monitors other than the BIS®.

Intraoperative Awareness and its Consequences

The incidence of AWR has been a subject of controversy.5–10 In the year 2000, Sandin et al.5 reported an incidence of 19/11,785 patients or 0.16% in a prospective study of AWR, which was supported by a multicenter study in the United States showing an incidence of 25/19,575 patients or 0.13%.7 Subsequent studies using both retrospective6,9 and prospective8,10 methodologies have had disparate findings. However, a population of patients in the recent Michigan Awareness Control Study (MACS) receiving no intervention demonstrated an awareness incidence of 5/3,384 or 0.15%.11 These prospectively gathered data strongly support the findings of Sandin et al.5 and Sebel et al.7, suggesting that an incidence of 1–2 cases/1,000 is a reproducible finding and should be used both to inform patients and guide future studies. Recent data suggest that the incidence of post-traumatic stress disorder is as high as 70% in patients who have experienced AWR.12 Given the potentially catastrophic psychological sequelae of awareness and the difficulty treating post-traumatic stress disorder, there is a strong motivation to prevent AWR from ever occurring.

Studies of the BIS® and Intraoperative Awareness

In 2004, a study by Ekman et al. found that the introduction of the BIS® monitor was associated with a reduction in AWR from 0.18 to 0.04% in a historical control group.13 This study suggested the effectiveness of the BIS® monitor in routine use, but was limited by its nonrandomized design. One notable difference between the historical control group and the BIS® group was the increased use of ETAC (target minimum alveolar concentration) monitoring that was concomitant with the introduction of the BIS® in this study.13

The B-Aware trial was the first prospective randomized controlled trial investigating the use of the BIS® monitor in the prevention of AWR.14 Patients at high risk of AWR were randomized to either routine care or a BIS®-guided protocol (target value, 40–60). Patients were asked structured questions15 2–6 h, 24–36 h, and 30 days postoperatively to assess AWR. Of those randomized to the BIS® group, 2/1,225 (0.17%) experienced definite AWR compared with 11/1,238 (0.91%) in the routine care group (P = 0.03).14 The results of the B-Aware trial suggested the efficacy of BIS® monitoring compared with clinical signs alone in reducing AWR in a high-risk population.

These studies motivated the consideration of BIS® monitoring or other processed electroencephalographic devices for standard use. However, a practice advisory of the American Society of Anesthesiologists in 2006 concluded that “brain function monitoring is not routinely indicated for patients undergoing general anesthesia, either to reduce the frequency of intraoperative awareness or to monitor depth of anesthesia.”16 There was insufficient evidence at that time to draw conclusions regarding the “general clinical applicability” of brain monitoring devices.

The B-Aware trial compared a BIS®-guided anesthetic with routine care, but it was unclear from this study whether the prevention of AWR was attributable to the electroencephalographic processing of the BIS® or the increased vigilance for insufficient anesthesia derived from the structured protocol of regularly recording BIS® values. Furthermore, there was no comparison of BIS® monitoring to potentially cost-effective alternatives. The B-Unaware trial addressed these limitations by comparing structured protocols based on the BIS® (target, 40–60) and ETAC (0.7–1.3).17 This study was conducted in high-risk patients but, in contrast to the B-Aware trial, was restricted to those receiving potent volatile anesthetics alone. The B-Unaware trial found no difference between the BIS®-guided and minimum alveolar concentration-guided protocols, with an AWR incidence of 0.21% in each group.17 Results of a subsequent Cochrane Database Review (published in 2007 and updated in 2010) suggested that the BIS® monitor might be useful in preventing AWR compared to clinical signs alone, but that ETAC protocols may also reduce AWR in patients at high risk of the complication who are receiving potent inhaled anesthetics.18

The most important limitation of both the B-Aware and B-Unaware trials was the imprecision (wide confidence intervals) of the results. The B-Unaware trial was, unlike the B-Aware trial, a single-center study. The BAG-RECALL trial was therefore designed to address the main limitations of the B-Aware and B-Unaware studies.19,20 BAG-RECALL was a prospective, 6,000 patient, multicenter, international, randomized controlled trial comparing BIS®-guided (40–60) and ETAC-guided (0.7–1.3 minimum alveolar concentration) protocols for the reduction of AWR. The results of the
BAG-RECALL trial did not support the hypothesis that a protocol based on the BIS® monitor was superior to that based on ETAC.20 Furthermore, using the Michigan Awareness Classification Instrument, it was found that the BIS®-guided protocol was not associated with fewer distressing definite and possible awareness events compared to the ETAC protocol.20

The B-Aware, B-Unaware, and BAG-RECALL trials were all conducted on patients at high risk for AWR and can thus be regarded as studies of efficacy. The MACS trial was designed to compare the effectiveness of BIS® and anesthetic concentration protocols in unselected surgical patients.21 In addition, the anesthetic concentration protocol of MACS factored in intravenous infusions such as propofol or dexmedetomidine. Thus, MACS was designed to include a broad range of AWR risk levels and anesthetic techniques. After 21,601 patients were recruited, the trial was terminated due to futility based on a prespecified analysis that was unable to detect a difference between BIS®-guided and anesthetic concentration-guided protocols.11 Technical factors resulted in a population of patients randomized to BIS® that received no intervention. Secondary post hoc analysis of this population revealed that the BIS® protocol significantly reduced the incidence of definite and possible AWR events compared with no intervention.11

Reconciling the Disparities of the Major Clinical Trials

There have been six major prospective trials that have investigated the potential benefit of brain monitoring in preventing AWR.11,13,14,17,20,22 On initial inspection, these studies have apparently conflicting findings. Importantly, the studies have different methodological approaches (e.g., randomization, inclusion criteria, use of structured protocols and anesthetic techniques), which could limit meta-analytic interpretations. However, careful reading of the individual trials reveals consistent findings. The B-Aware and MACS trials share a key methodological similarity in that they included patients receiving intravenous anesthetic infusions.11,14 The results of these studies are consistent in that they find the BIS® monitor superior to routine care in the prevention of AWR. This is supported by a recent randomized controlled trial of patients receiving total intravenous anesthesia, in which BIS® monitoring was associated with a significant reduction in definite AWR.22 The B-Unaware and BAG-RECALL trials, in contrast, were restricted to patients receiving potent inhaled agents in which ETAC could be monitored.17,20 Neither trial found the BIS® to be superior to ETAC protocols. Concordant with the B-Unaware and BAG-RECALL trials, the MACS trial was unable to detect an effectiveness difference in the BIS®-guided and anesthetic concentration-guided protocols.11 Tables 1 and 2 summarize the prospective trials that have evaluated a BIS®-guided protocol for the prevention of AWR.

Based on the current evidence derived from randomized controlled trials, it could be argued that the BIS® monitor plays a role in reducing intraoperative awareness in patients receiving heterogeneous anesthetics that include sedative-hypnotic infusions, while the ETAC protocol is a cost-effective alternative for patients receiving potent inhaled anesthetics. This interpretation is consistent with the conclusions of the Cochrane Database Review, which was based primarily on the B-Aware and B-Unaware trials.18 Figure 1 provides a suggested clinical pathway for the prevention of AWR in high risk and unselected surgical populations.

Prevention of Anesthetic Overdose

Aside from the hypothesized benefit of decreasing the incidence of AWR through the prevention of anesthetic underdosing, processed electroencephalograph monitors like the BIS® have been advocated for routine use to avoid anesthetic overdosing with resulting side effects including prolonged recovery, nausea, and vomiting.23,24 On theoretical grounds, the utility of the BIS® as a titration aid might be limited, as the BIS® tends to plateau over a wide range of inhaled anesthetic concentrations.25 Furthermore, the large randomized clinical trials—B-Aware, B-Unaware, BAG-RECALL and MACS—do not support the proposed benefit of BIS® monitoring for anesthetic titration. There was no demonstrable difference in measured volatile anesthetic concentrations between the BIS® and the control groups in any of these trials.11,14,17,20 Additionally, the quality of early postoperative recovery (i.e., pain intensity, incidence of nausea and vomiting, and time spent in the recovery area) was not meaningfully improved in patients who were randomized to the BIS®-guided protocols.11,26 The B-Aware, B-Unaware and BAG-RECALL trials have also tracked early and intermediate term (up to 5 yr) postoperative mortality. None of these trials have found a survival advantage attributable to BIS® monitoring.20,27–29 Emerging evidence suggests that using the BIS® to guide propofol administration might decrease postoperative delirium.30 It is not known whether a similar benefit might result when using potent inhaled anesthetics.

Other Brain Monitors

The current synthesis of evidence has focused primarily on the BIS®, because it is the only monitor that has been studied in a randomized controlled trial for the prevention of AWR. We are therefore unable to draw conclusions regarding the performance of other commercially available brain monitors in the prevention of AWR. However, we speculate that other monitors might yield comparable results. In support of this assertion, small studies comparing the BIS® and Entropy monitors revealed only subtle differences in predicting sevoflurane31 and propofol32–33 effect-site concentrations, or clinical indicators of anesthetic depth.34 Similarly, comparisons of the BIS® and other brain monitors (e.g., Narcotrend, A-Line ARX Index, Patient State Index and auditory evoked potentials) have revealed comparable performance in monitoring total intravenous35–39 and volatile40–42 anesthetics. Many
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Comparison Groups</th>
<th>Estimated Definite AWR Reduction or Increase with BIS Protocol</th>
<th>Precision (95% CI)</th>
<th>Comments</th>
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</table>
| Ekman et al. 200413         | Prospective Cohort            | Initial control cohort treated with routine care. Subsequent intervention cohort treated with BIS-guided protocol | ARR = 0.14% NNTB = 722                                           | ARR = 0.01% to 0.26% NNTB = 10657 to 380 | • Cohorts not concurrent  
• Only 80% of control cohort had ETAC monitoring  
• BIS superior |
| B-Aware Trial 200414        | Multicenter RCT               | BIS-guided protocol versus routine anesthetic care                               | ARR = 0.73% NNTB = 138                                          | ARR = 0.14% to 1.4% NNTB = 697 to 70      | • Patients at high risk for AWR  
• 43% of patients received TIVA  
• BIS superior |
| B-Unaware Trial 200817      | Single center RCT             | BIS-guided protocol versus ETAC-guided protocol                                   | ARR = 0% NNTB = ∞                                              | ARR = −0.57% to 0.56% NNTB = 177 to ∞    | • Patients at high risk for AWR  
• All patients received potent inhaled agent  
• BIS superiority not demonstrated |
| BAG-RECALL Trial 201120     | Multicenter RCT               | BIS-guided protocol versus ETAC-guided protocol                                   | ARR = 0.21% NNTB = 477                                         | ARR = −0.49% to 0.02% NNTB = 206 to ∞    | • Patients at high risk for AWR  
• All patients received potent inhaled agent  
• Trial was designed to evaluate superiority of BIS protocol; superiority of ETAC protocol was not considered  
• One patient in the BIS group spontaneously reported AWR 1 yr postoperatively  
• BIS superiority not demonstrated |
| Zhang et al. 201122         | Multicenter RCT               | BIS-guided protocol versus routine anesthetic care                               | ARR = 0.51% NNTB = 195                                          | ARR = 0.18% to 0.94% NNTB = 559 to 106    | • All patients received TIVA  
• BIS superior |
| Michigan Awareness Control Study 201211 | Effectiveness RCT            | BIS-guided protocol versus anesthetic concentration-guided protocol               | ARR = 0.07% NNTB = 147                                         | ARR = −0.04% to 0.17% NNTB = 2447 to ∞    | • Unselected surgical patients  
• Per protocol analysis (patients are analyzed according to the treatment they received)  
• BIS superiority not demonstrated |
| Michigan Awareness Control Study 201211 | Effectiveness RCT            | BIS-guided protocol versus routine anesthetic care                               | ARR = 0.1% NNTB = 1017                                         | ARR = −0.03% to 0.3% NNTB = 3405 to ∞     | • Per protocol analysis (patients are analyzed according to the treatment they received)  
• Patients received routine care when there was a technical problem with the BIS monitor  
• BIS superiority not demonstrated |

ARI = absolute risk increase; ARR = absolute risk reduction; AWR = awareness with recall; BIS = bispectral index; ETAC = end tidal anesthetic concentration; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomized controlled trial; TIVA = total intravenous anesthesia.
Table 2. Definite and Possible Awareness Events in Prospective Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Comparison Groups</th>
<th>Estimated Definite or Possible AWR Reduction or Increase with BIS Protocol</th>
<th>Precision (95% CI)</th>
<th>Comments</th>
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<tbody>
<tr>
<td>B-Aware</td>
<td>Multicenter RCT</td>
<td>BIS-guided protocol versus routine anesthetic care</td>
<td>ARR = 0.39%</td>
<td>NNTB = 260</td>
<td>• Possible AWR events included reports of dreaming as well as credible awareness experiences</td>
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<tr>
<td>Trial 2004</td>
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<td>BIS superiority not demonstrated</td>
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<td></td>
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<td></td>
<td>ARR = −0.75% to 1.53%</td>
<td>NNTH = 134 to ∞</td>
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<td>NNTHB = ∞ to 65</td>
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<td>B-Unaware</td>
<td>Single Center RCT</td>
<td>BIS-guided protocol versus ETAC-guided protocol</td>
<td>ARI = 0.31%</td>
<td>NNTH = 320</td>
<td>• Possible AWR events were credible awareness experiences</td>
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<td>Trial 2008</td>
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<td>BIS superiority not demonstrated</td>
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<td></td>
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<td></td>
<td>ARI = −1.07% to 0.37%</td>
<td>NNTH = 94 to ∞</td>
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<td>NNTHB = ∞ to 271</td>
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<td>BAG-RECALL</td>
<td>Multicenter RCT</td>
<td>BIS-guided protocol versus ETAC-guided protocol</td>
<td>ARI = 0.42%</td>
<td>NNTH = 239</td>
<td>• Possible AWR events were credible awareness experiences</td>
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<tr>
<td>Trial 2011</td>
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<td></td>
<td>Trial was designed to evaluate superiority of BIS protocol; superiority of ETAC protocol was not considered</td>
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<td></td>
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<td></td>
<td>ARI = 0.05% to 0.8%</td>
<td>NNTH = 1933</td>
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<tr>
<td>Zhang et al. 2011</td>
<td>Multicenter RCT</td>
<td>BIS-guided protocol versus routine anesthetic care</td>
<td>ARR = 0.64%</td>
<td>NNTB = 157</td>
<td>• Per protocol analysis (patients are analyzed according to the treatment they received)</td>
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<td>Possible AWR events were credible awareness experiences</td>
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<td>BIS superior</td>
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<td></td>
<td>ARI = 0.22%</td>
<td>NNTB = 446</td>
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<tr>
<td>Michigan</td>
<td>Effectiveness RCT</td>
<td>BIS-guided protocol versus anesthetic concentration-guided protocol</td>
<td>ARR = 0.12%</td>
<td>NNTB = 831</td>
<td>• Possible AWR events were credible awareness experiences</td>
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<tr>
<td>Awareness Control Study 2012</td>
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<td>BIS superiority not demonstrated</td>
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<td></td>
<td>ARI = −0.01% to 0.24%</td>
<td>NNTH = 8494</td>
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<td>NNTHB = ∞ to 411</td>
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<tr>
<td>Michigan</td>
<td>Effectiveness RCT</td>
<td>BIS-guided protocol versus routine anesthetic care</td>
<td>ARR = 0.3%</td>
<td>NNTB = 331</td>
<td>• Per protocol analysis (patients are analyzed according to the treatment they received)</td>
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<tr>
<td>Awareness Control Study 2012</td>
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<td>Possible AWR events were credible awareness experiences</td>
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<td>BIS superiority not demonstrated</td>
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<td></td>
<td>ARI = 0.11%</td>
<td>NNTB = 926</td>
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<td></td>
<td></td>
<td>ARI = 0.58%</td>
<td>NNTHB = 173</td>
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ARI = absolute risk increase; ARR = absolute risk reduction; AWR = awareness with recall; BIS = bispectral index; ETAC = end tidal anesthetic concentration; NNTB = number needed to treat to benefit; NNTH = number needed to treat to harm; RCT = randomized controlled trial; TIVA = total intravenous anesthesia.
commercially available monitors are also subject to the same delays in reflecting state changes that might be consistent with AWR. 44,45 Although the assumption that most brain monitors currently in clinical use appear to have similar strengths and limitations to the BiS® requires empirical study, we question, based on the results of MACS,11 whether it will be feasible to conduct comparative effectiveness trials of different depth-of-anesthesia monitors for the prevention of AWR.

Conclusion

Taken together, the prospective studies incorporating BIS®-based protocols provide proof of principle that a brain monitor can be effective in decreasing the incidence of AWR.11,13,14,17,20,22 There is also mounting evidence that incorporating structured protocols, including alerts for volatile anesthetic concentrations, is effective.11,17,20 Based on these trials alone, and consistent with the American Society of Anesthesiologists’ published advisory,16 brain monitoring cannot be considered obligatory to prevent AWR or reduce anesthetic consumption for general anesthesia based predominantly on a potent inhaled agent. However, a compelling case can be made to change routine practice by implementing a protocol designed to increase vigilance and to alert practitioners to possible AWR. More comprehensive approaches—such as integrating standard monitoring, ETAC, and electroencephalographic data for quantification of the depth of anesthesia—are theoretically appealing.46 When an intravenous sedative-hypnotic is administered as the primary anesthetic, the current evidence strongly suggests that incorporation of brain monitoring decreases AWR. This is especially true for total intravenous anesthesia.22 The trials provide encouragement about the potential utility of brain monitoring in anesthetic practice. They also reveal important limitations of current quantitative indices based on frontal electroencephalography monitoring.25 The results provide a strong impetus to refine brain monitors with an emphasis on moving away from statistical likelihood models toward approaches based on the neurobiology of anesthetic-induced unconsciousness.47 It is probable that future anesthetic practice will include routine monitoring of the brain.

References


Fig. 1. Evidence-based decision tree for protocol to prevent awareness with recall (AWR). BIS = bispectral index; ETAC = end tidal anesthetic concentration; MACS = Michigan Awareness Control Study; TIVA = total intravenous anesthesia.