Increased Risk of Intraoperative Awareness in Patients with a History of Awareness

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What We Already Know about This Topic

- It is not clear whether patients with a history of intraoperative awareness with explicit recall are at higher risk for awareness during general anesthesia

What This Article Tells Us That Is New

- In a matched cohort analysis of patients drawn from three trials including more than 25,000 patients, those with a history of intraoperative awareness had a five-fold increased incidence of awareness compared with propensity-matched controls who did not have a history of awareness
- Anesthetic management did not differ between the cohorts; in view of the likely increased risk of awareness, clinicians should consider modifying anesthetic management in patients with a history of awareness

ABSTRACT

Background: Patients with a history of intraoperative awareness with explicit recall (AWR) are hypothesized to be at higher risk for AWR than the general surgical population. In this study, the authors assessed whether patients with a history of AWR (1) are actually at higher risk for AWR; (2) receive different anesthetic management; and (3) are relatively resistant to the hypnotic actions of volatile anesthetics.

Methods: Patients with a history of AWR and matched controls from three randomized clinical trials investigating prevention of AWR were compared for relative risk of AWR. Anesthetic management was compared with the use of the Hotelling's T^2 statistic. A linear mixed model, including previously identified covariates, assessed the effects of a history

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 1A.

◆ This article is accompanied by an Editorial View. Please see: Pryor KO, Hemmings HC: Increased risk of awareness under anesthesia: An issue of consciousness or of memory? ANESTHESIOLOGY 2013; 119:1236–8.

of AWR on the relationship between end-tidal anesthetic concentration and bispectral index.

Results: The incidence of AWR was 1.7% (4 of 241) in patients with a history of AWR and 0.3% (4 of 1,205) in control patients (relative risk = 5.0; 95% CI, 1.3–19.9). Anesthetic management did not differ between cohorts, but there was a significant effect of a history of AWR on the end-tidal anesthetic concentration *versus* bispectral index relationship.

Conclusions: Surgical patients with a history of AWR are five times more likely to experience AWR than similar patients without a history of AWR. Further consideration should be given to modifying perioperative care and postoperative evaluation of patients with a history of AWR.

INTRAOPERATIVE awareness with explicit recall (AWR) occurs in 0.1–0.2% of patients undergoing general anesthesia[1] and may result in devastating psychological symptoms. Patients often experience significant anxiety and stress after an AWR event, and up to 70% of patients may develop posttraumatic stress disorder.[2–4] It has been suggested that patients who have experienced AWR during a previous surgery are at increased risk for AWR.[3,5] A review of 271 case reports of AWR indicated that 1.6% of these patients reported a prior history of AWR.[3] However, this review lacked a comparison group and was not able to estimate the increased risk attributable to a history of AWR. In the bispectral index (BIS) or Anesthetic Gas to Reduce Explicit Recall (BAG-RECALL) study, the percentage of patients reporting a prior history of AWR was significantly higher in those who experienced AWR compared with those who did not. However, this difference may be explained by unequal distributions of other risk factors for AWR.[6] To date, there are no compelling data that establish a history of AWR as an independent risk factor for AWR. A better understanding of the risk for AWR in patients with a history of AWR could positively impact clinical care by guiding changes in intraoperative management as well as systematic postoperative screening for AWR and its psychological sequelae.

This substudy of three randomized controlled trials of AWR prevention—B-Unaware,[7] BAG-RECALL,[6] and Michigan Awareness Control Study (MACS)[8]—investigates whether patients with a history of AWR (1) have a higher risk for AWR; (2) are cared for differently by anesthesia practitioners; and (3) require a higher concentration of volatile anesthetic to achieve BIS values suggested to be consistent with surgical anesthesia compared with a matched surgical cohort without a history of AWR.

Materials and Methods

Patient Cohort

The B-Unaware, BAG-RECALL, and MACS trials compared protocols based either on the BIS monitor® (Covidien, Boulder, CO) (a processed electroencephalographic index) or on end-tidal anesthetic concentration (ETAC) alarms to prevent AWR.[6,7,9] In the current retrospective cohort study, we performed secondary data analyses of the patients enrolled in these three randomized clinical trials to compare the incidence of AWR, the anesthetic management, and the relationship between BIS and ETAC in patients with a history of AWR to a matched control group without a history of AWR.

The B-Unaware trial, a single-center study, enrolled and assessed outcomes for 1,941 surgical patients undergoing general anesthesia between September 2005 and October 2006. The BAG-RECALL and MACS trials enrolled and assessed outcomes for 5,713 and 18,836 patients, respectively, between May 2008 and May 2010. The B-Unaware and BAG-RECALL trials studied patients considered to be at high risk for AWR, whereas the MACS trial studied an unselected surgical population. Further details of these studies have been previously described.[6–8] Each trial received approval from the appropriate institutional review board. Among the 26,490 patients enrolled in the three trials, we identified 241 patients who self-reported a history of AWR in prior surgeries. To control for potential imbalances in baseline characteristics between patients with and without a history of AWR, each patient with a history of AWR was matched to five controls based on demographic characteristics, comorbid conditions, and other risk factors for AWR. A ratio of 5:1 was selected for matching due to the low incidence of AWR. Selection of 1,205 control patients yielded a total sample size of 1,446.

Outcomes Measured

There were three main outcomes of interest in the current study: incidence of AWR, anesthetic management, and BIS–ETAC relationships in patients with a history of AWR compared with controls. Data regarding potential risk factors for AWR, including a prior history of AWR, daily alcohol consumption, and regular use of opiates, benzodiazepines, or anticonvulsants were obtained during the parent trials. For participants in the B-Unaware and BAG-RECALL trials, which comprise 52.6% of the sample in this study, this information was obtained by interview upon recruitment. For participants in the MACS trial, which comprise the remaining 47.4% of the study sample, this information was obtained by querying the medical record retrospectively. Postoperatively, interviewers evaluated patients for AWR with the modified Brice interview (appendix 1 for questions).[10] All patients reporting AWR in this screening had a follow-up interview by trained interviewers and anesthesiologists with experience in assessing AWR; data from the first two interviews were reviewed independently by members of a committee of senior anesthesiologists that determined whether patient reports were definite, possible, or no AWR. Reported memories judged to have a very high likelihood of occurring during the anesthetic and surgical periods were classified as definite AWR, whereas credible reports without compelling details

were classified as possible AWR. Finally, reported memories considered to have occurred in the preoperative or postoperative period were classified as no AWR. The outcome of anesthetic management was based on doses of sedative, analgesic, hypnotic, and paralytic medications administered and recorded by practitioners.

The measurement of ETAC and algorithm-based analysis of the electroencephalogram are commonly used surrogates for depth of anesthesia.[6,7,11] The BIS® monitor processes a frontal electroencephalographic signal to produce a number that is intended to reflect the depth of anesthesia or the hypnotic component of anesthesia. The BIS value ranges from 0, reflecting electroencephalographic suppression, to values approaching 100, which are consistent with wakefulness. We assessed BIS-ETAC relationships in a subset of patients at high risk of AWR from the B-Unaware and BAG-RECALL trials. ETAC of volatile agents and BIS values were recorded electronically at 1-s, 1-min, or 5-min intervals using TrendFace (ixellence GmbH, Wildau, Germany) or MetaVision (iMDsoft, Needham, MA) software.

Variables Analyzed

We converted doses of drugs in the same class to equivalents of one agent: opioid analgesics were converted to morphine equivalents, hypnotic agents to propofol equivalents, and neuromuscular-blocking agents to vecuronium equivalents. Opioid-conversion factors were obtained from the *Alberta Hospice Palliative Care Resource Manual*.[12] Doses of etomidate and thiopental were converted to propofol equivalents by using mean values of the dose range for induction provided in *Cusick's Anesthesia & Critical Care Reference Sheet*.[13] Doses of midazolam were considered separately. The 95% effective dose was used to convert neuromuscular-blocking agents to vecuronium equivalents.[13] ETAC values for volatile agents were converted into age-adjusted minimum alveolar concentration (aaMAC) values.[14] If patients received more than one drug from each class, the sum of equivalent doses was calculated. Any dose values outside of a pharmacologically plausible range were excluded (appendix 2). Outliers skewing the distribution were truncated.

Pharmacokinetically stable epochs of ETAC were identified to compare the relationship between BIS and ETAC, because steady-state ETAC levels take time to establish after changes in inspired anesthetic concentration. Stable epochs were defined as periods in which aaMAC values had not fluctuated more than 0.05 in the preceding 10 min and were identified using a MATLAB program (MathWorks, Natick, MA) previously described.[15] Data collected during pharmacokinetically stable epochs were then resampled to reduce BIS and ETAC measurements to 1-min intervals.

Statistical Analysis

We compared baseline patient characteristics, comorbidities, and other risk factors for AWR with independent samples *t* tests for continuous variables and chi-square tests for categorical variables. All continuous variables were normally distributed. Logistic regression was used to calculate propensity scores based on patient characteristics (age, sex, body mass index, American Society of Anesthesiologists physical status [ASA-PS], and smoking status), individual comorbidities (valvular heart disease, diabetes mellitus, coronary heart disease, dysrhythmias, chronic obstructive pulmonary disease, prior stroke, congestive heart failure, peripheral vascular disease, and hypertension), and individual risk factors for AWR (planned heart surgery, pulmonary hypertension, regular opiate use, regular benzodiazepine use, regular anticonvulsant use, and daily alcohol use). With the exception of the continuous variables age and body mass index, all variables included in the propensity score were dichotomous. By using the greedy matching algorithm,[16] each patient with a history of AWR was matched to five controls on sex, age, ASA, body mass index, a composite of comorbidities, a composite of risk factors for AWR, and the propensity score. In the matching algorithm, the following calipers were used: 0.005 for propensity score, 5 for age, 1 for composite of comorbidities, and 1 for composite of risk factors for AWR. All other factors were matched exactly. Comparisons of baseline patient characteristics, comorbidities, and risk factors for AWR were repeated to ensure successful matching. In addition, a comprehensive balancing test, the standardized difference in means of the propensity scores, was used to evaluate whether the matching algorithm produced cohorts with the same covariate distributions.[17] The primary outcome of this study was a comparison using relative risk of the incidence of AWR in patients with and without a history of AWR.

Routine perioperative management by anesthesia providers typically involves different types of drugs, such as benzodiazepines, intravenous induction agents, opioid analgesics, neuromuscular blockers, and volatile anesthetic agents. To compare multiple related dependent variables between the two groups, we calculated the Hotelling's T^2 statistic. This multivariate test computes a canonically derived mean using a linear combination of the dependent variables, representing overall anesthetic management, and compares this canonical variate between cohorts. To achieve multivariate normality, the dependent variables were transformed using the Box-Cox transformation procedure and then standardized. The Box's M assessed the homogeneity of the variance-covariance matrix at a significance level of 0.005 per previously published guidelines.[18] For all other statistical analyses, *P* value less than 0.05 was considered significant.

To determine whether patients with a history of AWR have an increased requirement for volatile anesthetic to achieve BIS values suggested to be consistent with surgical anesthesia, we assessed the relationship between ETAC and BIS. After removing pharmacokinetically unstable data, 594 patients remained in the analysis. A linear mixed-effects model was chosen for this analysis due to within-subject repeated measurements of

both ETAC and BIS. Both history of AWR and the interaction between ETAC and a history of AWR were included as predictors in the model. Age, sex, ASA-PS ≥4 (categorical variable: yes or no), nitrous oxide use (categorical variable: yes or no), midazolam greater than 2 mg (categorical variable: yes or no), and morphine equivalents greater than 50 mg (categorical variable: yes or no) were previously shown to be significant predictors of BIS values and were included as covariates in the model.[15] Residual plots were tested for homoscedascity. Results with a *P* value less than 0.05 were considered significant. All above statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC) and SPSS Statistics version 19 (IBM Corporation, Somers, NY).

Results

Of the 26,490 patients enrolled in the parent trials, 241 patients (0.9%) had a history of AWR. Characteristics for the overall sample (separated by history of AWR) are reported in table 1. Patients with a history of AWR were younger and had a higher body mass index than those without a history of AWR. In addition, a higher proportion of patients with a history of AWR were female, current smokers, opiate users, and anticonvulsant users. A lower proportion of patients with a history of AWR reported to be daily alcohol users compared with control patients. Furthermore, significant differences in ASA-PS between cohorts suggested

Table 1. Patient Demographic Characteristics, Comorbid Conditions, and Risk Factors for AWR for Total Sample

	Overall Sample (n = 26,257)	History of Awareness (n = 241)	No History of Awareness (n = 26,016)	*P* Value
Male	48.5%	36.9%	48.6%	<0.01
Age	54.2 ± 15.8	52.2 ± 14.6	54.3 ± 15.8	0.04
BMI (kg/m^2)	29.6 ± 7.7	30.8 ± 8.1	29.6 ± 7.7	0.02
ASA-PS				
=1	9.4%	2.5%	9.4%	
2–3	79.0%	82.6%	78.9%	
>3	11.7%	14.9%	11.6%	<0.01
Comorbid conditions (n = 24,349)				
Valvular heart disease	7.5%	6.2%	7.5%	0.47
Diabetes mellitus	14.0%	17.4%	14.0%	0.13
Coronary disease	16.3%	19.5%	16.3%	0.17
Dysrhythmias	7.8%	8.7%	7.8%	0.58
COPD	4.7%	9.1%	4.7%	<0.01
CVA/stroke	3.4%	5.8%	3.4%	0.04
Congestive heart failure	5.6%	7.5%	5.6%	0.20
Peripheral vascular disease	4.3%	6.2%	4.3%	0.14
Hypertension	45.1%	47.3%	45.1%	0.50
Number of comorbidities				
None	62.6%	53.1%	62.7%	
One	21.2%	27.8%	21.1%	
Two or more	16.2%	19.1%	16.2%	0.01
Current smoker	14.3%	21.2%	14.3%	<0.01
Risk factors for awareness				
Planned heart surgery	12.0%	10.0%	12.0%	0.33
Pulmonary hypertension	1.6%	2.1%	1.6%	0.52
Regular opiate use	24.5%	31.1%	24.5%	0.02
Regular benzodiazepine use	30.6%	32.0%	30.6%	0.64
Regular anticonvulsant use	3.7%	6.6%	3.7%	0.02
Daily alcohol use	10.6%	5.4%	10.6%	0.01
Number of risk factors				
None	39.7%	37.8%	39.8%	
One	40.2%	39.4%	40.2%	
Two or more	20.1%	22.8%	20.1%	0.56

Value presented are % or mean ± SD. *P* values were calculated using chi-square tests for categorical variables and independent samples *t* tests for continuous variables.

ASA-PS = American Society of Anesthesiologists physical status; AWR = awareness with explicit recall; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident.

Table 2. Patient Demographic Characteristics, Comorbid Conditions, and Risk Factors for AWR for Matched Sample

	Overall Sample (n = 1,446)	History of Awareness (n = 241)	No History of Awareness (n = 1,205)	*P* Value
Male	36.9%	36.9%	36.9%	1.00
Age (yr), mean ± SD	52.3 ± 14.5	52.2 ± 14.6	52.3 ± 14.5	0.94
BMI (kg/m^2), mean ± SD	30.8 ± 8.2	30.8 ± 8.1	30.8 ± 8.2	0.98
ASA-PS				
=1	2.4%	2.5%	2.4%	
2–3	83.3%	82.6%	83.4%	
>3	14.3%	14.9%	14.2%	0.95
Comorbid conditions				
Valvular heart disease	7.1%	6.2%	7.3%	0.55
Diabetes mellitus	18.1%	17.4%	18.3%	0.76
Coronary disease	18.9%	19.5%	18.8%	0.79
Dysrhythmias	9.1%	8.7%	9.2%	0.81
COPD	7.1%	9.1%	6.6%	0.17
CVA/stroke	4.0%	5.8%	3.7%	0.12
Congestive heart failure	6.5%	7.5%	6.3%	0.50
Peripheral vascular disease	6.6%	6.2%	6.6%	0.81
Hypertension	48.3%	47.3%	48.5%	0.73
Number of comorbidities				
None	53.8%	53.1%	53.9%	
One	26.7%	27.8%	26.5%	
Two or more	19.5%	19.1%	19.6%	0.91
Current smoker	21.2%	21.2%	21.2%	1.00
Risk factors for awareness				
Planned heart surgery	11.6%	10.0%	12.0%	0.38
Pulmonary hypertension	1.8%	2.1%	1.7%	0.72
Regular opiate use	32.0%	31.1%	32.2%	0.74
Regular benzodiazepine use	29.7%	32.0%	29.3%	0.41
Regular anticonvulsant use	5.2%	6.6%	4.9%	0.27
Daily alcohol use	5.2%	5.4%	5.2%	0.87
Number of risk factors				
None	36.5%	37.8%	36.2%	
One	42.9%	39.4%	43.6%	
Two or more	20.7%	22.8%	20.3%	0.45

Value presented are % or mean ± SD. *P* values were calculated using chi-square tests for categorical variables and independent samples *t* tests for continuous variables.

ASA-PS = American Society of Anesthesiologists physical status; AWR = awareness with explicit recall; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident.

that control patients were healthier, with a higher percentage of patients with ASA-PS1 and lower percentages of patients with ASA-PS 2–3 or ≥4. An attempt was made to decrease confounds attributable to other covariates potentially associated with AWR risk by matching as described in the Materials and Methods. No significant differences remained between cohorts after matching (table 2). Comparison of the standardized means of the propensity scores demonstrated no significant difference in the overall distributional balance of covariates between cohorts ($t(324) = -1.93$; $P > 0.05$), indicating that the greedy matching algorithm produced an adequate matched sample. The absolute number and incidence of AWR events in each cohort are shown in table 3. The incidence of AWR differed significantly between cohorts ($P = 0.03$); patients with a history of AWR were five times more likely to experience AWR than control patients (relative risk = 5.0; 95% CI, 1.3–19.9).

Approximately 4% of patients (N = 64) had incomplete information describing drug administration. For the 1,382 remaining patients, the means and SEM for each drug type are presented in table 4. The proportion of patients who received each drug type did not differ significantly between cohorts. All patients in this study received volatile anesthetic agents. Because drug doses were not normally distributed, these variables were transformed. Evaluation of the multivariate distribution of the transformed variables displayed

Table 3. Incidence of Intraoperative Awareness with Recall

	AWR	No AWR	Total
History of AWR	4 (1.7)	237 (98.3)	241
No history of AWR	4 (0.3)	1,201 (99.7)	1,205

Values are expressed as n (%).
AWR = awareness with explicit recall.

Table 4. Drug Administration

	Hx of AWR (n = 231)	No Hx of AWR (n = 1,151)
Doses		
Midazolam equivalents*	0.04 ± 0.00	0.03 ± 0.00
Propofol equivalents*	3.07 ± 0.12	3.05 ± 0.05
Morphine equivalents*	0.44 ± 0.03	0.44 ± 0.01
Vecuronium equivalents*	0.10 ± 0.01	0.11 ± 0.00
Median aaMAC	0.95 ± 0.01	0.95 ± 0.01

Values are expressed as n (%) or mean ± SEM.
* Doses are reported in mg/kg.
aaMAC = age-adjusted minimum alveolar concentration; AWR = awareness with explicit recall; Hx = history.

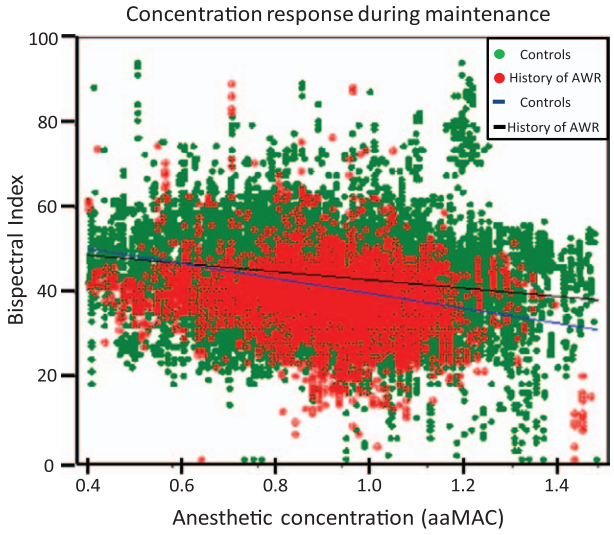

Fig. 1. Scattergram of bispectral index values against contemporaneous end-tidal anesthetic concentration during the maintenance phase for patients with a history of intraoperative awareness with explicit recall (AWR) (*red data points*) and for control patients (*green data points*). End-tidal anesthetic concentration measurements are expressed as age-adjusted minimum alveolar concentration (aaMAC). Regression lines estimated by the mixed linear effects model are shown across the data points for patients with a history of AWR (*black line*) and for control patients (*blue line*).

no substantial outliers. A Hotelling's T^2, using mean doses for each of the five drug types, was performed to determine whether the overall management differed between cohorts. The Box's M value was 23.1 with a *P* value of 0.085 indicating that the data satisfied the equality of covariance assumption. There was no difference in overall anesthetic management in patients with a history of AWR compared with matched controls ($F(5, 1{,}376) = 1.4$; $P = 0.239$; Hotelling's $T^2 = 6.9$).

After pharmacokinetic censoring of repeated measurements of ETAC and BIS, 35,801 BIS-aaMAC datapoints derived from 594 patients were analyzed in the mixed-effects model. A history of AWR was a significant predictor of BIS in the model ($\beta = -5.4$; $P = 0.0001$), indicating that after controlling for the other factors in the model, the presence of this risk factor decreases the projected intercept of the BIS–ETAC relationship by 5 units. The interaction between aaMAC and history of AWR was also significant ($\beta = 3.7$; $P = 0.0018$), indicating that in patients with a history of AWR, the magnitude of the slope of the BIS–ETAC relationship is less than that of the control patients. According to this model, increasing aaMAC by 0.1 in patients without a history of AWR would result in an average decrease in BIS of 1.8; whereas the same change in patients with a history of AWR would result in an average decrease in BIS of 1.5. The difference in the correlation between BIS and ETAC is represented graphically in figure 1.

Discussion

This is the first comparative study estimating the increased risk of AWR in patients with a history of AWR. We found that (1) patients with a history of AWR are at greater risk for AWR; (2) anesthesia practitioners do not seem to alter management for these patients; and (3) history of AWR is associated with a statistically significant difference in the BIS–ETAC relationship.

Although a history of AWR was suggested to be a risk factor for AWR as early as 1975,[3] few studies have provided data supporting this hypothesis. A review of AWR case reports conducted by Ghoneim *et al.*[3] identified a history of AWR as a risk factor. However, the lack of a control group did not allow quantitative estimation of the associated risk. In addition, case reports often lacked data regarding confounding variables. The results of the current study advance the field by demonstrating that a history of AWR increased the risk of AWR by a five-fold estimate after controlling for known confounding factors, and therefore does appear to be an independent risk factor for AWR.

It has been hypothesized that the most important contributing factor for AWR is underdosing of anesthesia relative to a patient's specific requirements.[3] Underdosing may occur because of surgical factors, anesthetic factors, or patient factors. For example, during cardiac, trauma, and obstetric surgeries, the concern for hemodynamic stability may lead the practitioner to limit the amount of anesthetic administered.[19–21] In addition, malfunction of the anesthetic delivery equipment or certain anesthetic management regimens, such as the use of total intravenous anesthesia or neuromuscular blockade, may result in unintended underdosing

of anesthesia.[3] Finally, an acquired or genetic resistance to the hypnotic or amnesic actions of certain anesthetic agents may increase anesthetic requirements or render certain anesthetics ineffective in some individuals.[3,22–24] Modifying anesthetic management in patients with an increased risk for developing AWR might help prevent an AWR event; however, there are no guidelines for treating these patients due to the paucity of evidence regarding whether or how anesthesia providers change their anesthetic regimen.[25]

Clinical Implications

The 2006 ASA Practice Advisory for intraoperative awareness included a history of AWR as a potential risk factor for AWR. Although there is a lack of evidence supporting the efficacy of specific pharmacologic interventions to prevent AWR, several modifications of anesthetic administration have been proposed for high-risk patients. These include increased inhaled anesthetic concentration to ensure unconsciousness, increased use of benzodiazepines to prevent memory, and the avoidance of neuromuscular blockers to preserve motility.[26] Suggestions to increase the dosage of certain anesthetic agents are based on the hypothesis that patients with a relative resistance to these agents may require higher concentrations for adequate anesthesia.

The current study, from several tertiary academic medical centers, suggests that there is no substantial modification of anesthetic care for patients with a history of AWR. The adjusted five-fold increase in AWR risk with a history of the complication provides the first compelling evidence that changes in anesthesia practice are necessary to reduce what is one of the highest incidences of AWR (1.7%) reported in the modern literature. The methodology of this study may even have resulted in an underestimation of the problem in that virtually all patients recruited to the parent trials were entered into a treatment arm aimed at preventing AWR. As such, a history of AWR should prompt consideration of measures to prevent AWR and minimize patient distress including: (1) a preoperative discussion with the patient regarding further risk, (2) increased doses and multimodal approaches to anesthesia and analgesia, (3) use of a brain monitor that can assist in suggesting adequate depth of anesthesia, and (4) postoperative screening for AWR at multiple time points for psychiatric referral if experienced. However, precise recommendations regarding intraoperative management should be tempered at this time, as the mechanism responsible for the increased risk of AWR in patients with a history of AWR is unclear. We speculate that the interventions of the parent trials (BIS or MAC alarms) prevented the majority of preventable reasons for AWR (*e.g.*, empty vaporizer) and therefore unmasked some individuals that might be intrinsically resistant to hypnotic or amnesic effects of general anesthesia. The current study identified a reduced sensitivity of BIS values to changes in ETAC, but it is unlikely that this statistical difference has major clinical impact and is sufficient to account for the increased incidence of AWR experienced by the patients with a history of AWR.

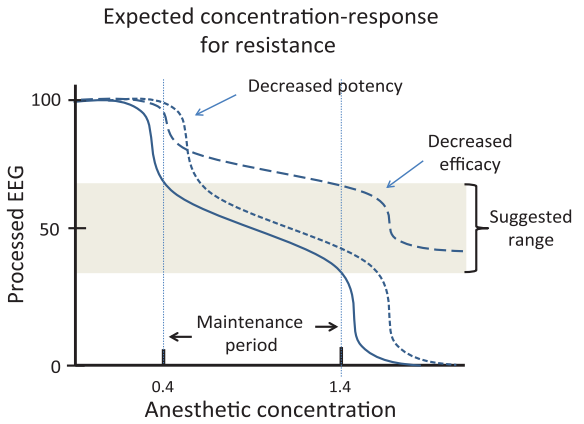

Fig. 2. Hypothetical concentration–response curves. The *solid line* represents the relationship between processed electroencephalography (EEG) value and the anesthetic concentration for controls. The *dotted line* represents the expected relationship for patients who are resistant to anesthesia due to decreased potency of the anesthetic. The *hashed line* represents the expected relationship for patients who are resistant to anesthesia due to decreased efficacy of the anesthetic.

Scientific Implications

Whitlock *et al.*[15] demonstrated that although BIS correlates unpredictably with aaMAC for individual patients, there is an average negative correlation between aaMAC and BIS values for the population during the maintenance phase of anesthesia. Resistance to the hypnotic actions of inhaled anesthetics could be manifest as either reduced potency or efficacy and would result in predictable shifts in the relationship between BIS and aaMAC (fig. 2). If resistance to anesthetic effect is due to a decrease in anesthetic potency, this might produce a right shift in the relationship between BIS and ETAC (fig. 2). Alternatively, if resistance is due to decreased anesthetic efficacy, this might result in higher BIS values at all ETAC concentrations with a higher (nonzero) BIS value at the highest ETAC concentrations. Although there was a small significant difference in the relationship between BIS and aaMAC, this difference was not strongly suggestive of a resistance to the hypnotic actions of anesthetics in patients with a history of AWR. Genetic variations might result in resistance to the hypnotic or amnesic actions of certain anesthetic agents although such variations have not yet been identified in humans. In an experimental model, mutations of the α_5 subunit of the γ-aminobutyric acid$_A$ receptor render mice resistant to the amnesic, but not hypnotic, actions of etomidate.[24] It is conceivable that a genetic resistance to some or all anesthetic agents may account for the predisposition for AWR in patients with a history of AWR. Although challenging given the rarity of the complication, pharmacogenomic analysis and other mechanistic details could help guide clinical practice. Previous suggestions to increase doses of inhaled anesthetics and benzodiazepines would only be effective if a reduction in drug *potency* was the underlying

problem. However, such an increase would make little or no difference in resistance due to decreased drug *efficacy*. Mechanistic studies may clarify whether it is possible to reduce the incidence of AWR in patients with a history of AWR with specific alterations in anesthetic management.

Limitations

AWR is a rare postoperative complication and thus this study is limited by the small number of AWR events in each cohort. Previous AWR events were self-reported by patients during enrollment for the parent trials. As such, review of records was not adequate to determine whether these patients truly experienced AWR during a prior surgery. Furthermore, to explore resistance to anesthesia, we assume that BIS is a reliable surrogate for depth of anesthesia. Given the limitations of our understanding of the neural correlates of consciousness, we do not yet have a validated (surrogate) metric for the hypnotic effect of volatile anesthetics. Although the relationship between BIS and ETAC displays marked inter- and intraindividual variability, there is a significant negative correlation for a population in the maintenance range. Extrapolation of this linear relationship beyond this range is invalid; thus, the estimated intercept is meaningless because the relationship is not linear for the entire range of anesthetic concentration. In addition, this analysis did not provide any data regarding amnesic actions of anesthetics in these patients. Finally, although the parent trials were randomized, the current study was retrospective and used a matched cohort. There is the potential for hidden confounders that explain the observed differences between the two groups.

Conclusion

History of AWR confers an adjusted five-fold increase in risk of AWR, even in the setting of preventive interventions. These data should prompt a careful preoperative discussion of AWR risk in patients reporting a history of the complication, intraoperative vigilance for potentially insufficient anesthesia or analgesia, and systematic postoperative assessment to screen for AWR and its psychological consequences. Further translational research is required to clarify whether genetic variations contribute to the increased risk of AWR in this vulnerable surgical population.

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Appendix 1. Modified Brice Questionnaire

1. What was the last thing you remember before going to sleep?
2. What is the first thing you remember after waking up?
3. Do you remember anything between going to sleep and waking up?
4. Did you dream during your procedure?
5. What was the worst thing about your operation?

Appendix 2. Upper Dose Limit for Drug Conversion (Beyond Which Values Were Excluded)

Drug	Dose (mg)
Atracurium	500
Cisatracurium	200
Etomidate	50
Fentanyl	20
Hydromorphone	20
Meperidine	300
Methadone	100
Midazolam	100
Morphine	200
Pancuronium	50
Propofol	6,200
Rocuronium	250
Sufentanil	10
Thiopental	2,000
Vecuronium	50