Postoperative Recovery with Bispectral Index *versus* Anesthetic Concentration–guided Protocols

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ABSTRACT

Background: Use of the bispectral index (BIS) monitor has been suggested to decrease excessive anesthetic drug administration, leading to improved recovery from general anesthesia. The purpose of this substudy of the B-Unaware and BAG-RECALL trials was to assess whether a BIS-based anesthetic protocol was superior to an end-tidal anesthetic concentration–based protocol in decreasing recovery time and postoperative complications.

Methods: Patients at high risk for awareness were randomized to either BIS-guided or end-tidal anesthetic concentration–guided general anesthesia in the original trials. Outcomes included time to postanesthesia care unit discharge readiness, time to achieve a postoperative Aldrete score of 9–10, intensive care unit length of stay, postoperative nausea and vomiting, and severe postoperative pain. Univariate Cox regression and chi-square tests were used for statistical analyses.

Results: The BIS cohort was not superior in time to postanesthesia care unit discharge readiness (hazard ratio, 1.0; 95% CI, 1.0–1.1; n = 2,949), time to achieve an Aldrete score of 9–10 (hazard ratio, 1.2; 95% CI, 1.0–1.4; n = 706), intensive care unit length of stay (hazard ratio, 1.0; 95% CI, 0.9–1.1; n = 2,074), incidence of postoperative nausea and vomiting (absolute risk reduction, −0.5%; 95% CI, −5.8 to 4.8%; n = 789), or incidence of severe postoperative pain (absolute risk reduction, 4.4%; 95% CI, −2.3 to 11.1%; n = 759).

Conclusions: In patients at high risk for awareness, the BIS-guided protocol is not superior to an anesthetic concentration–guided protocol in time needed for postoperative recovery or in the incidences of common postoperative complications.

What We Already Know about This Topic

- Whether use of bispectral index monitoring speeds recovery from surgery compared to routine clinical practice is controversial

What This Article Tells Us That Is New

- In a secondary analysis of nearly 3,000 patients at high risk of awareness randomized to anesthetic titration by bispectral index monitoring or an end-tidal anesthetic concentration protocol, groups did not differ in time to postanesthesia care unit discharge, time to achieve an Aldrete score of 9–10, or the incidence of postoperative nausea or vomiting or severe pain

RECOVERY from anesthesia is a critical perioperative period from the perspective of both physiologic stability and patient satisfaction. Postoperative nausea and vomiting (PONV) and severe pain are two of the most common outcomes reported during this period[1] and are among the most distressing for patients.[2] Furthermore, faster recovery can accelerate operating room turnover and reduce labor costs in the postanesthesia care unit (PACU).[3] Thus, delayed or complicated recovery from general anesthesia can have a considerable impact on patient safety, patient satisfaction, recovery room resources, and costs of patient care.

The bispectral index (BIS) processed electroencephalogram has frequently been investigated as a candidate depth-of-anesthesia monitor intended to decrease the incidence of intraoperative awareness and to reduce excessive anesthetic drug administration. Targeting the appropriate anesthetic dose to an individual may lead to reduced incidence of delayed or complicated recovery.[4–12] The B-Aware study was

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a multicenter, randomized, controlled trial in which patients at high risk for intraoperative awareness were anesthetized using either a BIS monitor or routine monitoring of clinical signs, with the primary outcome being intraoperative awareness.[13] Patients randomized to BIS monitoring had a 1-min shorter median time to eye opening and a 3-min shorter median time to PACU discharge.[4] The authors noted that this difference was statistically significant but clinically modest. In contrast, a meta-analysis conducted by the Cochrane Database of Systematic Reviews reports that BIS monitoring during surgery is associated with shorter PACU length of stay.[5] A large trial in which BIS was used according to clinical discretion,[6] an audit of surgery before and after the introduction of universal BIS monitoring,[7] and a meta-analysis of ambulatory surgery patients[8] all found that BIS monitoring was associated with a decreased incidence of PONV. The effect on postoperative pain is unclear, with one study finding that BIS monitoring is associated with lower postoperative pain scores[9] and another finding no effect.[10] Titrating adjunctive sedative–hypnotic infusions to higher BIS values during spinal anesthesia has been associated with a reduced incidence of postoperative delirium,[10] which in turn has been linked to a shortened length of stay in the intensive care unit (ICU).[11] Despite the inconsistent effects on these outcomes reported in various studies, it has been proposed that it is justified to use the BIS in every general anesthetic.[14]

The B-Unaware[15] and BAG-RECALL[16] clinical trials found that a BIS-based anesthetic protocol was not superior to an end-tidal anesthetic concentration (ETAC)–based protocol for preventing intraoperative awareness in patients at high risk for awareness. The difference between these trials and the previously discussed B-Aware trial is that these studies compared a BIS-based protocol to an ETAC-based protocol, whereas the B-Aware study compared a BIS-based protocol to routine clinical practice. The current investigation is a prespecified substudy of the B-Unaware and BAG-RECALL trials. The aim of this substudy was to determine whether, in patients at high risk for awareness, the BIS-based anesthetic protocol was superior to the ETAC-based protocol used in these trials in relation to postanesthesia recovery times, the incidence of PONV, and the incidence of severe postoperative pain.

Materials and Methods

Patient Population

The B-Unaware and BAG-RECALL trials included adult patients at high risk for intraoperative awareness who underwent surgery with general anesthesia using a potent volatile anesthetic agent.[15,16] Patients were classified as being at high risk for intraoperative awareness if they had one or more of the following risk factors: preoperative long-term use of anticonvulsants, opiates, benzodiazepines, or cocaine; cardiac ejection fraction less than 40%; history of awareness with recall; history of difficult intubation or anticipated difficult intubation; American Society of Anesthesiologists physical status IV or V; aortic stenosis; end-stage lung disease; marginal exercise tolerance not resulting from musculoskeletal dysfunction; pulmonary hypertension; planned open-heart surgery; and daily alcohol consumption. Patients were enrolled in the B-Unaware trial from August 2005 through September 2006 at Washington University in St. Louis. Patients were enrolled in the BAG-RECALL trial from March 2008 through April 2010 at Washington University in St. Louis, the University of Chicago, and the University of Manitoba (Winnipeg, Manitoba, Canada). This substudy includes patients from the St. Louis site only. Patients who were transferred from the operating room to the ICU were excluded, except for the analysis of ICU length of stay. Patients who were transferred from the operating room to the PACU and subsequently sent to the ICU were excluded from the analyses of time to PACU discharge readiness and time to achieve an Aldrete score of 9–10. Data on PONV, severe postoperative pain, and time to reach an Aldrete score of 9–10 were available only for patients who were enrolled after an electronic medical record system was implemented in the PACU at Washington University in September 2009. The Human Research Protection Office at Washington University School of Medicine approved this study, and patients provided written informed consent for inclusion in either the B-Unaware or the BAG-RECALL trial.

Procedures

In brief, patients in the B-Unaware and BAG-RECALL trials were electronically randomized in blocks of 100 to receive general anesthesia based either on an ETAC-guided protocol or a BIS-guided protocol. The patients, PACU staff, ICU staff, and study personnel were blinded with respect to group allocation. BIS values were obtained using the BIS Quatro Sensor (Covidien, Boulder, CO). In the ETAC-guided protocol, an alarm sounded when the ETAC went outside the target range of 0.7–1.3 times the age-adjusted minimum alveolar concentration. Age-adjustment was performed using charts published by Nickalls and Mapleson.[17] BIS values were not displayed for patients randomized to the ETAC-based protocol, but were recorded. In the BIS-guided protocol, an alarm sounded when the BIS went outside the target range of 40–60; ETAC values were available during these operations. BIS values and ETAC values were recorded at minimum intervals of 1 min by means of electronic recording of anesthesia data with the use of MetaVision software (iMDsoft, Needham, MA), by direct electronic transfer of data to Microsoft Excel (Microsoft Corp., Redmond, WA), or by direct electronic transfer of data with the use of TrendFace Solo® software (ixellence GmbH, Wildau, Germany). These data were used to determine the median ETAC and BIS values during the maintenance period of surgery, excluding induction and emergence. Manual records of anesthesia and digital photographs of

monitor trends were used as alternative sources of data in the rare instances that the computer data or the electronic anesthesia records were incomplete.

The outcome measures of the current study included time to PACU discharge readiness, time to achieve an Aldrete score greater than or equal to 9, ICU length of stay, PONV in the PACU, and severe postoperative pain in the PACU. Table 1 provides a description of the Aldrete score.[18] Some patients were excluded from the analyses of certain outcomes, as described in the previous section. PACU discharge readiness was assessed by the PACU attending physician based on the following criteria: the patient was hemodynamically stable, had an Aldrete score greater than or equal to 9, had no nausea or vomiting, and had well-controlled pain. While in the PACU, patients were closely monitored by nurses (two patients per nurse). When the nurse felt the patient was ready for discharge, he or she activated a signal for the PACU resident to evaluate the patient. If the resident agreed, the attending physician assessed the patient. Time to achieve an Aldrete score greater than or equal to 9 was measured from the time of application of dressings to the surgical site and was recorded by the PACU nurse. ICU length of stay was defined as the time from ICU admission to ICU discharge. PONV was determined by documented nurse observation or administration of antiemetics in the PACU. Pain was assessed approximately every 10 min using the numerical rating system, and patients who reported a pain score of 8 or greater within 60 min after PACU admission were considered to have severe postoperative pain.[19]

Statistical Analysis

All statistical analyses were performed using SPSS version 19 (IBM Corp., Armonk, NY). The preoperative and perioperative characteristics of the ETAC and BIS cohorts were compared using chi-square tests or Mann-Whitney *U* tests as appropriate. Differences in time to PACU discharge readiness, time to achieve an Aldrete score of 9–10, and ICU length of stay between the two groups were compared using univariate Cox regressions, whereas differences in incidence of PONV and severe postoperative pain were compared using chi-square analysis. Differences in the time-based endpoints are presented as hazard ratios, which indicate how much more likely a patient in the BIS group is to achieve the outcome of interest at any given time point, compared to a patient in the ETAC group. For these outcomes, the absolute risk reduction for a patient in the group experiencing prolonged recovery (time greater than the 90th percentile) and the associated number needed to treat were also determined. Differences in the incidence of PONV and severe postoperative pain are presented as absolute risk reduction (ARR) and number needed to treat (NNT). As a measure of precision, a 95% CI was calculated for each hazard ratio, ARR, and NNT presented.

To account for the potential interaction effects among covariates known to impact postoperative recovery, multivariate Cox proportional hazards regression and multivariate logistic regression were performed. All predictors were entered into the multivariate analyses without the use of univariate analyses to filter out insignificant variables.[20] If values for any of the predictor variables were missing for a patient, that patient was excluded from the multivariate regression; no missing values were imputed. Values of $P < 0.05$ were considered to be significant. To test the overall goodness-of-fit or calibration of the resulting models, the likelihood ratio was evaluated for the Cox regressions and the Hosmer-Lemeshow test was assessed for the logistic regressions. In addition, the C statistic was used to provide a measure of the ability of each logistic regression model to discriminate between those patients who experienced PONV and severe postoperative pain *versus* those who did not.

In addition to BIS or ETAC group randomization, 12 variables were included in the multivariate analyses based on their importance in past studies. Patient variables included sex,[4,6,21–27] smoking status,[25,26,28] age,[6,22,24,26–32] and American Society of Anesthesiologists physical status.[4,27] Smoking status was included as a dichotomous variable indicating whether the patient self-identified as a current smoker. Age was included as a continuous variable, not rounded to the nearest year. Perioperative factors included length of surgery,[4,6,26,27,32–34] intraoperative administration

Table 1. Components of the Aldrete Score*

	2 Points	1 Point	0 Points
Activity	Moves all 4 extremities voluntarily or on command	Moves 2 extremities voluntarily or on command	Move 0 extremities
Respiration	Can deep breathe and cough freely	Dyspnea or limited breathing	Apneic
Circulation	BP ±20% of preanesthetic level	BP ±20–50% of preanesthetic level	BP beyond ±50% of preanesthetic level
Consciousness	Fully awake	Arousable on calling	Not responding
Color	Pink	Pale, dusky, blotchy, jaundiced, other	Cyanotic

* Aldrete scores document overall postoperative recovery on a scale from 0–10 based on five objective parameters (Aldrete JA, Kroulik D: A postanesthetic recovery score. Anesth Analg 1970; 49:924–34[18]).

BP = blood pressure.

of opiates,[35] neuromuscular blockers, neostigmine,[36] and antiemetics.[37] Opiate doses were converted to morphine equivalents using equianalgesic conversion factors published in the *Alberta Hospice Palliative Care Resource Manual*[38] and then normalized by patient weight. Neuromuscular blocker doses were converted to vecuronium equivalents using 95% effective doses (ED95) published in Cusick's *Anesthesia & Critical Care Reference Sheet*[39] and then normalized by patient weight. Antiemetic doses were converted to ondansetron equivalents using usual doses presented in a review by Golembiewski et al.[40] and then normalized by patient weight. In addition, a variable was created to indicate whether the identity of the surgical procedure placed the patient at high risk for delayed postoperative recovery. Abdominal, thoracic, and orthopedic procedures were identified as having high risk for delayed recovery because these operations have previously been associated with the longest mean PACU length of stay[32] and the highest incidence of postoperative pain.[31] The product of median ETAC and length of surgery was also included as a measure of cumulative anesthetic dose, and the median BIS value was included as a surrogate measure of average anesthetic depth.

Results

Of the 1,931 B-Unaware patients and 4,700 BAG-RECALL patients for whom data were available, 5,884 patients were included in this substudy (fig. 1). Time to PACU discharge readiness was measured in 2,949 patients who were transferred from the operating room to the PACU and were not subsequently sent to the ICU. Time to achieve an Aldrete score of 9 was measured in 706 patients who were transferred from the operating room to the PACU and were not subsequently sent to the ICU and who entered the study after an electronic medical record was implemented in the PACU in September 2009. ICU length of stay was measured in 2,074 patients who were transferred from the operating room to the ICU. PONV was assessed in 789 patients and severe postoperative pain was assessed in 759 patients who were transferred from the operating room to the PACU and were enrolled after an electronic medical record was implemented in the PACU in September 2009. A small number of patients who had been assigned to the BIS- or ETAC-based protocol received regional anesthesia or total IV anesthesia instead, as indicated in the original B-Unaware and BAG-RECALL publications.[15,16] These patients were excluded from the analysis. No patient assigned to the BIS-based protocol was treated following the ETAC-based protocol, and *vice versa*. The preoperative and perioperative characteristics of the patients who were admitted to the PACU but were not subsequently transferred to the ICU are shown in table 2. The patients randomized to the BIS- and ETAC-based protocols did not differ with respect to any of the variables tested. The patients who were admitted to the ICU exhibited similar characteristics.

The unadjusted hazard ratio for a patient in the BIS group being ready for discharge from the PACU was 1.045 (95% CI, 0.972–1.124; $P = 0.232$) (fig. 2A). Of the 2,949 patients assessed, 139 patients in the BIS group (9.5%) and 156 patients in the ETAC group (10.6%) experienced a

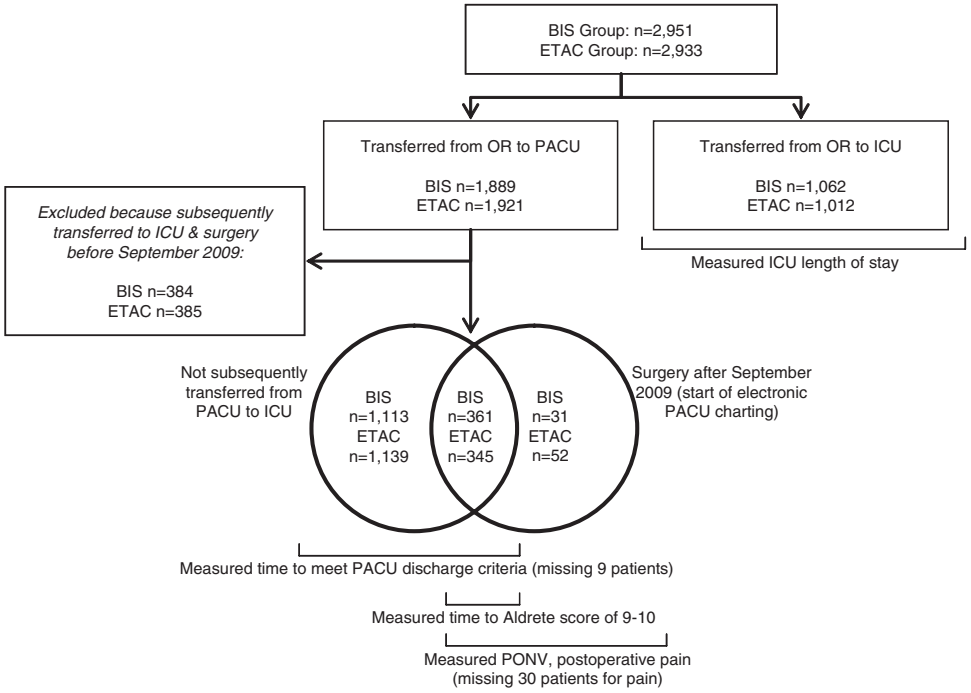

Fig. 1. Patients in the B-Unaware and BAG-RECALL trials included in this study. BIS = bispectral index; ETAC = end-tidal anesthetic concentration; ICU = intensive care unit; OR = operating room; PACU = postanesthesia care unit; PONV = postoperative nausea/vomiting.

Table 2. Characteristics of Patients Observed in the Postanesthesia Care Unit Who Were Not Subsequently Admitted to the Intensive Care Unit (n = 2,958)*

	BIS Group	ETAC Group	*P* Value
No. of patients	1,474	1,484	
Patient characteristics			
Female sex	726 (49%)	757 (51%)	0.339
Current smoker	402 (27%)	395 (27%)	0.688
Mean age, yr (range)	59 (50–68)	58 (48–68)	0.100
ASA physical status			0.356
I	25 (2%)	35 (2%)	
II	429 (29%)	427 (29%)	
III	823 (56%)	845 (57%)	
IV	197 (13%)	175 (12%)	
High-risk surgery†	913 (64%)	889 (63%)	0.290
Length of surgery, min	98 [50–168]	99 [51–170]	0.705
Intraoperative drugs			
Opiates, morphine equivalents/kg	0.36 [0.20–0.74]	0.37 [0.20–0.75]	0.528
NMB, vecuronium equivalents/kg	0.14 [0.09–0.20]	0.13 [0.08–0.20]	0.607
Neostigmine, μg/kg	29 [0–50]	29 [0–50]	0.925
Antiemetics, ondansetron equivalents/kg	0 [0–0.02]	0 [0–0.01]	0.190
Cumulative anesthetic dose (MAC × min)	99 [46–171]	92 [43–169]	0.430
Median BIS	41 [36–45]	40 [35–46]	0.471

* For categorical variables, data are presented as frequency (percent), and *P* values were obtained using the χ^2 test comparing the BIS and ETAC groups. For continuous variables, data are presented as median [interquartile range], and *P* values were obtained using the Mann-Whitney *U* test comparing the BIS and ETAC groups. Similar results were obtained for patients who were sent to the intensive care unit. † High-risk surgery includes abdominal, thoracic, and orthopedic procedures.

ASA = American Society of Anesthesiologists; BIS = bispectral index; ETAC = end-tidal anesthetic concentration; MAC = minimum alveolar concentration; NMB = neuromuscular blockade.

prolonged time (>228 min) to PACU discharge readiness. This represents an ARR of 1.1% (95% CI, −1.0 to 3.3%) and an NNT to benefit (NNTB) of 90 (95% CI: NNTB, 30–∞; NNT to harm [NNTH], ∞–94). The unadjusted hazard ratio for a patient in the BIS group, compared with a patient in the ETAC group, achieving an Aldrete score of 9–10 was 1.164 (95% CI, 0.976–1.389; *P* = 0.091) (fig. 2B). Of the 706 patients assessed, 36 patients in the BIS group (9.9%) and 35 patients in the ETAC group (10.1%) experienced prolonged time to achieve an Aldrete score of 9–10 (>190 min). This represents an ARR of 0.2% (95% CI, −4.3 to 4.6%) and an NNTB of 579 (95% CI: NNTB, 22–∞; NNTH, ∞–23). The unadjusted hazard ratio for a patient in the BIS group being discharged from the ICU was 1.002 (95% CI, 0.918–1.092; *P* = 0.972) (fig. 2C). Of the 2,074 patients assessed, 109 patients in the BIS group (10.3%) and 100 patients in the ETAC group (9.9%) experienced prolonged ICU length of stay (>9 days). This represents an ARR of −0.4% (95% CI, −3.0 to 2.2%) and an NNTH of 261 (95% CI: NNTB, 45–∞; NNTH, ∞–34).

There was no significant association between BIS/ETAC randomization and PONV (chi-square test with 1 degree of freedom = 0.031, *P* = 0.860). Of the 789 patients assessed, 70 patients in the BIS group (17.9%) and 69 patients in the ETAC group (17.4%) experienced PONV. This is an ARR of −0.5% (95% CI, −5.8 to 4.8%) and represents an NNTH of 209 (95% CI: NNTB, 20–∞; NNTH, ∞–17). There was no significant association between BIS or ETAC randomization and severe postoperative pain (chi-square test with 1 degree of freedom = 1.643, *P* = 0.200). Of the 759 patients assessed for severe postoperative pain, 120 patients in the BIS group (31.4%) and 135 patients in the ETAC group (35.8%) experienced severe pain. This is an ARR of 4.4% (95% CI, 2.3–11.1%) and represents an NNTB of 22 (95% CI: NNTB, 9–∞; NNTH, ∞–43).

After adjusting for patient characteristics and perioperative variables known to have an impact on postoperative recovery, there was still no difference between the BIS and ETAC cohorts with respect to any of the outcomes measured. The multivariate Cox regression for time to PACU discharge readiness included 1,193 patients (table 3). The adjusted hazard ratio for a patient in the BIS group, compared with a patient in the ETAC group, being ready for discharge from the PACU was 1.086 (95% CI, 0.968–1.218). The Cox regression model had a highly significant likelihood ratio characteristic of 164 on 13 degrees of freedom (*P* < 0.0001). The Cox multivariate regression for time to achieve an Aldrete score of 9–10 included 561 patients (table 3). The adjusted hazard ratio for a patient in the BIS group, compared with a patient in the ETAC group, achieving an Aldrete score of 9–10 was 1.137 (95% CI, 0.932–1.387). The Cox regression model had a highly significant

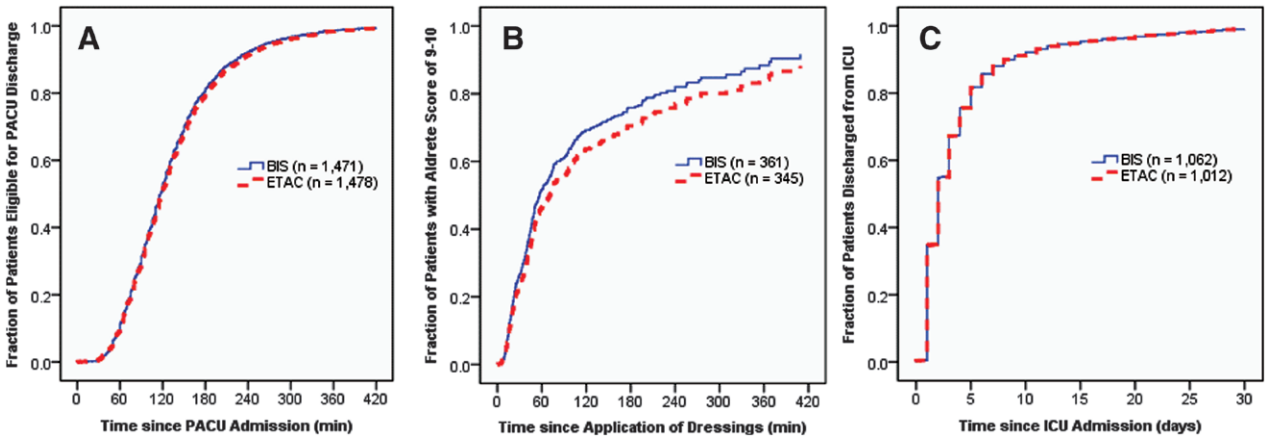

Fig. 2. Time needed for recovery in patients randomized to the bispectral index (BIS)–guided and end-tidal anesthetic concentration (ETAC)–guided protocols. (*A*) Time to meet postanesthesia care unit (PACU) discharge criteria. (*B*) Time to achieve an Aldrete score of 9–10. (*C*) Length of stay in the intensive care unit (ICU).

Table 3. Predictors of Time to Postanesthesia Care Unit Discharge Readiness (n = 1,193), Time to Achieve an Aldrete Score of 9–10 in the Postanesthesia Care Unit (n = 561), and Intensive Care Unit Length of Stay (n = 1,098)*

	PACU Discharge Readiness, HR (95% CI)	Aldrete Score 9–10, HR (95% CI)	ICU Length of Stay, HR (95% CI)
Anesthetic protocol			
ETAC	Reference	Reference	Reference
BIS	1.086 (0.968–1.218)	1.137 (0.932–1.387)	0.981 (0.870–1.106)
Patient characteristics			
Female sex	0.901 (0.801–1.014)	0.800 (0.653–0.979)	0.805 (0.708–0.915)
Current smoker	0.693 (0.801–1.172)	0.900 (0.711–1.140)	1.008 (0.870–1.168)
Age	0.996 (0.991–1.000)	0.995 (0.987–1.003)	0.990 (0.986–0.995)
ASA physical status			
I–II	Reference	Reference	Reference
III–IV	0.945 (0.828–1.078)	0.788 (0.623–0.998)	0.566 (0.365–0.879)
High-risk surgery†	0.844 (0.743–0.958)	0.856 (0.682–1.074)	1.069 (0.813–1.405)
Length of surgery	0.998 (0.997–0.999)	0.998 (0.993–1.002)	0.996 (0.995–0.998)
Intraoperative drugs			
Opiates	0.802 (0.737–0.872)	0.923 (0.826–1.031)	0.949 (0.888–1.015)
NMB	1.007 (0.545–1.861)	0.469 (0.142–1.554)	0.832 (0.457–1.515)
Neostigmine	0.995 (0.993–0.998)	0.994 (0.990–0.999)	1.007 (1.004–1.010)
Antiemetics	0.176 (0.042–0.736)	2.089 (0.466–9.359)	‡
Cumulative anesthetic dose	1.000 (0.999–1.000)	0.998 (0.993–1.002)	1.002 (1.001–1.004)
Median BIS	0.996 (0.990–1.002)	0.993 (0.983–1.004)	0.996 (0.987–1.005)
Likelihood ratio	$\chi^2(13) = 164$, $P < 0.0001$	$\chi^2(13) = 92$, $P < 0.0001$	$\chi^2(12) = 101$, $P < 0.0001$

* Each of these Cox proportional hazards models was generated using forced entry of all predictor variables in a single block. For PACU length of stay and Aldrete score outcomes, patients who were subsequently transferred to the intensive care unit were excluded. For intensive care unit length of stay, only patients transferred directly from the operating room to the intensive care unit were included. † High-risk surgery includes abdominal, thoracic, and orthopedic procedures. ‡ No patients who were sent to the ICU received intraoperative antiemetics.

ASA = American Society of Anesthesiologists; BIS = bispectral index; CI = confidence interval; ETAC = end-tidal anesthetic concentration; HR = hazard ratio; ICU = intensive care unit; MAC = minimum alveolar concentration; NMB = neuromuscular blockade; PACU = postanesthesia care unit.

likelihood ratio characteristic of 92 on 13 degrees of freedom ($P < 0.0001$). The multivariate Cox regression for ICU length of stay included 1,098 patients (table 3). The adjusted hazard ratio for a patient in the BIS group, compared with a patient in the ETAC group, being discharged from the ICU was 0.981 (95% CI, 0.870–1.106). The Cox regression model had a highly significant likelihood ratio characteristic of 101 on 12 degrees of freedom ($P < 0.0001$).

The multivariate logistic regression for PONV included 627 patients (table 4). The adjusted odds ratio for a patient in the BIS group, compared with the ETAC group, experiencing PONV was 0.978 (95% CI, 0.642–1.492). This logistic regression had a fair C-statistic value of 0.610 and a Hosmer-Lemeshow chi-square test characteristic of 3.9 with 8 degrees of freedom ($P = 0.86$), indicating that although overall model fit is fair, the numbers of PONV events are not significantly different from those predicted by the model. The multivariate logistic regression for severe postoperative pain included 602 patients (table 4). The adjusted odds ratio for a patient in the BIS group, compared with the ETAC group, experiencing severe postoperative pain was 0.812 (95% CI, 0.562–1.172). This logistic regression had a C-statistic of 0.683 and a Hosmer-Lemeshow test characteristic of 13.7 on 8 degrees of freedom ($P = 0.09$), indicating that although the overall model fit is fair, the numbers of pain events are not significantly different from those predicted by the model.

Discussion

The primary aim of this analysis was to determine whether following a BIS-guided protocol rather than an ETAC-guided protocol for anesthetic administration would improve specific recovery metrics following general anesthesia in patients at high risk for intraoperative awareness, as defined by our methodology. No significant differences were found in time to PACU discharge readiness, time to achieve an Aldrete score of 9–10, ICU length of stay, incidence of PONV, or incidence of severe postoperative pain. No differences were observed even after adjusting for prognostically important patient characteristics and perioperative variables. These results differ from a report by the Cochrane Database of Systematic Reviews that found that BIS monitoring was associated with faster recovery.[5] These results also contrast with the findings of several trials that found that BIS monitoring was associated with a reduced incidence of PONV.[6–8] The results presented here are consistent with the B-Aware trial, in which the BIS protocol was similarly not associated with clinically relevant improved recovery compared with routine

Table 4. Predictors of Postoperative Nausea and Vomiting (n = 627) and Severe Postoperative Pain (n = 602)*

	Nausea and Vomiting, OR (95% CI)	Severe Pain, OR (95% CI)
Anesthetic protocol		
ETAC	Reference	Reference
BIS	0.978 (0.642–1.492)	0.812 (0.562–1.172)
Patient characteristics		
Female sex	1.463 (0.945–2.263)	1.291 (0.887–1.880)
Current smoker	1.377 (0.856–2.213)	1.143 (0.748–1.747)
Age	0.987 (0.970–1.004)	0.992 (0.978–1.007)
ASA physical status		
I–II	Reference	Reference
III–IV	0.765 (0.473–1.237)	0.932 (0.601–1.446)
High-risk surgery†	0.881 (0.535–1.451)	2.051 (1.293–3.251)
Length of surgery	0.994 (0.985–1.003)	1.001 (0.994–1.009)
Intraoperative drugs		
Opiates	0.944 (0.753–1.182)	2.037 (1.573–2.639)
NMB	3.063 (0.343–27.308)	0.417 (0.054–3.227)
Neostigmine	1.006 (0.996–1.016)	1.005 (0.996–1.014)
Antiemetics	0.428 (0.010–17.920)	0.096 (0.002–4.201)
Cumulative anesthetic dose	1.006 (0.997–1.014)	1.002 (0.994–1.009)
Median BIS	0.977 (0.951–1.003)	1.005 (0.982–1.027)
C statistic	0.610	0.683
Hosmer-Lemeshow	$\chi^2(8) = 3.9$, $P = 0.87$	$\chi^2(8) = 13.7$, $P = 0.09$

* Each of these logistic regression models was generated using forced entry of all predictor variables in a single block. Postoperative nausea and vomiting was determined by documented patient reports or administration of antiemetics in the postanesthesia care unit. Severe postoperative pain was defined as a numerical rating system score of 8 or greater within 60 min of postanesthesia care unit admission. † High-risk surgery includes abdominal, thoracic, and orthopedic procedures.

ASA = American Society of Anesthesiologists; BIS = bispectral index; ETAC = end-tidal anesthetic concentration; MAC = minimum alveolar concentration; NMB = neuromuscular blockade; OR = odds ratio.

care, notwithstanding a 1-min decrease in median time to eye opening and a 3-min decrease in median time to PACU discharge.[4] These results are also consistent with the recent Michigan Awareness Control Study, in which a BIS-based protocol was not associated with a clinically meaningful decrease in median time to PACU discharge readiness (95 min *vs.* 98 min) or reduced incidence of postoperative nausea or vomiting (7% *vs.* 8%) when compared with an anesthetic concentration–based protocol in a diverse surgical population.[41]

One possible explanation for the different results in the B-Unaware and BAG-RECALL trials compared with some previous trials might have been that the current trials included only patients at high risk for intraoperative awareness, as defined by our methodology, whereas previous trials enrolled a wider variety of patients. It is possible that BIS monitoring produces no benefit in relation to postoperative recovery among patients who are at high risk for awareness but does produce a benefit in other populations. However, the Michigan Awareness Control Study found results similar to these in a population not limited to those at high risk for awareness.[41] Another possible explanation for these differences lies in the differing protocols for anesthetic administration used in these various studies. In many previous trials, patients were randomized to receive anesthesia with a BIS-guided protocol *versus* routine clinical practice. Such a study design does not address the possibility that the use of a protocol of any kind to guide anesthetic management might potentially modify the anesthesiologist's practice through promoting vigilance and potentially bias the results. In the B-Unaware and BAG-RECALL trials, the use of an ETAC-based protocol (*i.e.*, a protocol-based active comparator rather than routine clinical practice) to guide anesthetic management in the control group addresses this possibility. Another possible explanation for the difference in results is that the anesthesiologists in the B-Unaware and BAG-RECALL trials were not informed that postoperative recovery parameters would be evaluated as secondary outcomes, mitigating a Hawthorne effect or other biases that could potentially be present in a small efficacy study.

It is possible that a protocol targeting BIS values between 45 and 60, as opposed to the protocols in the B-Aware, B-Unaware, and BAG-RECALL trials, which targeted BIS values between 40 and 60, would reveal the benefit of the BIS in relation to postoperative recovery. However, recent evidence suggests that the BIS value tends to a plateau value in the low 40s over a clinically relevant range of anesthetic concentrations.[42–44] This is corroborated by results of several large clinical trials in which mean BIS values during anesthetic maintenance have been between 37 and 47.[13,15,16,45–48] Titrating anesthetic concentration to achieve BIS values between 45 and 60 appears to be difficult to accomplish in clinical practice, although one recent large study reported a median BIS value of 53 (95% CI, 48–57) in a group managed with a BIS-guided protocol.[49] Furthermore, intraoperative median BIS values were not independently associated with any of the postoperative recovery times, the incidence of severe postoperative pain, or the incidence of PONV (tables 3 and 4). Therefore, this study does not provide evidence to support the hypothesis that maintaining higher intraoperative median BIS values leads to more rapid postoperative recovery or improved quality of recovery.

This study has several important limitations. Although no differences in any of the measures were found, the 95% CIs for several of the outcomes evaluated included clinically significant differences at the extremes. For example, the 95% CI of the NNT to prevent a case of severe postoperative pain has a lower bound of 9. Thus, this study does not exclude the possibility that clinically relevant differences between the BIS and ETAC protocols do exist in relation to recovery parameters. Both multivariate logistic regressions have fair C statistics, suggesting that some unmeasured variables have a major impact on the emergence of PONV and postoperative pain. PACU discharge readiness was measured using the hospital's routine protocols, so it is possible that some patients waited longer than others to be assessed for discharge by the attending physician. However, the PACU staff was blinded with respect to anesthetic protocol, so any artificially prolonged times to PACU discharge readiness were probably distributed equally between the BIS and ETAC cohorts. Also, time to achieve an Aldrete score of 9 or 10 would not have been subject to this stipulation, as this time was recorded by the nurse caring for the patient in the PACU. As already mentioned, because this study included only patients who were at high risk for intraoperative awareness, applying the results to the general surgical population is not warranted. The results of this study also do not exclude the possibility that intraoperative BIS monitoring may be beneficial with respect to other outcomes. For example, the recent Cognitive Dysfunction after Anesthesia trial identified a potential role of BIS-guided anesthesia in reducing the incidence of postoperative delirium and cognitive decline.[49] Finally, although practitioner bias is often a potential confounder in clinical trials, it is unlikely that the results of this study reflect practitioner bias, as many different anesthesiologists and certified registered nurse anesthetists participated over a period of nearly 5 yr.

Overall, this study advances the field by demonstrating that the use of a BIS-guided protocol rather than an ETAC-guided protocol to titrate anesthesia in patients at high risk for awareness, as defined in this study, does not result in improved anesthetic recovery as assessed by time to achieve an Aldrete score of 9–10, time to PACU discharge readiness, PONV incidence, and severe postoperative pain occurrence. Similarly, a BIS-guided protocol does not result in a shorter ICU length of stay in this population. The results of this trial contrast with meta-analyses of efficacy trials conducted by the Cochrane Database of Systematic Reviews[5] but are congruent with the results of the recently reported Michigan

Awareness Control Study,[41] a large effectiveness trial including a diverse surgical population.

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