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Postoperative Delirium in a Substudy of Cardiothoracic Surgical Patients in the BAG-RECALL Clinical Trial

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Abstract

Background—Postoperative delirium in the intensive care unit (ICU) is a frequent complication after cardiac or thoracic surgery and is associated with increased morbidity and mortality.

Methods—In this single-center substudy of the BAG-RECALL trial (NCT00682825) we screened patients after cardiac or thoracic surgery in the ICU twice daily for delirium using the Confusion Assessment Method for the ICU. The primary outcome was the incidence of delirium in patients who had been randomized to intraoperative Bispectral Index (BIS)-guided and end-tidal anesthetic concentration-guided depth of anesthesia protocols. As a secondary analysis, a Bayesian stochastic search variable selection strategy was used to rank a field of candidate risk factors for delirium, followed by binary logistic regression.

Results—Of 310 patients assessed, 28/149 (18.8%) in the BIS group and 45/161 (28.0%) in the end-tidal anesthetic concentration group developed postoperative delirium in the ICU (odds ratio 0.60, 95% confidence interval 0.35-1.02, p=0.058). Low average volatile anesthetic dose, intraoperative transfusion, ASA physical status, and EuroSCORE were identified as independent predictors of delirium.

Discussion—A larger randomized study should determine whether brain monitoring with BIS or an alternative method decreases delirium after cardiac or thoracic surgery. The association between low anesthetic concentration and delirium is a surprising finding and could reflect that patients with poor health are both more sensitive to the effects of volatile anesthetic drugs and are also more likely to develop postoperative delirium. Investigation of candidate methods to prevent delirium should be prioritized in view of the established association between postoperative delirium and adverse patient outcomes.

Introduction

Delirium is an acute change in cognition and concentration that complicates the postoperative course of 10-40% of cardiothoracic surgical patients. Patients who suffer delirium after cardiac surgery are at increased risk of persistent cognitive impairment,[1] functional decline[2] and death,[3] and postoperative delirium is associated with increased hospital length of stay and higher costs.[4] Many risk factors for postoperative delirium have been identified, such as those in the review by Marcantonio.[5]; variables such as patient age, preexisting cognitive impairment or dementia, and duration and invasiveness of operation are commonly cited.

An association between postoperative delirium and excessive intraoperative anesthetic exposure has been hypothesized. Studies have investigated the use of brain monitoring, such as the Bispectral Index (BIS)® (Covidien, Boulder, CO) monitor, to guide anesthetic titration in order to decrease postoperative delirium. Three randomized studies in noncardiac and nonthoracic surgical populations have found a decrease in delirium with BIS-guided anesthesia.[6-8] It is unknown whether BIS guidance decreases delirium after cardiac and thoracic surgery. There has been little inquiry into associations between postoperative

delirium and intraoperative variables, such as arterial blood pressure, total anesthetic dose, and depth of anesthesia. A small study of cardiac surgery patients suggested that targeting higher arterial blood pressure during cardiopulmonary bypass was associated with decreased postoperative delirium.[9] Patients undergoing cardiac and thoracic surgery are particularly vulnerable to physiologically significant intraoperative and postoperative derangements in perfusion and oxygenation, and at our institution receive postoperative care in a single specialized intensive care unit (ICU).

We therefore performed this predetermined single-site substudy of the BAG-RECALL clinical trial (NCT00682825) to determine whether there was a difference in postoperative delirium between patients randomized to BIS-guided or end-tidal anesthetic concentration (ETAC)-guided protocols. Secondarily, we assessed the contribution of patient and intraoperative variables to postoperative delirium in the ICU after major cardiac and/or thoracic surgery.

Methods

Ethics committee approval and study design

This was a prespecified single-site substudy of the BAG-RECALL multicenter clinical trial.[10] Approval was granted by the Washington University Human Research Protection Office, and all participants gave written consent for participation in the BAG-RECALL trial, which assessed patients for intraoperative awareness, as well as for this substudy, which assessed patients for postoperative delirium. Patients receiving care in the cardiothoracic ICU after major cardiac and/or thoracic surgery at a quaternary care center were screened twice daily for delirium using the Confusion Assessment Method for the ICU (CAM-ICU). Data on preoperative comorbidities, intraoperative vital signs and drug administration were collected to investigate risk factors for developing postoperative delirium.

Patient population

The BAG-RECALL trial enrolled 6,100 patients undergoing general anesthesia at three international centers. Enrolled patients were at increased risk for intraoperative awareness based on published risk factors for that complication; major criteria included planned open-heart surgery, ejection fraction (EF) < 40%, history of intraoperative awareness, history of or anticipated difficult intubation, ASA physical status (PS) 4 or 5, aortic stenosis, end-stage lung disease, pulmonary hypertension, marginal exercise tolerance, or daily use of certain neuroactive medications or alcohol. Patients were randomized to either an ETAC-guided (alerts for <0.7 or >1.3 age-adjusted minimum alveolar concentration [MAC]) or BIS-guided (alerts for BIS>60 or BIS<40) protocol. The primary outcome of that trial was the incidence of intraoperative awareness in the two groups. This substudy included consecutive patients enrolled in the BAG-RECALL trial who received care in the cardiothoracic ICU at Barnes-Jewish Hospital in St. Louis from 8/20/2009 through 4/19/2010.

Delirium assessments

Delirium assessments were performed twice daily until postoperative day 10 or ICU discharge, whichever occurred first, using the CAM-ICU.[11] A single critical care nurse (BT)

performed the majority of assessments, and abstracted documented CAM-ICU assessments performed by other nursing staff from patient charts when necessary. All staff performing CAM-ICU assessments had the same standardized institutional training on the proper procedures for conducting the examination. ICU staff, including nurses, physicians, and BT, were all blinded to BIS or ETAC group assignment. The Richmond Agitation and Sedation Scale [12] grading was used to determine whether the delirium was hyperactive or hypoactive.

Collection of other data

Patient demographics and comorbidities were documented as part of the BAG-RECALL trial, and were used to conduct a modified European System for Cardiac Operative Risk Evaluation (EuroSCORE) as a measure of perioperative mortality risk.[13] Some comorbidities included in EuroSCORE calculation were not collected for the BAG-RECALL population. A history of cardiac surgery and presence of extracardiac arteriopathy were not documented for our population. Preoperative tests of neurologic function were not performed; however, all patients met criteria for inclusion in BAG-RECALL, which excluded patients with significant neurological disease, and enrolled only those presenting for elective surgery. Additionally, while the EuroSCORE stratifies patients with congestive heart failure into those with a cardiac EF between 30 and 50%, which is worth one EuroSCORE point, and those with an EF below 30, worth two EuroSCORE points, patients in BAG-RECALL were stratified by whether their EF was above or below 40%. To address this, patients with an EF < 40% were given 1.5 points for the purposes of calculating EuroSCORE, and those with an EF ≥ 40% were given no additional points.

Intraoperative monitoring data, including vital signs, BIS values, and ETAC, were automatically archived every minute by our intraoperative anesthetic record documentation system (Metavision, iMDsoft, Needham, MA). All patients received invasive arterial blood pressure monitoring. Volatile anesthetic concentration was converted into age-adjusted MAC equivalents, summed across all volatile anesthetic drugs being delivered.[14]

Statistical analysis

When not specifically stated, statistical analyses were performed in PASW Statistics version 18 (SPSS Statistics, IBM Corporation, Somers, NY). The primary outcome, comparison in delirium incidence between patients randomized to BIS-guided and ETAC-guided protocols, was assessed with a chi square test. As enrollment to this substudy commenced towards the end of the BAG-RECALL trial, we were limited in recruitment number accordingly. We estimated that 300 patients could be enrolled in this substudy, which would provide 84% power with a 2-sided p value of 0.05 to detect an absolute reduction of 15% in delirium incidence between the two groups, assuming an incidence of 30% in one group.

The second aim of the study was to evaluate candidate variables for association with postoperative delirium. To reduce the probability of type 1 error, only 14 independent variables were considered, selected on the basis of a literature search and hypotheses generated by the study group. Continuous predictors were EuroSCORE, preoperative hemoglobin, duration of cardiopulmonary bypass, duration of mean arterial blood pressure < 75 mmHg, duration of BIS < 45, duration of concurrent mean arterial blood pressure < 75

mmHg, BIS < 45, and ETAC< 0.7 age-adjusted MAC, total midazolam dose (mcg/kg/hr of operation), total fentanyl dose (mcg/kg/hr of operation), total norepinephrine dose (mcg/kg/min), average ETAC during anesthetic maintenance, and number of units of donor packed red blood cells (pRBCs) administered intraoperatively. Dichotomous variables were whether the patient consumed ethanol daily,[15] whether the ASA PS was greater than 3, and whether the patient was allocated to the BIS or the ETAC group in the BAG-RECALL trial. Candidate variable data were complete for all participants.

The commonly used technique of establishing univariate relationships between predictors and the outcome of interest is flawed from a statistical perspective, resulting in unnecessary expansion of alpha error. The relatively small size of our dataset made it unlikely that, using typical stepwise binary logistic regression techniques, we would appropriately identify one single "best" model; small study populations with a large number of covariates are vulnerable to "overfitting," or fitting to idiosyncrasies in the data rather than true population relationships.[16] Thus, we used a Bayesian stochastic search variable selection (SSVS) approach[17,18] to search over all possible main effect models (i.e., $2^{14} = 16{,}384$) and obtained posterior probability for each model to be the "true" model. SSVS was done with WinBUGS 1.4.3 (http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml). This method also produces estimates of the probability for each independent variable to be in the "true" model, which we can use to rank the importance of independent variables. The SSVS method is an iterative algorithm using the Gibbs sampler that can be easily implemented in WinBUGS. O'Hara and Sillanpää[19] discussed Bayesian variable selection techniques in their review.

After individual predictors were ranked according to their posterior probabilities, we conducted binary logistic regression with the top five predictors (all with posterior probability greater than 0.5). The model was used to generate predicted probabilities for calculation of a c-statistic to assess model fit, as well as to provide odds ratios associated with the candidate predictors. A p value of < 0.05 was considered to indicate statistical significance.

Exploratory post hoc meta-analysis

Based on an approach suggested in *The Lancet*,[20,21] we conducted a post hoc meta-analysis, in which the findings of the current trial were combined meta-analytically with the three other randomized studies in noncardiac and nonthoracic surgical populations that have incorporated BIS-guided care as an intervention and have evaluated postoperative delirium as the primary outcome.[6-8] A DerSimonian-Laird random effects meta-analysis was conducted using the R statistical environment (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

From 8/24/2009 to 4/19/2010, 337 consecutive patients enrolled in the BAG-RECALL trial received treatment in the cardiothoracic ICU of our institution and were considered for

inclusion in this substudy. Of those 337 patients, 13 (3.8%) had no documented delirium screens, two (0.6%) did not receive cardiac or thoracic surgery, and 12 (3.6%) had an incomplete electronic intraoperative record. Thus, 310 patients, all with at least one CAM-ICU assessment, are included in this substudy. (Figure 1) Characteristics of the study group are in Appendix 1. Excluded patients were significantly younger than but otherwise similar to included patients.

Of the 310 patients in the substudy, 73 (23.5%) had a positive CAM-ICU assessment for delirium at least once during their care in the ICU. One hundred four patients (33.5%) were missing at least one documented CAM-ICU assessment within the first three days after surgery. Patients with missing data were no more or less likely to have had delirium (chi square $p = 0.394$).

Of the 73 patients who were delirious during the study, 56 (76.7%) experienced only hypoactive delirium, 8 (11.0%) had both hyper- and hypoactive delirium (i.e., a mixed phenotype), and 5 (6.8%) had only hyperactive delirium. Another 4 patients did not have a documented Richmond Agitation and Sedation Scale score at the time of at least one episode of delirium and their phenotype could not be conclusively determined.

A diagnosis of delirium in the ICU was associated with increased ICU and hospital length of stay and increased rates of mortality. ICU discharge occurred at a median of 2.0 days (95% confidence interval [CI] 1.7-2.3) postoperatively for those without delirium, and at 8.0 (95% CI 7.1-8.9) days for those with delirium ($p<0.001$). Hospital discharge occurred at a median of 7.0 days (95% CI 6.4-7.6) versus 17.0 (95% CI 14.3-19.7) days for those without and with delirium, respectively ($p<0.001$). Excluding patients who died in-hospital, patients without delirium were more likely to be alive at last follow-up (94.3% versus 84.1% for those who were nondelirious and delirious, respectively; $p=0.008$).

Incidence of delirium in the BIS and ETAC groups

Table 1 shows comparisons between patients in BIS and ETAC groups, and suggests that randomization did result in balanced groups in this substudy. Of the 310 patients assessed, 28/149 (18.8%) in the BIS group and 45/161 (28.0%) in the ETAC group developed postoperative delirium in the ICU (odds ratio 0.60, 95% CI 0.35-1.02, p=0.058). Table 1 shows that patients in the BIS group also had a significantly shorter stay in the ICU.

Delirium prediction model

Table 2 shows the characteristics of patients with and without delirium. The stochastic search variable selection approach returned probabilities of the 14 candidate predictors for inclusion in the “true” model (Table 3). In order of importance to the model, those variables with > 0.5 probability of inclusion, followed parenthetically by their exact probability of inclusion, were average maintenance ETAC (0.97), units of pRBCs (0.92), ASA PS 4 (versus 1, 2 or 3) (0.71), EuroSCORE (0.58), and norepinephrine dose in mcg/kg/min (0.56). In other words, ETAC and pRBCs were in nearly all of the SSVS models; EuroSCORE and norepinephrine dose were in approximately half of the SSVS models.

A generalized additive logistic regression model analysis indicated that no transformations were necessary for those variables to achieve linearity with the logit (not shown). The five predictors together with randomization group (BIS or ETAC) were entered into binary logistic regression. The overall model was significant ($p< 0.001$), with a Nagelkerke R-square of 0.294. The Hosmer and Lemeshow lack-of-fit test was nonsignificant ($p = 0.40$), indicating appropriate model fit. Variance inflation factors (VIFs) were all less than 1.5; the average VIF was 1.16, indicating absence of substantive collinearity among the predictors. Independent predictors of postoperative delirium are in Table 4. Norepinephrine dose and randomization group were not significant in the model; however, average ETAC, units of pRBCs, ASA PS, and EuroScore were significant. A sensitivity analysis excluding patients undergoing thoracic surgery found substantively identical results (not shown).

A receiver operator characteristic curve was constructed using predicted probability of developing delirium as estimated by the binary logistic regression model. The c-statistic of the curve was 0.79 (95% CI 0.74 – 0.85; $p< 0.001$), indicating a significant improvement in predictive power over chance.

Exploratory meta-analysis

Meta-analysis of data from the three published trials and the present study (Table 5) demonstrates that BIS-guided anesthesia is associated with less risk of postoperative delirium (Figure 2), with a summary odds ratio of 0.56 (95% CI, 0.42-0.73, heterogeneity p value = 0.54).

Discussion

We found found a 9.2% nonsignificant reduction in postoperative delirium in the BIS-guided group, with both a raw and adjusted odds ratio of approximately 0.6 (Table 2, Table 4). This is consistent with other published trials (Table 5)[6-8] which, taken together, demonstrate an odds ratio of 0.56 for BIS-guided anesthesia (Figure 2). Because of the exploratory nature of the meta-analysis presented here, this finding must be viewed as preliminary. However, it does lend support to the need for a large trial to confirm or refute the effectiveness of BIS guidance in preventing delirium.

There are several plausible mechanisms by which BIS guidance could decrease postoperative delirium. One hypothesis is that electroencephalogram (EEG) or BIS guidance leads to avoidance or minimization of periods of EEG burst suppression or persistent suppression. These EEG patterns are not seen during physiological sleep and have been associated with adverse outcomes in ICU patients.[22] Results from the SuDoCo clinical trial (ISRCTN36437985) suggested that percentage of time with an intraoperative burst suppression ratio higher than zero was an independent risk factor for postoperative delirium with an estimated hazard ratio of 2.5 (95% CI, 1.23-4.91, p value = 0.01).[8] When BIS values are below 20-30, the EEG burst suppression ratio is inversely correlated with the BIS and is probably a major determinant of the BIS.[23] In the current trial, however, the patients randomized to the ETAC group and the patients who were delirious in the ICU did not have an increased proportion of intraoperative time with BIS <20 (Tables 1 and 2). Future

research should attempt to clarify how intraoperative EEGbased monitoring could decrease postoperative delirium.

Four independent predictors of postoperative delirium were identified in this study: number of units of pRBCs administered intraoperatively, ASA PS, EuroSCORE, and average ETAC. ASA PS is a subjective measure of preoperative comorbidities and patient condition, while EuroSCORE more objectively measures comorbidities and surgical risk. EuroSCORE has been identified as a significant, independent predictor of delirium risk in a cardiac surgical population, though neither study considered ASA physical status.[24,25] While some features of the EuroSCORE had to be estimated in our population, composite metrics reduce the risk of a type 1 error compared with including individual characteristics. EuroSCORE is a significant predictor of other adverse outcomes in cardiac surgical patients, including prolonged ICU length of stay[26] and mortality, both in a large multicenter population[27] and in a population from our institution.[28] While the association between ASA PS and postoperative delirium has been better studied in noncardiac surgical populations,[29,30] it is not surprising that ASA PS is related to postoperative delirium in this cardiothoracic surgical population as well. Furthermore, red blood cell transfusion has also been identified as a risk factor for postoperative delirium in cardiac surgical patients[25,31] and was confirmed to be associated with delirium risk in our population.

One of the most interesting findings of this analysis was the association between average ETAC and postoperative delirium. There are three potential explanations for this finding. First, the simple interpretation is that administering increased volatile anesthetic concentration results in protection against delirium. A second, and in our view more likely, explanation is that there may be an epiphenomenal association, whereby patients who are at risk for delirium are also treated differently intraoperatively by the anesthesia professional providing their care, as manifested by relatively lower concentrations of administered anesthetic. Our findings are consistent with a third explanation, that vulnerable patients receive a relative overdose of anesthetic drug and develop delirium. Although the dose they receive is less than that of patients who do not develop delirium, given the underlying susceptibility, it is nonetheless a relative overdose. However, if a relative overdose in vulnerable surgical patients were to increase the risk of postoperative delirium, we would expect regional anesthesia to be associated with a lower incidence of postoperative delirium than general anesthesia. A meta-analysis of small trials that randomized surgical patients to regional or general anesthesia surprisingly found no change in risk for delirium with general anesthesia (odds ratio, 0.88; 95% CI, 0.51 to 1.51).[32]

Patients with a high EuroSCORE, who were ASA PS 4, and who received more intraoperative blood transfusions, were more likely to become delirious, suggesting that delirious patients were more vulnerable to cardiovascular instability. We hypothesize that frailty is reflected in both the cardiovascular system and the brain as reduced “cognitive reserve,” which has been advanced as an encompassing theme common to many nonmodifiable risk factors for postoperative delirium.[33] Thus, cardiovascular sensitivity to anesthesia, a situation in which anesthesia professionals may therapeutically decrease volatile anesthetic delivery rates, may characterize patients at particular risk for postoperative delirium because of concomitant cognitive vulnerability. This second

hypothesis is not mutually exclusive with the third, wherein vulnerable patients receive a relative overdose of anesthesia even at concentrations much lower than those without unusual vulnerability. Biochemically, the idea of precipitating factors (e.g., surgical inflammation, anesthetic drugs) acting on a vulnerable substrate has been explored by Maclullich et al. as "maladaptive sickness behavior," where an insult to a vulnerable limbichypothalamic-pituitary axis induces an inappropriate or uncontrolled stress response, manifested as delirium.[34] Thus, patients with maladaptive stress responses may be those who are less likely to receive high concentrations of volatile anesthetics because of concomitant cardiovascular frailty.

The major limitation of this study is its small sample size, rendering it vulnerable to imprecise findings and type II error. Also, no baseline formal assessment for preexisting delirium or other cognitive screening was performed; however, patients enrolling in the BAG-RECALL trial participated in an informed consent discussion before their surgery and were deemed able to consent. Recent studies comparing CAM-ICU diagnoses of delirium to those made with DSM-IV criteria,[35] the nursing delirium screen (Nu-DeSc),[36] and even unstructured bedside nursing evaluation[37] have found lower sensitivity than previously reported, particularly in verbal patients; thus, this study may tend to underestimate delirium rates. Missing CAM-ICU assessments in our study population also may have resulted in an underestimate of delirium rates. Liberal inclusion of candidate predictors in statistical models is also subject to criticism;[16] however, we attempted to mitigate that effect by pursuing a stochastic search variable selection strategy, avoiding the use of iterative logistic regression, and using composite metrics when possible. Although our variables of interest were selected *a priori*, this statistically permissive approach produces a model which should be taken as hypothesis-generating only. This was also a single-center study conducted at a quaternary care center, and our findings might not be readily generalizable to a lower-acuity cardiothoracic surgical population.

In summary, we did not find that randomization to the BIS or ETAC-guided protocols decreased postoperative delirium in this patient population, but the results remain consistent with previous findings suggesting that BIS guidance decreases delirium after major surgery. There is therefore a need for a large randomized study to clarify whether or not EEG-guided anesthesia, with BIS or an alternative method, decreases postoperative delirium, specifically after cardiac or thoracic surgery. Furthermore, the mechanism by which EEG guidance could decrease delirium requires elucidation. The average ETAC during anesthetic maintenance, intraoperative units of pRBCs administered, EuroSCORE and ASA PS are significant independent predictors of postoperative delirium in a cardiothoracic surgical population. Some of these factors may be modifiable, and they may be usefully incorporated into clinical screens to identify patients who are at increased risk of delirium after cardiac and thoracic surgery.

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Appendix 1

Characteristics of patient cohort followed for development of delirium and those excluded for missing data or other reasons.

		Included	Excluded	*P* value
Number of patients		310	27	
Age		61.6 ± 14.1	53.8 ±14.5	0.007*
Sex	Male	194 (62.6%)	15 (55.6%)	0.47†
	Female	116 (37.4%)	12 (44.4%)	
Race	Caucasian	254 (81.9%)	22 (81.5%)	0.31†
	African-American	38 (12.3%)	5 (18.5%)	
	Other/Unknown	18 (5.8%)	0	
Alive at last follow-up		270 (87.1%)	24 (88.9%)	0.79†
BAG-RECALL study group	BIS group	149 (48.1%)	10 (37.0%)	0.27†
	ETAC group	161 (51.9%)	17 (63.0%)	
Duration of surgery (minutes)		259 ± 86	245 ±69	0.41*
Surgery with CPB		245 (78.6%)	20 (74.1%)	0.55†
ICU length of stay (days)		3 (2 – 6)	2 (1 – 6)	0.35‡
Hospital length of stay (days)		8 (6 – 12)	7 (5 – 9)	0.30‡
Type of surgery	CABG only	78 (25.2%)	9 (33.3%)	0.027†
	>1 of CABG, valve, Maze	30 (9.7%)	1 (3.7%)	
	Aortic aneurysm	40 (12.9%)	2 (7.4%)	
	Valve only	76 (24.5%)	8 (29.6%)	
	Other cardiac	47 (15.2%)	3 (11.1%)	
	Thoracic	39 (12.6%)	2 (7.4%)	
	Not cardiac or thoracic	0	2 (7.4%)	

*Student's t-test.

†chi square.

‡Mann-Whitney U test.

Abbreviations: BIS, Bispectral Index. ETAC, end-tidal anesthetic concentration.CPB, cardiopulmonary bypass.ICU, intensive care unit. CABG, coronary artery bypass graft.

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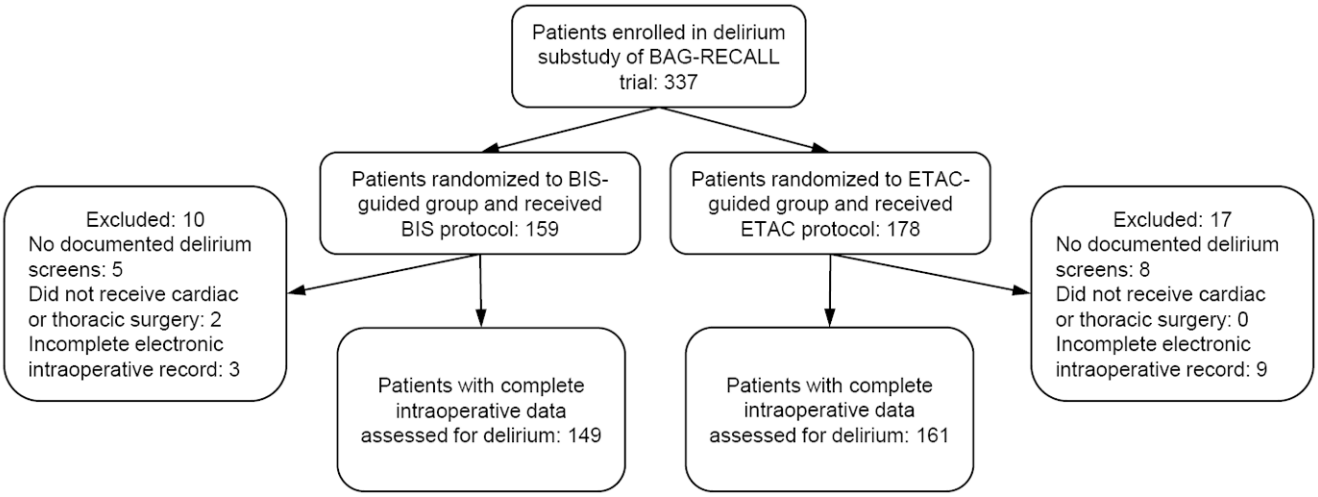

Figure 1.

Consort diagram for the study. BIS, bispectral index. ETAC, end-tidal anesthetic concentration.

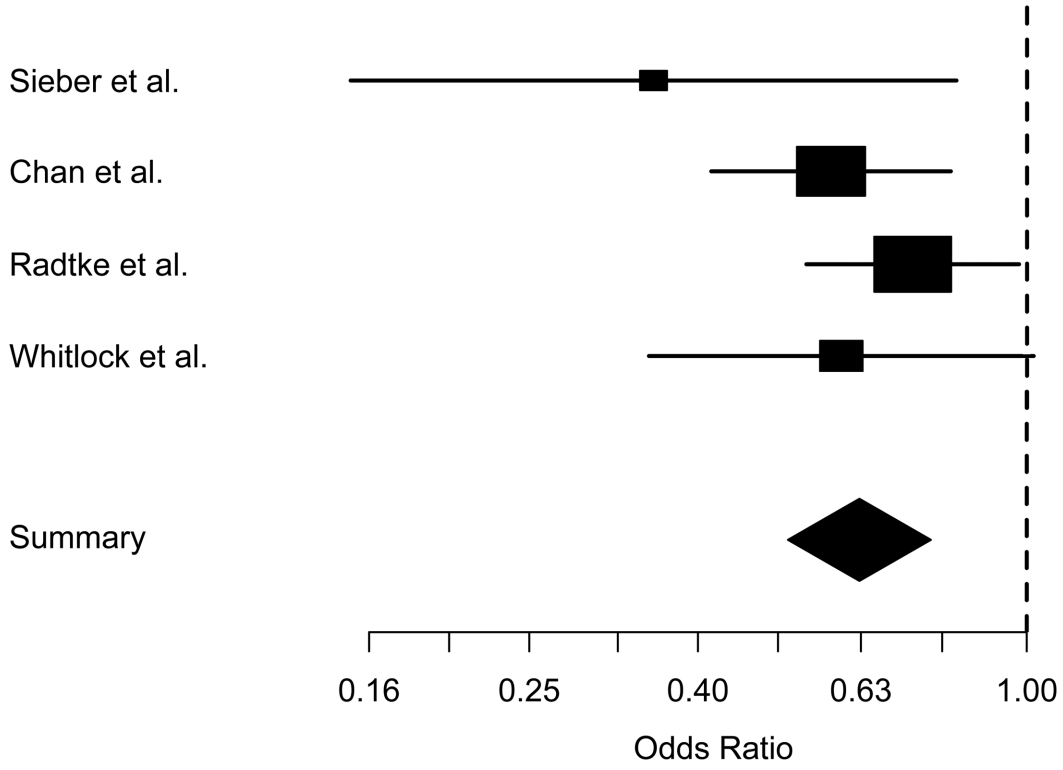

Figure 2.

Meta-analysis of randomized controlled trials assessing postoperative delirium with intraoperative Bispectral Index (BIS) guidance of anesthesia compared with an alternative approach (i.e., usual care or an alternative protocol). Odds ratios less than one favor BIS guidance.

Table 1

Comparison Between Bispectral Index (BIS) and End-Tidal Anesthetic Concentration (ETAC) Groups

		BIS (149 patients)	ETAC (161 patients)	*P* value
Age		62±14	61±14	0.55 *(2)*
Sex	Male	93	101	0.95*(1)*
	Female	56	60	
Race	Caucasian	122	132	
	African-American	18	20	0.98 *(1)*
	Other/Unknown	9	9	
Alive at last follow-up		132	137	0.36 *(1)*
Duration of surgery (minutes)		311±88	319±92	0.43 *(2)*
Surgery with CPB		119	126	0.73 *(1)*
ICU length of stay (days)		3 (1-6)	4 (2-8)	0.006 *(3)*
Hospital length of stay (days)		8 (6-13)	9 (5-16)	0.36 *(3)*
Proportion of intraoperative time with BIS <20		0 (0 – 0.036)	0 (0 – 0.024)	0.88 *(3)*
Ever experienced BIS<20		64 (43.0%)	69 (42.9%)	0.99 *(1)*
Type of surgery	CABG only	40	38	0.89 *(1)*
	>1 of CABG, valve, Maze	13	17	
	Aortic aneurysm	19	21	
	Valve only	39	37	
	Other cardiac	22	25	
	Thoracic	16	23	

(1) Chi square.

(2) T-test.

(3) Mann-Whitney U test.

Parametric data presented as mean ± standard deviation, nonparametric as median (interquartile range).

CPB, cardiopulmonary bypass. ETAC, end-tidal anesthetic concentration. ICU, intensive care unit

Table 2

Characteristics of study patients, stratified by delirium status. Univariate comparison was only performed for BIS versus ETAC group because of the randomized design of the BAG-RECALL parent trial; no further univariate "prescreening" tests were performed as discussed in the Methods section.

Descriptor		Delirious (n=73)	Nondelirious (n=237)	P value
Age		63.3±12.4	61.0±14.5	
Female sex		32 (44%)	84 (35%)	
Duration of surgery		350±83	305±90	
Type of surgery	Aorta	15	25	
	CABG only	13	65	
	Valve only	15	61	
	>1 CABG, Valve, Maze	8	22	
	Other Heart	17	30	
	Thoracic	5	34	
BIS group		28 (38%)	121 (51%)	0.058*(1)*
ASAPS 4		66 (90%)	162 (68%)	
EuroSCORE		6 (4-7)	4 (2-6)	
Units pRBCs		2 (1-4)	1 (0-2)	
Average ETAC during maintenance		0.79±0.12	0.85±0.11	
Norepinephrine dose (mcg/kg/min)		0.05 (0.01 - 0.09)	0.02 (0-0.05)	
Fentanyl dose (mcg/kg/hr)		2.40±1.83	1.93±1.30	
Daily alcohol use		5 (6.8%)	27 (11%)	
Preoperative hemoglobin		11.7±2.1	12.7±2.0	
Midazolam dose (mcg/kg/hr)		6.2 (2.6-12.5)	4.8 (1.0-8.8)	
Duration of MAP<75mmHg, BIS<45, & ETAC<0.7 MAC		13 (3.5-42.5)	10 (2-23)	
Minutes of cardiopulmonary bypass		115±63	89±65	
Duration of MAP<75		175±88	155±80	
Duration of BIS<45		212±99	202±102	
Proportion of intraoperative time with BIS <20		0 (0-0.034)	0 (0-0.026)	
Ever experienced BIS<20		33 (45.2%)	100 (42.2%)	

(1) Chi square.

Abbreviations: CABG, coronary artery bypass grafting. BIS, Bispectral Index. ASAPS, American Society of Anesthesiologists Physical status. pRBCs, packed red blood cells. ETAC, end-tidal anesthetic concentration. MAP, mean arterial blood pressure. MAC, age-adjusted minimum alveolar concentration.

Table 3

Results of stochastic search variable selection. Predictors with > 0.50 probability of inclusion, as well as the randomized intervention, were entered into a subsequent binary logistic regression.

	Variable	Probability of inclusion
Entered in binary logistic regression	Age-adjusted average MAC during maintenance	0.972
	Units pRBCs	0.923
	ASA PS 4	0.711
	EuroSCORE	0.578
	Norepinephrine dose (mcg/kg/min)	0.559
Forced into model	Assigned to BIS or ETAC group in BAG-RECALL	0.102
Not included	Fentanyl dose (mcg/kg/hour)	0.271
	Daily alcohol use	0.126
	Preoperative hemoglobin (g/dL)	0.025
	Midazolam dose (mcg/kg/hour)	0.008
	Duration of MAP < 75 mmHg, BIS < 45, and ETAC < 0.7 MAC	0.001
	Minutes of cardiopulmonary bypass	<0.001
	Duration of MAP< 75 mmHg	<0.001
	Duration of BIS < 45	<0.001

Abbreviations: MAC, minimum alveolar concentration. pRBCs, packed red blood cells. ASAPS, American Society of Anesthesiologists physical status. BIS, Bispectral Index. ETAC, end-tidal anesthetic concentration. MAP, mean arterial blood pressure.

Table 4

Independent relationships among candidate predictors including BIS or ETAC group and the outcome of postoperative delirium, using non-iterative binary logistic regression.

Variable	Binary logistic regression		
	Odds ratio	95% CI	*P* value
BIS group	0.62	0.34 – 1.15	0.127
Average maintenance ETAC (aaMAC)	0.70 (per 0.1 aaMAC increase)	0.53 – 0.92	0.010
Units pRBCs	1.26 (per 1 unit)	1.10 – 1.43	0.001
ASAPS 4 (vs 1, 2, 3)	2.88	1.18 – 6.94	0.020
EuroSCORE	1.20 (per 1 point increase)	1.07 – 1.36	0.002
Norepinephrine dose (mcg/kg/min)	Not significant; point estimate 58, CI 0.026-1.3E5		0.301

Abbreviations: CI, confidence interval. BIS, Bispectral Index. ETAC, end-tidal anesthetic concentration. aaMAC, age-adjusted minimum alveolar concentration. pRBCs, packed red blood cells. ASA PS, American Society of Anesthesiologists Physical Status.

Table 5

Published trials randomizing patients to BIS-guided anesthesia or usual care or another comparator for reduction of postoperative delirium

Study	Patient population	Group 1 (n)	Group 2 (n)	Odds ratio for delirium (group 1 vs group 2)
Sieber et al.(7), 2010	≥65yo, hip fracture repair under spinal anesthesia with propofol sedation	BIS ≥ 80 (57)	BIS ≈ 50 (57)	0.35 (0.15-0.82)
Chan et al.(6), 2013	>60yo, elective major noncardiac surgery	BIS-guided (450)	Routine care (452)	0.58 (0.41-0.80)
Radtke et al.(8), 2013	>60yo, elective major noncardiac surgery	BIS-guided (575)	Routine care (580)	0.73 (0.54-0.98)
Whitlock et al. (present article)	Elective cardiac and thoracic surgery	BIS-guided (149)	ETAC-guided (161)	0.60 (0.35-1.02)
Meta-analysis of the above studies		(1231)	(1250)	0.56 (0.42-0.73)