# A Randomized Controlled Trial of Anesthesia Guided by Bispectral Index Versus Standard Care: Effects on Cognition

***Zohn Centimole, PhD, CRNA***
***John Eichhorn, MD***
***Susan K. Frazier, PhD, RN, FAHA***
***Gregory A. Jicha, MD, PhD***
***Mary Kay Rayens, PhD***
***John F. Watkins, PhD***
***Sarah F. Centimole, MA***
***Debra K. Moser, PhD, RN, FAAN***

*Postoperative cognitive dysfunction, a subtle deterioration of cognitive function after exposure to anesthetics, is reported in 10% to 50% of surgical cases. Delivery of excessive inhalation anesthetics based on minimum alveolar concentration produces greater deep hypnotic times, which may contribute to postoperative cognitive dysfunction. This study tested the impact on cognitive function of balanced anesthetic using electroencephalographic (EEG) guidance vs usual anesthesia. We studied 88 surgical patients: 45 randomly assigned to balanced anesthetic technique with EEG guidance and 43 to standard treatment. Cognitive function was evaluated with the Cambridge Neuropsychological Test Automated Battery-Mild Cognitive Impairment at 3 intervals (preoperatively, 3-5 days postoperatively, and 3-5 months postoperatively). Additionally, 37 age- and sex-matched individuals not undergoing surgery or anesthesia were evaluated at the same intervals. Better outcomes were seen in the intervention group compared with usual care in the short-term/visual memory cognitive domain (P = .02) at 3 to 5 days, but not at 3 to 5 months. Delivery of anesthesia using EEG monitoring systems can reduce cumulative deep hypnotic time without negatively affecting patient physiologic stress, surgical conditions, or cognitive function. Our findings provide data to support optimal anesthetic approaches to improve cognitive function after anesthesia with volatile anesthetics.*

***Keywords:*** Anesthesia technique, mild cognitive impairment, postoperative cognitive dysfunction.

Postoperative cognitive dysfunction (POCD) is a subtle deterioration of cognitive function observed after surgical procedures with anesthetics. In POCD, deficits in advanced cognitive function and memory continue after appropriate anesthetic drug half-lives have expired.[1] The incidence of POCD ranges from 10% to 50% depending on definitions, study designs, sample sizes, and neurocognitive measures used.[2,3] This cognitive decline is associated with increased 1-year mortality as well as morbidity and family/caregiver stress.[4] Socially, these deficits also lead to earlier retirement and greater reliance on social financial support systems.[5]

Inhalation anesthetics have neuropathogenic effects similar to the changes seen in dementias, including Alzheimer disease (AD).[6-9] Mild cognitive impairment (MCI) is a prodromal classification of the dementias, affecting cognitive domains similarly to POCD.[10] Based on the known properties of inhalation anesthetics, researchers have suggested that anesthetic techniques with greater cumulative deep hypnotic time result in a greater degree of POCD.[11,12] It is possible to decrease cumulative deep hypnotic time by using derived electroencephalographic (EEG) monitoring to titrate volatile anesthetics, but this method is not yet standard therapy.[11,12] One of the major modalities for delivering EEG-guided anesthesia is the Bispectral Index (BIS, Covidien, now Medtronic). To provide rigorous data on the neurocognitive outcomes associated with BIS-guided anesthesia, we conducted a randomized controlled trial of BIS-guided anesthesia vs standard anesthesia care using concentration-guided techniques.

The aim of this study was to determine the impact of BIS-guided anesthesia vs standard anesthesia care on neurocognitive scores from preoperative baseline, 3 to 5 days postoperatively, and 3 to 5 months postoperatively between individuals undergoing anesthetic for surgical procedures lasting longer than 2 hours. We hypothesized that BIS-guided anesthesia compared with standard anesthesia care will result in less postoperative cognitive impairment.

## Methods

• ***Design.*** This study was a prospective, randomized controlled trial. Parallel study groups underwent anesthesia

for select surgical procedures. Study participants (N = 88) were randomly assigned to BIS-guided anesthesia (group 1, n = 45) or standard anesthesia care (group 2, n = 43). The standard anesthesia care group underwent anesthesia with inhalation anesthetics titrated around minimum alveolar concentration (MAC) values. Patients in the BIS-guided anesthesia group underwent titration using BIS. We used BIS in a tight reference range to avoid deep anesthesia (ie, BIS < 40) by maintaining a BIS range of 45 to 60. Participants completed the Cambridge Neuropsychological Test Automated Battery–Mild Cognitive Impairment (CANTAB-MCI) at 3 intervals: preoperatively, at 3 to 5 days postoperatively, and at 3 to 5 months postoperatively. This state-of-the-art, highly sensitive neurocognitive testing system is easy for patients of all ages to use and has been shown to obtain valid and reproducible outcomes.[13-16]

• ***Sample and Setting.*** Patients aged 45 to 70 years undergoing general anesthesia for an elective surgical procedure scheduled to last approximately 2 hours at an academic medical center who met selection criteria and agreed to participate were eligible for enrollment. After baseline data collection, computer randomization was used to randomly assign patients to receive general anesthesia with either BIS-guided anesthesia or standard anesthesia care.

Inclusion criteria for participants was assessment as ASA classes 1 through 4 and scheduled for surgeries requiring general endotracheal anesthesia with a neuromuscular paralytic agent. Only participants successfully completing the Motor Screening Task test from the CANTAB-MCI were invited to participate in the study.

We excluded individuals with substantial cardiorespiratory or other end-organ disease (ie, unstable angina, uncontrolled diabetes, severe peripheral vascular disease), inadequate English, and/or substance abuse. We also excluded individuals with preexisting neurologic diseases as well as neurosurgical candidates. These exclusion criteria were chosen because these types of patients have a known high potential for cognitive impairment unrelated to POCD or for postoperative complications that introduce potential confounders.

Patients were referred to the study by physicians and/or nurse practitioners working in the Preoperative Clinic and by surgeons in the medical center. Study staff recruited individuals who fit the inclusion and exclusion criteria after completing a preoperative screening interview.

• ***Intervention.*** Anesthetic technique for both surgical groups included standard induction with available agents, neuromuscular paralysis guided by a nerve stimulator, inhalation anesthetic, and intraoperative monitoring in accordance with the guidelines of the medical center's Department of Anesthesiology and the ASA. Invasive monitoring, including arterial pressure, and central venous pressure was performed at the discretion of the anesthesia provider.

The BIS monitors were applied to both groups. The anesthesia provider for patients in the standard anesthesia care group did not see the BIS values. Titration and administration of anesthesia were performed according to standard clinical practice. In the BIS-guided anesthesia group, the anesthesia provider titrated the volatile anesthetic to maintain a BIS range of 45 to 60, but not less than 0.5 age-adjusted MAC, as measured by the Apollo anesthesia machine version 4.1 (Draeger).

Physicians and nurse anesthetists who volunteered for the study underwent a well-defined training period and used well-defined anesthetic plans. Data were collected from the anesthetic record after each case. Intraoperatively, anesthesia clinicians could have aborted the study protocol as they deemed necessary for participant stability and safety, but this never occurred.

## Measures

• ***Demographic and Clinical Data.*** The following patient demographic variables were collected by an interview-based questionnaire: age, sex, race/ethnicity, marital status and whether the patient lives alone, education level, and annual income.

The ASA classification, previous anesthetics, current medication regimen, drugs used during surgery, physical examination findings, total intraoperative anesthetic time, perioperative narcotic exposure, and comorbidities were obtained from the anesthetic record. Inhalation anesthetic type as well as inspired and expired concentrations were recorded, as were BIS scores.

• ***Neurocognitive Testing.*** The CANTAB-MCI system was used to measure cognitive function and is a computerized, touch screen–based group of 5 tests. The CANTAB-MCI battery includes the Motor Screening Task, Delayed Matching to Sample, Rapid Visual Information Processing, Paired Associates Learning, and Reaction Time. Tests are scored by the number of correct responses and/or time to complete the task as appropriate. The Motor Screening Task (2 minutes) is a simple introduction to the touch screen. This task functions as a screening test for visual, movement, and comprehension difficulties. Inability of the subject to complete the Motor Screening Task rendered that person ineligible for use of the CANTAB-MCI. None of our patients were excluded based on the Motor Screening Task result.

The CANTAB-MCI was used to measure cognitive function in 4 domains: memory, attention, short-term/visual memory, and speed of processing.

• *Memory Domain.* The Delayed Matching to Sample (10 minutes) was used to assess cognition in the memory domain for nonverbalizable patterns, testing both simultaneous and short-term visual memory domains. Our outcome measure was the Delayed Matching to Sample percent correct.

• *Attention Domain.* Testing with the Rapid Visual

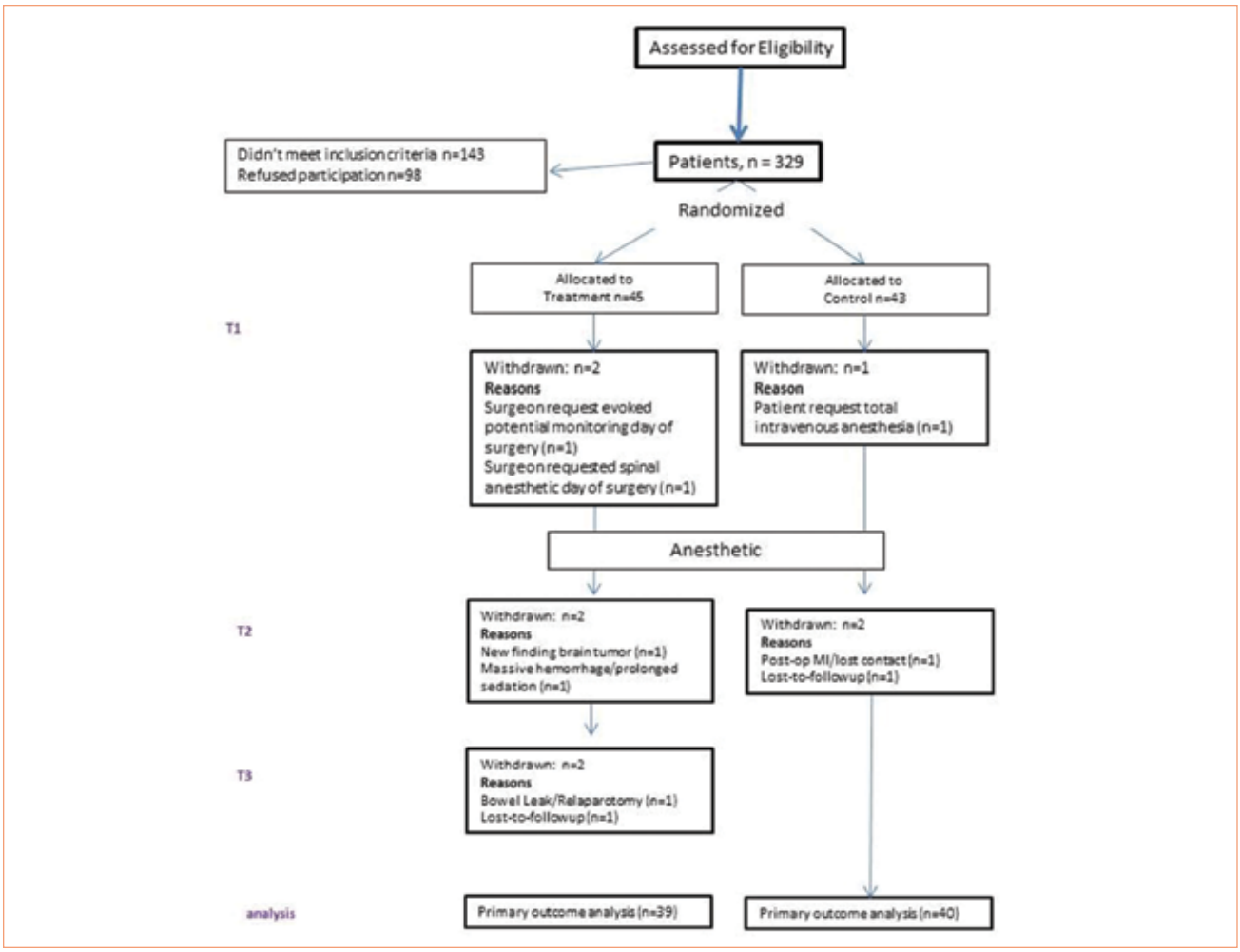


**Figure 1.** CONSORT Diagram of Patient Flow Through the Study
Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; MI, myocardial infarction; post-op, postoperative.

Information Processing (7 minutes) sustained attention by assessing ability to recall a sequence of digits. Inability to sustain attention is a characteristic of delirium; thus, this measure assists in the differentiation of dementia or MCI from delirium. The Rapid Visual Information Processing is sensitive for the visual sustained attention domain. We used 2 outcome measures to reflect this domain: Rapid Visual Information Processing A′ (A prime) and Rapid Visual Information Processing median latency.

• *Short-Term/Visual Memory Domain.* The Paired Associates Learning (10 minutes) was used to assess the short-term/visual memory domain. The Paired Associates Learning is useful for assessing individuals with questionable dementia, MCI, AD, and age-related memory loss. Patients are asked to associate visual patterns that cannot be verbalized with spatial locations on the computer screen. We used 2 outcome measures to reflect this domain: Paired Associates Learning total errors 6 shapes adjusted and Paired Associates Learning total errors adjusted.

• *Speed of Processing Domain.* The final domain test is the Reaction Time (5 minutes). The Reaction Time is a speed of processing/latency domain task with a comparative history (the 5-choice task) and uses a procedure to separate response latency from movement time. This allows for control for participants with tremor. We used 4 outcome measures to reflect this domain. The Reaction Time mean simple reaction time and the Reaction Time median simple reaction time measure the speed at which the participant releases the press pad button in response to a stimulus. Reaction Time median simple movement time is the time, measured in milliseconds, taken to touch the stimulus after the press pad has been released in response to a single stimulus. This is a measurement of the motor speed and is sensitive for slowing. Reaction Time median 5-choice movement is the median of the measurement of speed with which the press pad button is released in response to a stimulus in any of 5 locations.

To demonstrate that the CANTAB-MCI does not change across a 3-month period as a result of repeated testing and without some neurologic event, we enrolled 37 older adults who were not undergoing surgery to take the CANTAB-MCI at 3 time points (ie, baseline, 3-7 days,

| Characteristic | Total (N = 79) | BIS-guided anesthesia (n = 39) | Standard anesthesia (n = 40) | *P* |
|---|---|---|---|---|
| Age, years, mean (SD) | 59.1 (6.6) | 59.6 (6.8) | 58.5 (6.4) | .456 |
| Female sex, No. (%) | 50 (63.3) | 24 (61.5) | 26 (65.0) | .818 |
| Race/ethnicity, No. (%) | | | | .550 |
| White | 73 (92.4) | 35 (89.7)) | 38 (95.0) | |
| African American | 4 (5.1) | 2 (5.1) | 2 (5.0) | |
| Other | 2 (2.6) | 2 (5.1) | 0 (0) | |
| Education, No. (%) | | | | .201 |
| High school or some college | 55 (69.6) | 13 (33.3) | 15 (37.5) | |
| College graduate or greater | 24 (30.4) | 26 (66.7) | 25 (62.5) | |
| Annual income, $, No. (%) | | | | .399 |
| < 25,000 | 21 (26.6) | 8 (20.5) | 13 (32.5) | |
| 25,001-75,000 | 35 (44.3) | 21 (53.8) | 14 (35.0) | |
| > 75,001 | 23 (29.1) | 10 (25.6) | 13 (32.5) | |
| Currently married, No. (%) | 54 (68.4) | 28 (71.8) | 26 (65.0) | .630 |
| Body mass index, kg/m$^2$, mean (SD) | 32 (8.1) | 31.4 (7.6) | 32.7 (8.6) | .489 |
| Anesthetic vapor, No. (%) | | | | .808 |
| Sevoflurane | 4 (5.1) | 2 (5.1) | 2 (5.0) | |
| Desflurane | 50 (63.3) | 26 (66.7) | 24 (60.0) | |
| Isoflurane | 25 (31.6) | 11 (28.2) | 14 (35.0) | |
| Premedication, No. (%) | | | | .084 |
| None | 29 (36.7) | 12 (30.8) | 17 (42.5) | |
| Midazolam | 13 (16.5) | 4 (10.3) | 9 (22.5) | |
| Opioid | 37 (46.9) | 23 (59.0) | 14 (35.0) | |
| Anesthesia time, h:min, mean (SD) | 3:30 (0:58) | 3:27 (0:57) | 3:32 (0:59) | .71 |
| ASA physical status, No. (%) | | | | .823 |
| 2 | 37 (46.8) | 19 (48.7) | 18 (45.0) | |
| 3 | 42 (36.5) | 20 (51.3) | 22 (55.0) | |
| Baseline SBP, mm Hg, mean (SD) | 134 (15.8) | 133 (17.1) | 136 (14.5) | .387 |
| Surgical procedure, No. (%) | | | | .394 |
| Open abdominal | 20 (25.3) | 9 (23.1) | 11 (27.5) | |
| Laparoscopic/other | 13 (16.5) | 9 (23.1) | 4 (10.0) | |
| PLIF | 31 (39.2) | 13 (33.3) | 7 (17.5) | |
| Minimally invasive back | 15 (19.2) | 8 (20.5) | 18 (45.0) | |
| Medical history, No. (%) | | | | |
| Anxiety/depressive disorder | 15 (17.4) | 8 (18.2) | 7 (16.7) | > .999 |
| Coronary artery disease | 12 (14.0) | 6 (13.6) | 6 (14.3) | > .999 |
| Obstructive sleep apnea | 20 (23.3) | 13 (29.6) | 7 (16.6) | .36 |
| Diabetes | 22 (27.6) | 11 (25.0) | 11 (26.2) | .82 |
| Tobacco abuse, No. (%), N = 86 | | | | .701 |
| None | 41 (47.7) | 20 (45.5) | 21 (50.0) | |
| Current/former abuse | 45 (52.3) | 24 (54.5) | 21 (50.0) | |

**Table 1.** Comparison of Baseline Characteristics Between Two Study Arms (N = 79)[a]
Abbreviations: BIS, Bispectral Index; PLIF, posterior lateral interbody fusion spine; SBP, systolic blood pressure.
[a]Some percentages do not total to 100 because of rounding.

and 3 months). They were of similar age, gender, education level, income level, race-ethnicity, and marital status as the surgical groups. Their mean (SD) age was 60 (7) years, and 68% were female. Examination of their data revealed no changes across any of the time points in any components of the cognitive testing (data not shown).

• ***Protocol.*** The study was carried out after approval was obtained from the appropriate university institutional review board, and after informed consent was received. After successful completion of the screening Motor

| | Inspired concentration, mean (SD) | | | Expired concentration, mean (SD) | | |
|---|---|---|---|---|---|---|
| **Anesthetic vapor** | **Intervention** | **Control** | ***P*** | **Intervention** | **Control** | ***P*** |
| Sevoflurane | 1.8 (0.12) | 2.5 (0.35) | .025 | 1.5 (0.35) | 2.0 (0.20) | .36 |
| Desflurane | 4.4 (0.84) | 6.1 (1.0) | < 0.001 | 3.8 (0.63) | 5.6 (1.9) | .008 |
| Isoflurane | 1.5 (0.86) | 1.9 (0.37) | < 0.001 | 1.1 (0.78) | 1.2 (0.19) | .25 |

**Table 2.** Mean Concentration of Inspired and Expired Vapor Used During Anesthesia Compared Between Intervention and Control (Standard Anesthesia) Groups

Screening Task, a full consent form was completed when the patient agreed to participate. The CANTAB-MCI battery was administered at baseline after consent was given (test time 1). A version of the battery was administered on postanesthetic days 3 to 5 (test time 2), in the patient's hospital room, surgical clinic, or location convenient to the patient. Three to 5 days is an appropriate period that would ensure the drug half-lives have expired. The battery was again administered at 3 to 5 months (test time 3) at a location convenient to the patient.

• ***Data Analysis.*** Data analysis included a descriptive summary, including means and standard deviations or frequency distributions, as appropriate. Comparisons of the groups at baseline was done using 2-sample *t* tests, $\chi^2$ tests of association, or analysis of variance (ANOVA).

To address the specific aim, we used a 2-way mixed design (ie, 1 within-subjects variable [time] and 1 between-subjects variable [group]) repeated-measures ANOVA. Each of the assumptions of repeated-measures ANOVA (no significant outliers, the dependent variable is approximately normally distributed for each level of the independent variable, and sphericity) was tested. The only violation across the various dependent measures was violation of the sphericity assumption, which was managed with use of adjusted *P* values based on the Greenhouse-Geisser method. When a significant interaction was found, post hoc testing was done. Additionally, a sensitivity analysis was performed using mixed modeling. Data analysis was conducted using SPSS version 22 (IBM Corp); an $\alpha$ level of < .05 used throughout.

With an $\alpha$ level of .05 and 34 individuals in each group, the power of the repeated-measures ANOVA *F* test to detect a significant main effect or interaction was at least 80%, assuming that the ratio of group means to the standard deviation of the observations in the populations was at least 0.25. Cohen[17] considers this a medium effect size. This power analysis was conservative because the methods used to estimate the repeated-measures models (namely mixed modeling) is robust with respect to missing data, as long as they are missing at random. Power analysis was conducted with sample size software (nQuery Advisor, v.6.02 Statsols).

## Results

We screened patients from October 2014 through June 2015, with the last follow-up completed in September 2015. Of the 329 patients eligible for enrollment, 143 did not meet eligibility criteria and 98 chose not to participate (Figure 1). Of the 88 patients scheduled for surgery who were enrolled, 45 were randomly assigned to the BIS-guided anesthesia arm and 43 to the control arm of standard anesthesia care. There was no difference in the rate of withdrawal from the 2 surgical groups (*P* = .33). Patients who withdrew from the study were not significantly different from patients who remained in the study on demographic or clinical characteristics measured at baseline, including time 1 CANTAB-MCI scores.

Demographic and clinical characteristics of patients by total sample and group assignment are summarized in Table 1. There were no significant differences between the 2 groups on any demographic or clinical characteristic.

• ***Anesthetic Vapor.*** Demonstrating the expected difference between the BIS-guided and standard anesthesia care groups, there were significant differences in mean concentration of inspired vapors between the groups (Table 2). The mean inspired concentrations of anesthesia vapor were lower in the BIS-guided group.

• ***Safety.*** With regard to safety of the intervention, there were no adverse effects seen in either group intraoperatively. Satisfactory anesthesia was provided for every patient in both groups. There were no instances of operative recall in either group at 3 to 5 days or 3 to 5 months postoperatively, even in the intervention group with age-adjusted MAC levels as low as 0.5.

• ***Effect of EEG-Guided Therapy vs Standard Anesthesia.*** The impact of the intervention on cognitive function was measured in 4 cognitive domains: memory (Delayed Matching to Sample percent correct), attention (Rapid Visual Information Processing A′ and Rapid Visual Information Processing median latency), visual memory (Paired Associates Learning total errors 6 shapes adjusted and Paired Associates Learning total errors adjusted), and speed of processing (Reaction Time mean and median simple reaction times, Reaction Time median simple movement time, and Reaction Time median 5-choice movement).

• *Memory.* There was no group by time interaction effect for the outcome Delayed Matching to Sample percent correct, demonstrating that memory scores across time were not different between the groups (Table 3).

• *Attention.* For both indicators of this domain, Rapid Visual Information Processing A′ (*P* = .58) and Rapid

| Neurocognitive test and domain | Time | BIS-guided, mean (SD) | Standard anesthesia, mean (SD) | Overall *P* value interaction of group by time |
|---|---|---|---|---|
| Memory (nonverbalizable/patterns) | | | | |
| DMS percent | Baseline | 85.6 (10.0) | 81.7 (11.5) | |
| correct | Time 2 | 83.1 (12.6) | 78.3 (16.7) | .74 |
| | Time 3 | 82.7 (12.0) | 80.3 (13.1) | |
| Memory (short-term/visual) | | | | |
| PAL total errors | Baseline | 39.4 (34.4) | 41.6 (32.1) | |
| adjusted | Time 2 | 34.7 (29.6) | 57.4 (43.7) | .02 |
| | Time 3 | 25.7 (21.8) | 33.2 (30.5) | |
| PAL total errors | Baseline | 12 (10.1) | 11.3 (9.6) | |
| 6 shapes | Time 2 | 7.5 (9.9) | 13.6 (12.5) | .02 |
| adjusted | Time 3 | 6.6 (5.9) | 8.3 (9.3) | |
| Attention (visual sustained) | | | | |
| RVP A´ | Baseline | 0.88 (0.05) | 0.87 (0.06) | |
| | Time 2 | 0.87 (0.06) | 0.85 (0.07) | .58 |
| | Time 3 | 0.89 (0.05) | 0.89 (0.06) | |
| RVP median | Baseline | 444.1 (114.6) | 451.8 (150.1) | |
| latency | Time 2 | 498.3 (179.0) | 518.8 (218.3) | .55 |
| | Time 3 | 457.4 (150.8) | 439.5 (137.7) | |
| Processing speed/ latency | | | | |
| RTI mean simple | Baseline | 347.4 (103.7) | 349.6 (92.7) | |
| Reaction Time | Time 2 | 390 (88.4) | 438.6 (117.7) | .03 |
| | Time 3 | 362 (121.5) | 343.5 (67.5) | |
| RTI median | Baseline | 309.3 (54.7) | 316.4 (59.1) | |
| simple Reaction | Time 2 | 355.7 (61.6) | 394 (84.4) | .07 |
| Time | Time 3 | 312.6 (56.1) | 319 (51.4) | |
| RTI median | Baseline | 590.9 (332.4) | 522.3 (130.8) | |
| simple | Time 2 | 576.3 (145.2) | 615.7 (216.4) | .15 |
| movement time | Time 3 | 494.9 (86.9) | 485.7 (97.4) | |
| RTI median 5- | Baseline | 545.4 (202.9) | 507.6 (118.4) | |
| choice | Time 2 | 567.7 (144.6) | 640.4 (266.5) | .06 |
| movement | Time 3 | 486.1 (84.7) | 474.1 (94.0) | |

**Table 3.** Neurocognitive Function Scores Between Two Surgical Groups Across Time
Abbreviations: BIS, Bispectral Index; DMS, Delayed Matching to Sample; PAL, Paired Associates Learning; RTI, Reaction Time; RVP, Rapid Visual Information Processing.

Visual Information Processing median latency ($P$ = .55), there was no group by time interaction (see Table 3).

• *Short-Term/Visual Memory Domain.* There was a significant group by time interaction in the overall test for both indicators, Paired Associates Learning total errors 6 shapes adjusted ($P$ = .02) and Paired Associates Learning total errors adjusted ($P$ = .02), of this domain (see Table 3).

Post hoc testing revealed that with regard to the Paired Associates Learning total errors 6 shapes adjusted, the scores between the 2 groups were similar at baseline ($P$ = .75), but the trajectory across time diverged at time 2 ($P$ = .019) in that the BIS-guided group had better (lower) scores than did the standard anesthesia care group (Figure 2) after surgery. In the BIS-guided group, there was a significant improvement in scores between times 1 and 2 ($P$ = .016) and between times 1 and 3 ($P$ = .001). At time 3, there were no differences between groups ($P$ = .32).

In regard to Paired Associates Learning total errors adjusted, post hoc testing revealed that the scores between the 2 groups were similar at baseline ($P$ = .76) and at time 2 ($P$ = .21). At time 3, the groups diverged ($P$ = .01), with the BIS-guided group having better (lower) scores than the standard anesthesia care group had. The BIS-guided group demonstrated a significant improvement in scores between times 1 and 2 ($P$ = .01) and times 2 and 3 ($P$ = .07).

• *Speed of Processing/Latency.* The indicator Reaction

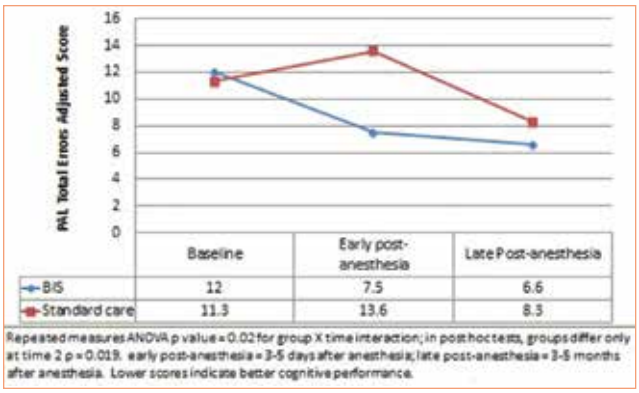


**Figure 2.** Paired Associates Learning (PAL) Total Errors 6 Shapes Adjusted Across Time by Group

Abbreviations: ANOVA, analysis of variance; BIS, Bispectral Index; early post-anesthesia, 3-5 days after anesthesia; late post-anesthesia, 3-5 months after anesthesia.

Time mean simple reaction time demonstrated a significant group by time interaction ($P$ = .03). None of the other indicators were found to have significant group by time interactions (see Table 3). Regarding these 3, Reaction Time median simple reaction time ($P$ = .07), Reaction Time median simple movement time ($P$ = .15), and Reaction Time median 5-choice movement time ($P$ = .06), there were no group by time interactions (see Table 3). There was a main effect of time for all 4 ($P$ < .001, $P$ < .001, $P$ = .001, and $P$ < .001, respectively).

Post hoc testing revealed that in regard to the Reaction Time mean simple reaction time, the scores between the 2 groups were similar at baseline ($P$ = .92), but the trajectory across time diverged at time 2 ($P$ = .04) in that the BIS-guided group had better (lower) scores vs the standard anesthesia care group. At time 3, there were again no differences between groups ($P$ = .4).

Mixed modeling was used to perform a sensitivity analysis. Our findings were unchanged.

## Discussion

We examined the impact of BIS-guided anesthesia on cognitive outcomes using a state-of-the art neurocognitive testing computerized platform and, unlike others, we tested specific cognitive domains. We demonstrated significantly lower volatile anesthesia exposure in the intervention group (BIS-guided anesthesia) compared with the standard anesthesia care group. We demonstrated the safety of the intervention in that there were no adverse events associated with its use. We also demonstrated cognitive decline in the visual memory domain in the standard anesthesia care group vs BIS-guided anesthesia group in the 3- to 5-day postsurgery period compared with baseline, but not at the 3- to 5-month period. This reflects that POCD occurs in specific domains but may be time limited, reflecting the findings of some previous studies.[3,4]

Reflecting the main effect of time seen in the regression analyses with both the 2 surgical groups alone, and the 3 group analyses, both surgical groups demonstrated postoperative depression in cognitive function in every outcome measure (with the exception of Delayed Matching to Sample), but in every instance, the standard anesthesia care group's was more pronounced. These findings indicate there is a higher cognitive obstacle in the memory domains encountered by patients exposed to a higher cumulative dose of volatile anesthetic. The outcome measures Paired Associates Learning total errors adjusted and Paired Associates Learning total errors 6 shapes adjusted were both found to be statistically significant. The Paired Associates Learning component of the CANTAB-MCI battery reflects the greatest impairment and severity of dysfunction in MCI and AD.[18] The finding of Paired Associates Learning total errors adjusted is of greatest concern because of a close relationship with amnestic MCI.[19] Hippocampal atrophy and loss of function is a known pattern beginning in MCI and advancing in AD. The recall of objects in space is a process involving the hippocampus directly tested in the Paired Associates Learning.[20] Junkkila and colleagues[19] found that the Paired Associates Learning total errors adjusted variable accounted for the largest difference between amnestic MCI and mild AD. This outcome measure reflects a significant cognitive decline in the visual memory domain. The association of these findings and the known neuropathologic inflammatory sequel of these anesthetics suggest these volatile anesthetics are not benign.

The memory impairments noted in our study with the use of standard anesthesia not guided by EEG have the potential to adversely influence patient discharge. If patients have memory impairments, they will be unable to adequately process and remember important discharge instructions. Even when instructions are written, they are very commonly standard instructions that lack the specificity and detail needed for each individual patient. Patients and family members have substantial difficulty remembering instructions even under ideal situations,[21] and our results suggest that most middle-aged and older postoperative patients have enough POCD to impair their ability to retain the information needed for successful discharge and recovery.

Our findings differ from two of the most recent studies investigating use of derived EEG guidance as a means to reduce the incidence of POCD. A large German study led by Radtke et al[22] failed to find a significant difference in POCD between derived EEG guidance and standard anesthesia care at day 7 ($P$ = .372) nor day 90 ($P$ = .062). Our study differs in that we used volatile anesthetics exclusively for maintenance, rather than introducing macromolar anesthetics (propofol), which could be considered a confounder. Other differentiation between the studies was that we used the complete CANTAB-MCI battery and examined differences in specific domains that

we explicated a priori. Previous investigators who used the CANTAB-MCI reported cognitive function as a global phenomenon (despite the fact that the CANTAB-MCI has no such measures), failing to take advantage of the precision offered by assessing cognitive function in domains. The CANTAB-MCI battery was designed for sensitivity in MCI, which shares affected domains with POCD. Radtke and colleagues used 3 CANTAB pretests of pattern recognition memory, spatial recognition memory, and choice reaction time. Pattern recognition memory and spatial recognition memory are designed to help prepare for the more robust Paired Associates Learning test. The remainder of their battery consisted of tests administered orally (a visual-verbal learning test and the Stroop Color-Word Test).[22] Although the number of patients in their study was respectable (n = 1,155), the differences in methods could easily account for the different findings.

The second of the derived EEG guidance studies before ours, by Chan et al,[12] found higher levels of POCD at 3 months ($P$ = .02) rather than 1 week ($P$ = .06), opposite to the findings of our study and much of the previous literature. Although the findings are similar in that BIS-monitored care demonstrates less POCD, the dramatic difference in early vs late findings could be related to the neurocognitive battery used in the trial by Chan et al. In addition, similar to Radtke and associates,[22] there were a number of patients (n = 99, 11%) who received macromolar anesthetic maintenance (propofol), presenting confounders.

Although our study had the strength of being a randomized controlled study, it has limitations. The primary limitation was the smaller sample size, which limited our ability to determine any heterogeneity of treatment effect because we could not perform subgroup analyses.

Nevertheless, our study represents the first use of the complete CANTAB-MCI battery in a study of POCD. The CANTAB-MCI was developed and tested in populations with MCI. Our study demonstrates that the CANTAB-MCI is sensitive enough to detect cognitive changes in the surgical anesthetic population. The study has demonstrated ease-of-use and no burden for users in the perioperative environment. The BIS monitor allowed for anesthetic titration to low levels without experiencing an episode of recall. This study provides empirical evidence to support previous authors' recommendations of BIS-guided titration as effective for POCD, especially in individuals over 60 years of age.[23]

## Conclusion

This study provides important data on patient neurocognitive outcomes that will assist anesthesia providers to make evidence-based decisions about the optimal anesthetic techniques to promote best patient outcomes. Careful titration, as guided by the BIS monitor, by experienced anesthetic providers can lead to a measurable improvement in patient outcomes. Taken in concert with previous findings, our results suggest that BIS-guided anesthesia is safe, results in lower total overall volatile anesthetic exposure, and leads to fewer disturbances in cognitive function; thus, BIS-guided anesthesia should be considered by more providers as the standard of care.

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## AUTHORS

Zohn Centimole, PhD, CRNA, is a staff anesthetist at the University of Kentucky Albert B. Chandler Medical Center, Lexington, Kentucky. This trial was conducted in partial fulfillment of requirements for the degree of Doctor of Philosophy at the University of Kentucky College of Nursing, Lexington, Kentucky.

John Eichhorn, MD, is a professor of anesthesiology at the University of Kentucky, Lexington, Kentucky.

Susan K. Frazier, PhD, RN, FAHA, is an associate professor and PhD program director in the University of Kentucky College of Nursing.

Gregory A. Jicha, MD, PhD, is a professor of neurology, director of clinical research activities, and senior investigator in the Sanders-Brown Center on Aging at the University of Kentucky.

Mary Kay Rayens, PhD, is a biostatistician and professor in the University of Kentucky College of Nursing.

John F. Watkins, PhD, is a professor and director of graduate studies in the Graduate Center for Gerontology at the University of Kentucky.

Sarah F. Centimole, MA, is a certified CANTAB test administrator and researcher at the University of Kentucky.

Debra K. Moser, PhD, RN, FAAN, is a professor and endowed chair of nursing in the University of Kentucky College of Nursing.

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