Prevention of intraoperative awareness in a high-risk surgical population

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Prevention of Intraoperative Awareness in a High-Risk Surgical Population


**ABSTRACT**

**BACKGROUND**
Unintended intraoperative awareness, which occurs when general anesthesia is not achieved or maintained, affects up to 1% of patients at high risk for this complication. We tested the hypothesis that a protocol incorporating the electroencephalogram-derived bispectral index (BIS) is superior to a protocol incorporating standard monitoring of end-tidal anesthetic-agent concentration (ETAC) for the prevention of awareness.

**METHODS**
We conducted a prospective, randomized, evaluator-blinded trial at three medical centers. We randomly assigned 6041 patients at high risk for awareness to BIS-guided anesthesia (with an audible alert if the BIS value was <40 or >60, on a scale of 0 to 100, with 0 indicating the suppression of detectable brain electrical activity and 100 indicating the awake state) or ETAC-guided anesthesia (with an audible alert if the ETAC was <0.7 or >1.3 minimum alveolar concentration). In addition to audible alerts, the protocols included structured education and checklists. Superiority of the BIS protocol was assessed with the use of a one-sided Fisher’s exact test.

**RESULTS**
A total of 7 of 2861 patients (0.24%) in the BIS group, as compared with 2 of 2852 (0.07%) in the ETAC group, who were interviewed postoperatively had definite intraoperative awareness (a difference of 0.17 percentage points; 95% confidence interval [CI], −0.03 to 0.38; P=0.98). Thus, the superiority of the BIS protocol was not demonstrated. A total of 19 cases of definite or possible intraoperative awareness (0.66%) occurred in the BIS group, as compared with 8 (0.28%) in the ETAC group (a difference of 0.38 percentage points; 95% CI, 0.03 to 0.74; P=0.99), with the superiority of the BIS protocol again not demonstrated. There was no difference between the groups with respect to the amount of anesthesia administered or the rate of major postoperative adverse outcomes.

**CONCLUSIONS**
The superiority of the BIS protocol was not established; contrary to expectations, fewer patients in the ETAC group than in the BIS group experienced awareness. (Funded by the Foundation for Anesthesia Education and Research and others; BAG-RECALL ClinicalTrials.gov number, NCT00682825.)

*Members of the BIS or Anesthetic Gas to Reduce Explicit Recall (BAG-RECALL) Research Group are listed in the Supplementary Appendix, available at NEJM.org.
unintended intraoperative awareness is defined as the experience and explicit recall of sensory perceptions during surgery, which can lead to post-traumatic stress disorder in as many as 70% of those who experience it. In patients at high risk for intraoperative awareness, the incidence of awareness may approach 1%. An estimated 20,000 to 40,000 patients experience awareness yearly in the United States alone. Some cases of awareness might occur as a result of inadequate anesthetic dosing and therefore constitute potentially preventable medical errors.

A potent inhaled anesthetic agent is incorporated in the majority of general anesthetics, and concentrations of exhaled anesthetic are routinely measured. The minimum alveolar concentration (MAC) is the concentration of anesthesia required to prevent 50% of subjects from moving in response to a noxious surgical stimulus. When the end-tidal anesthetic-agent concentration (ETAC) is approximately 0.33 MAC, 50% of subjects do not respond appropriately to oral commands, and maintaining the ETAC at greater than 0.7 MAC during surgery is thought to decrease the incidence of awareness.

Candidate depth-of-anesthesia monitors based on electroencephalographic data have been developed, partly with the aim of preventing awareness. The most widely used is the bispectral index (BIS) monitor (Covidien), which processes a single frontal electroencephalographic signal with the use of a proprietary algorithm to calculate a dimensionless number that is intended to indicate the patient’s level of consciousness. BIS values range from 0, indicating the suppression of detectable brain electrical activity, to 100, indicating the awake state. A target range between 40 and 60 has been advocated both to prevent awareness and to reduce the dose of anesthetic agent that has to be administered.

Simple, but rigorous, protocol-based interventions can decrease perioperative complications and death. The incorporation of information technology into structured protocols to provide support for clinical decision making could improve patient safety and prevent medical errors. The adoption of technologic advances should be driven first by a compelling demonstration of clinical benefit and second by evidence of cost-effectiveness.

The B-Aware trial, involving 2500 patients, showed that administration of anesthesia with the use of a BIS protocol, as compared with standard anesthetic practice, decreased the incidence of intraoperative awareness by 0.74 percentage points (95% confidence interval [CI], 0.14 to 1.40) among patients at high risk for this complication. The B-Unaware trial (ClinicalTrials.gov number, NCT00281489) showed a reduction of 0 percentage points (95% CI, −0.56 to 0.57) in the incidence of awareness with a BIS protocol, as compared with an ETAC protocol. The B-Unaware trial also showed that the BIS protocol was not associated with a reduction in the amount of anesthesia administered or in postoperative mortality.

Both protocols in the B-Unaware trial resulted in an incidence of awareness in high-risk patients that was lower than the predicted incidence (0.2% with both protocols vs. 1.0% predicted). However, the B-Unaware trial had important limitations. Most important, with 1941 patients, the confidence interval for the reduction in awareness was wide and did not rule out a clinically significant benefit (0.56 percentage points) attributable to BIS monitoring. Furthermore, the trial was conducted at a single center. We therefore designed the three-center, international BIS or Anesthetic Gas to Reduce Explicit Recall (BAG-RECALL) trial to investigate whether a structured BIS protocol was superior to a structured ETAC protocol in decreasing the incidence of intraoperative awareness among patients at high risk for this complication.

Methods

Study Oversight

We conducted the study at three medical centers. A detailed description of the experimental protocol for the BAG-RECALL study has been published previously. The human studies committees at Washington University in St. Louis, University of Chicago, and University of Manitoba approved the study. The guidelines of the Consolidated Standards of Reporting Trials were followed in the conduct of the study and the reporting of results. The study was designed, the data were collected and analyzed, and the manuscript was prepared exclusively by the study investigators, all of whom made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and the analyses, as well as the adherence of this report to the study protocol.

Patients

Patients 18 years of age or older who were undergoing elective surgery were evaluated for eligibil-
ity. Patients were eligible if they were at high risk for intraoperative awareness and were undergoing general anesthesia with isoflurane, sevoflurane, or desflurane. The criteria for identifying patients at high risk for awareness were based on previous studies, reviews, and guidelines. Patients at high risk were defined as those with at least one risk factor (Table 1). Patients who had dementia, who were unable to provide written informed consent, or who had a history of stroke with residual neurologic deficits were excluded.

**STUDY DESIGN**

In this prospective study, 6100 prerandomization designations were generated electronically in blocks of 100, divided equally between the groups. Labels indicating BIS group or ETAC group were sealed in opaque, numbered envelopes. Eligible patients underwent randomization after providing written informed consent. The anesthesia practitioners were aware of the patients' group assignments, but the patients, the postoperative interviewers, the expert reviewers, and the statistician were not.

**PROCEDURES**

A BIS Quatro (Covidien) sensor was applied to the forehead of each patient. Patients in the ETAC group had monitors configured to conceal the BIS number, so the anesthesia practitioners were unaware of the BIS values. The practitioners in both groups could view the ETAC. Summaries of the BIS and ETAC protocols were given to the practitioners to provide education and to increase adherence to the protocol.

In the BIS group, an audible alarm was set to indicate when the BIS value exceeded 60 or fell below 40; no ETAC alarms were set in the BIS group, nor was there any recommendation to maintain the ETAC within any specific range. In the ETAC group, an audible alarm was set to indicate when the ETAC fell below 0.7 or exceeded 1.3 age-adjusted MAC. In the event that alarm settings were unavailable for ETAC, alarms were set for inspired anesthetic agents. During cardio-pulmonary bypass, the concentration of anesthetic agent was measured from the effluent of the cardiopulmonary-bypass machine. A sign was affixed to the anesthesia machines reminding practitioners to check the BIS value or the ETAC and to consider whether the patient might be aware. It was not the intention of the BIS and ETAC protocols to prescribe or restrict the use of anesthetic agents. For example, practitioners could decrease anesthetic administration at their discretion if a patient's condition was hemodynamically unstable, which itself can increase the risk of awareness. The protocols were designed to increase vigilance and to provide warnings that patients might be aware. BIS values and ETACs were recorded at minimum intervals of 1 minute by means of an electronic recording of anesthesia data with the use of MetaVision software (iMDsoft), by direct electronic transfer of data to Microsoft Excel (Microsoft), or by direct electronic transfer of data with the use of TrendFace Solo software (ixellence). 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.

Intraoperative awareness was assessed with the use of a modified Brice questionnaire. Patients were evaluated within 72 hours after surgery and at 30 days after extubation. Patients who, at either interview, reported memories of the period between “going to sleep” and “waking up” were contacted by a different evaluator, who asked additional structured questions. Every patient who reported such memories was offered referral to a psychologist. After all the patients completed the study, three experts independently reviewed the responses to the questionnaire from patients who had reported memories and determined whether the reported event involved definite awareness, possible awareness, or no awareness. The experts assigned each event of definite or possible awareness to one of the categories of the Michigan Awareness Classification Instrument. The same committee also reviewed awareness events for the Michigan Awareness Control Study (NCT00689091). In the event of a divergence of opinion, a fourth expert reviewer, who reviews cases for the Anesthesia Awareness Registry of the American Society of Anesthesiologists, made the final determination.

**STATISTICAL ANALYSIS**

The primary outcome measure was the incidence of intraoperative awareness in the BIS and ETAC groups. We based our projected estimates of the incidence of awareness among high-risk patients on the results of the B-Aware and the B-Unaware trials. The null hypothesis was that the BIS protocol is not superior to the ETAC protocol in preventing intraoperative awareness. The alternative hypothesis was that the BIS protocol is superior.
in preventing intraoperative awareness. We estimated that with 6000 patients, the study would have 87% power to detect a clinically significant reduction of 0.4 percentage points in the incidence of definite awareness with the BIS protocol, as compared with the ETAC protocol (from 0.5% in
the ETAC group to 0.1% in the BIS group), at a one-tailed alpha level of 0.05, with the use of Fisher’s exact test. As a prespecified secondary analysis, we planned to use a one-sided Fisher’s exact test to determine whether there was a lower incidence of definite or possible awareness in the BIS group than in the ETAC group.23 As a post hoc secondary analysis, we used Fisher’s exact test to determine whether there was a lower incidence in the BIS group of awareness that caused distress. A chi-square test, Fisher’s exact test, unpaired Mann–Whitney U test, or unpaired Student’s t-test was used, as appropriate, for other comparisons. A modified intention-to-treat analysis was performed, which included all patients who underwent randomization and who were assessed for intraoperative awareness. Other than the assessments of awareness events, all significance testing was two-sided, and P values of less than 0.05 were considered to indicate statistical significance. The statistical analysis was performed with the use of the R statistical software package, version 2.13.0 (R Foundation for Statistical Computing) and Analyze-it software, version 2.11 (Analyze-it Software).

RESULTS

PATIENTS

Of an estimated 49,000 patients who were screened, 6041 were enrolled over the course of a 25-month period, from May 2008 through May 2010. A total of 5809 patients were included in the trial, of whom 5713 (98.3%) completed at least one postoperative interview and were included in the primary outcome analysis (Fig. 1). A total of 5413 patients (93.2%) completed the postoperative interviews at both times — within 72 hours after surgery and at 30 days after extubation. All the patients were treated with the protocol to which they had been randomly assigned. In the case of 6 patients in the ETAC group, practitioners were aware of BIS values for part of the time during the surgery. Table 1 shows the baseline characteristics of the patients and their risk factors for awareness.

INTRAOPERATIVE AWARENESS

In total, 49 patients, including patients from all three enrollment sites, reported having memories of the period between “going to sleep” and “waking up” at the end of surgery. Experts determined that 9 patients had definite intraoperative awareness (incidence, 0.16%; 95% CI, 0.08 to 0.30), and 27 patients had definite or possible awareness (incidence, 0.47%; 95% CI, 0.32 to 0.68). There were fewer cases of awareness in the ETAC group than in the BIS group, which was contrary to the expected result (i.e., contrary to the alternative hypothesis of the trial). The grading of awareness events according to the Michigan Awareness Classification Instrument31 is shown in Table 2. The comparisons of the frequency of awareness events between the BIS group and the ETAC group are shown in Table 3. Additional information about awareness experiences is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Table 4 shows the characteristics of patients who had definite or possible awareness, as compared with the rest of the patients in the study. Patients who experienced awareness, as compared with patients who did not, met a median of one additional inclusion criterion and had a median of one additional preexisting medical condition. A total of 5 of the 9 patients who experienced definite awareness and 6 of the 18 patients who experienced possible awareness did not have either BIS values of greater than 60 or ETAC values of less than 0.7 age-adjusted MAC. Overall, during the maintenance of anesthesia, the BIS was less than 0.7 age-adjusted MAC a median of 84.8% of the time (interquartile range, 67.2 to 95.3).

There were no important differences between the groups in the doses of sedative, hypnotic, opioid analgesic, or neuromuscular-blocking drugs administered. Specifically, midazolam was administered to 80.8% of the patients in the BIS group and to 79.7% of the patients in the ETAC group. During maintenance of anesthesia, the median ETAC in the ETAC group and in the BIS group was 0.9 age-adjusted MAC (interquartile range, 0.8 to 1.0), and the median BIS in both groups was 41 (interquartile range, 38 to 45). The median ETAC values were similar at the three study sites (0.8 age-adjusted MAC in Chicago, 0.9 age-adjusted MAC in St. Louis, and 0.9 age-adjusted MAC in Winnipeg), as were the median BIS values (43 in Chicago, 41 in St. Louis, and 43 in Winnipeg). The 30-day mortality was 1.96% (57 of 2907 patients) in the BIS group and 2.21% (64 of 2902 patients) in the ETAC group (a difference of 0.24 percentage points; 95% CI, −0.50 to 0.99). In both groups, the median length of stay in the hospital was 7.0 days, and the median length of stay in the intensive care unit was 2.1 days.
DISCUSSION

The results of the BAG-RECALL trial do not support the superiority of the BIS protocol over the ETAC protocol in preventing intraoperative awareness among patients at high risk for this complication. The overall incidence of awareness was lower than anticipated, suggesting that both protocols were likely to have had efficacy, but the finding of fewer cases in the ETAC group than in the BIS group was contrary to the expected result. The 95% confidence interval for the difference in definite awareness includes, at one extreme, a 0.03 percentage-point benefit attributable to BIS monitoring, which represents a number needed to treat of 3333 high-risk patients to prevent one episode of awareness.

Figure 1. Screening, Randomization, and Follow-up.
BIS denotes bispectral index, and ETAC end-tidal anesthetic-agent concentration.
Prevention of Intraoperative Awareness

The BAG-RECALL trial addressed the major limitations of the B-Unaware trial. In particular, the current study was substantially larger than the B-Unaware trial and was conducted at three international sites, and minor risk factors for awareness were not used as enrollment criteria. The findings of the B-Unaware trial and the current trial regarding definite and possible awareness are congruent. Furthermore, similar to the findings in the B-Unaware trial, the results of the BAG-RECALL trial did not show that the ETAC protocol was associated with an increase in postoperative mortality or in the amount of anesthetic agent administered.

Several other key implications of the BAG-RECALL trial warrant discussion. ETAC alarms at less than 0.7 age-adjusted MAC should be considered to be an effective active comparator in future studies of the prevention of intraoperative awareness, and the ETAC protocol used in this trial should be evaluated in the general surgical population. With some awareness events apparently occurring with BIS values below 60, decreasing anesthetic concentration solely on the basis of a BIS value of less than 60 is not recommended. Also, the risk of awareness might be incrementally increased with additional risk factors and coexisting conditions. Finally, notwithstanding major advances in our understanding of consciousness and anesthesia, until we clarify fully the mechanisms and measurement of anesthetic-induced unconsciousness and amnesia, some patients are still likely to have this complication.

Despite its wide scope, the BAG-RECALL trial has a number of limitations. Most important, it was designed to study the BIS and ETAC protocols in high-risk patients undergoing general anesthesia that is based predominantly on a potent inhaled agent; its results should not be extrapolated beyond this population. Second, the ETAC protocol

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BIS Group (N=2861)</th>
<th>ETAC Group (N=2852)</th>
<th>P Value‡</th>
<th>Difference, BIS–ETAC percentage points (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite awareness: primary outcome</td>
<td>7 (0.24)</td>
<td>2 (0.07)</td>
<td>0.98</td>
<td>0.17 (~0.03 to 0.38)</td>
</tr>
<tr>
<td>Definite or possible awareness: prespecified secondary outcome</td>
<td>19 (0.66)</td>
<td>8 (0.28)</td>
<td>0.99</td>
<td>0.38 (0.03 to 0.74)</td>
</tr>
<tr>
<td>Distressing experience of awareness: post hoc secondary outcome</td>
<td>8 (0.28)</td>
<td>1 (0.04)</td>
<td>0.99</td>
<td>0.24 (0.04 to 0.45)</td>
</tr>
</tbody>
</table>

*BIS denotes bispectral index, and ETAC end-tidal anesthetic-agent concentration.
‡ One-tailed P values were calculated to test the null hypothesis that BIS is not superior to ETAC and the alternative hypothesis that BIS is superior to ETAC. A one-tailed P value of less than 0.05 with the use of Fisher’s exact test would suggest that the null hypothesis should be rejected and the alternative hypothesis accepted.
Table 4. Characteristics of Patients with and Patients without Intraoperative Awareness.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Definite or Possible Intraoperative Awareness (N = 27)</th>
<th>No Intraoperative Awareness (N = 5686)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>61±13.2</td>
<td>60±14.3</td>
<td>0.89</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>15 (55.6)</td>
<td>3285 (57.8)</td>
<td>0.82</td>
</tr>
<tr>
<td>Body-mass index‡</td>
<td>30±10.1</td>
<td>30±8.4</td>
<td>0.73</td>
</tr>
<tr>
<td>Race — no. (%)‡</td>
<td></td>
<td></td>
<td>0.26</td>
</tr>
<tr>
<td>White</td>
<td>20 (74.1)</td>
<td>4773 (83.9)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (25.9)</td>
<td>913 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria met — no. of patients (%)¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned open-heart surgery</td>
<td>14 (51.9)</td>
<td>2027 (35.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>4 (14.8)</td>
<td>517 (9.1)</td>
<td>0.30</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>3 (11.1)</td>
<td>264 (4.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Use of opiates</td>
<td>8 (29.6)</td>
<td>1458 (25.6)</td>
<td>0.66</td>
</tr>
<tr>
<td>Benzodiazepine use</td>
<td>5 (18.5)</td>
<td>894 (15.7)</td>
<td>0.60</td>
</tr>
<tr>
<td>Anticonvulsant use</td>
<td>3 (11.1)</td>
<td>420 (7.4)</td>
<td>0.45</td>
</tr>
<tr>
<td>Daily alcohol consumption</td>
<td>6 (22.2)</td>
<td>881 (15.5)</td>
<td>0.30</td>
</tr>
<tr>
<td>ASA status 4‖</td>
<td>13 (48.1)</td>
<td>1960 (34.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>End-stage lung disease</td>
<td>1 (3.7)</td>
<td>115 (2.0)</td>
<td>0.43</td>
</tr>
<tr>
<td>History of intraoperative awareness</td>
<td>3 (11.1)</td>
<td>88 (1.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>History of or anticipated difficult intubation</td>
<td>0</td>
<td>469 (8.2)</td>
<td>0.20</td>
</tr>
<tr>
<td>Cardiac ejection fraction &lt;40%</td>
<td>5 (18.5)</td>
<td>506 (8.9)</td>
<td>0.18</td>
</tr>
<tr>
<td>Marginal exercise tolerance</td>
<td>14 (51.9)</td>
<td>2636 (46.4)</td>
<td>0.57</td>
</tr>
<tr>
<td>Composite no. of inclusion criteria</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>2–4</td>
<td>1–3</td>
<td></td>
</tr>
<tr>
<td>Composite no. of preexisting medical conditions</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>1–4</td>
<td>1–3</td>
<td></td>
</tr>
<tr>
<td>Received midazolam — no. (%)¶</td>
<td>18 (66.7)</td>
<td>4566 (80.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Bispectral index</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>40</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>37–45</td>
<td>38–45</td>
<td></td>
</tr>
<tr>
<td>ETAC in MAC equivalents</td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.87</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0.84–1.02</td>
<td>0.80–0.99</td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. ETAC denotes end-tidal anesthetic-gas concentration, and MAC minimum alveolar concentration.
† P values were calculated with the use of Fisher’s exact test or the chi-square test with Yates’ correction for categorical variables. For differences between means, P values were calculated with the unpaired Student’s t-test; for differences between medians, P values were calculated with the Mann–Whitney U test.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Race was determined on the basis of information in the medical records.
¶ A patient could have more than one inclusion criterion.
‖ The American Society of Anesthesiologists (ASA) physical status classification system is used to assess a patient’s physical status before surgery. Scores range from 1 (indicating a normal, healthy patient) to 6 (indicating a brain-dead patient whose organs are being removed for donor purposes); a score of 4 indicates a patient with severe systemic disease that is a constant threat to life.
was evaluated against only one of many available electroencephalogram-derived monitors. Third, it is conceivable that a protocol that is based on both BIS and ETAC alerts would perform better than one based on either approach alone. Fourth, it is difficult to know whether practitioners might become desensitized to either protocol; many people find audible alerts distracting, especially with a high rate of false alarms.\(^5\) Fifth, when a rare outcome is assessed, missing data can have an important effect. Although a small number of patients were not interviewed postoperatively, as shown in Figure 1, in most cases, this was because they did not awaken and died before the initial interview. Finally, in the case of a rare event such as awareness, unidentified risk factors such as genetic resistance to anesthetic agents could have been unevenly distributed between the BIS and ETAC groups despite randomization and could have confounded the results.

The BAG-RECALL trial did not demonstrate the superiority of a BIS protocol over a protocol incorporating standard ETAC monitoring for the prevention of intraoperative awareness. Implementation of an ETAC-based protocol would require a brief, structured educational program, measurement of the exhaled concentration of volatile anesthetic agent, routine setting of audible alarms for threshold ETAC values, and checklists to maintain vigilance by the practitioner. Similar to other structured protocols that have enjoyed widespread adoption,\(^13-15\) an ETAC protocol like the one used in this trial could be implemented for patients at high risk for awareness who are undergoing general anesthesia with a potent inhaled agent.

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No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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**REFERENCES**


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