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Does the Use of Electroencephalographic Bispectral Index or Auditory Evoked Potential Index Monitoring Facilitate Recovery after Desflurane Anesthesia in the Ambulatory Setting?

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Background: **Analogous to the Bispectral Index® (BIS®) monitor, the auditory evoked potential monitor provides an electroencephalographic-derived index (AAI), which is alleged to correlate with the central nervous system depressant effects of anesthetic drugs. This clinical study was designed to test the hypothesis that intraoperative cerebral monitoring guided by either the BIS or the AAI value would facilitate recovery from general anesthesia compared with standard clinical monitoring practices alone in the ambulatory setting.**

Methods: **Sixty consenting outpatients undergoing gynecologic laparoscopic surgery were randomly assigned to one of three study groups: (1) control (standard practice), (2) BIS guided, or (3) AAI guided. Anesthesia was induced with 1.5–2.5 mg/kg propofol and 1–1.5 μg/kg fentanyl given intravenously. Desflurane, 3%, in combination with 60% nitrous oxide in oxygen was administered for maintenance of general anesthesia. In the control group, the inspired desflurane concentration was varied based on standard clinical signs. In the BIS- and AAI-guided groups, the inspired desflurane concentrations were titrated to maintain BIS and AAI values in targeted ranges of 50–60 and 15–25, respectively. BIS and AAI values, hemodynamic variables, and the end-tidal desflurane concentration were recorded at 5-min intervals during the maintenance period. The emergence times and recovery times to achieve specific clinical endpoints were recorded at 1- to 10-min intervals. The White fast-track and modified Aldrete recovery scores were assessed on arrival in the PACU, and the quality of recovery score was evaluated at the time of discharge home.**

Results: **A positive correlation was found between the AAI and BIS values during the maintenance period. The average BIS and AAI values (mean ± SD) during the maintenance period were significantly lower in the control group (BIS, 41 ± 10; AAI, 11 ± 6) compared with the BIS-guided (BIS, 57 ± 14; AAI, 18 ± 11) and AAI-guided (BIS, 55 ± 12; AAI, 20 ± 10) groups. The end-tidal desflurane concentration was significantly reduced in the BIS-guided (2.7 ± 0.9%) and AAI-guided (2.6 ± 0.9%) groups compared with the control group (3.6 ± 1.5%). The awakening (eye-opening) and discharge times were significantly shorter in the BIS-guided (7 ± 3 and 132 ± 39 min, respectively) and AAI-guided (6 ± 2 and 128 ± 39 min, respectively) groups compared with the control group (9 ± 4 and 195 ± 57 min, respectively). More importantly, the median [range] quality of recovery scores was significantly higher in the BIS-guided (18 [17–18]) and AAI-guided (18 [17–18]) groups when compared with the control group (16 [10–18]).**

Conclusion: **Compared with standard anesthesia monitoring practice, adjunctive use of auditory evoked potential and BIS monitoring can improve titration of desflurane during general anesthesia, leading to an improved recovery profile after ambulatory surgery.**

PREVIOUS studies have suggested that cerebral monitoring can result in a faster emergence from general anesthesia.[1–4] However, these early studies failed to demonstrate consistent benefits with respect to facilitating discharge or improving the quality of recovery. A recent publication by Ahmad *et al.*[5] reported that the use of the electroencephalographic Bispectral Index® (BIS®) monitor (Aspect Medical Systems, Inc., Newton, MA) for titrating the maintenance anesthetic drug failed to reduce the time to discharge after ambulatory surgery. However, these findings have been questioned because of methodologic concerns regarding the study design.[6]

Analogous to the BIS® monitor, the electroencephalographic-derived index (AAI) of the auditory evoked potential (AEP) uses the middle latency auditory evoked potential response to a predefined auditory stimulus. The middle latency auditory evoked potential has been alleged to possess potential advantages over the BIS because it measures the central nervous system responsiveness to a specific auditory stimulus rather than simply measuring the resting state of the brain.[7] Recently, Struys *et al.*[8] evaluated the accuracy of the BIS and AAI values in predicting effect site concentrations of propofol and the probability of patient movement. These investigators found that both BIS and AAI values predicted the propofol effect site concentration, the level of sedation, and loss of consciousness but not the response to a noxious stimulus. However, there have been no published studies directly comparing the clinical utility of these two cerebral monitors with respect to their effects on the titration of a volatile anesthetic and the recovery profile after ambulatory anesthesia.

Therefore, we designed this randomized double-blinded clinical study to evaluate the comparative effects

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of AAI and BIS monitoring on recovery after ambulatory anesthesia when they were used as adjuvants to standard clinical monitoring practices. The hypothesis to be tested was that cerebral monitoring with the AEP or BIS® monitor would facilitate a faster emergence from general anesthesia and thereby lead to a shorter time to discharge after ambulatory surgery.

Materials and Methods

After obtaining institutional review board approval at Cedars-Sinai Medical Center in Los Angeles, California, 60 healthy outpatients scheduled to undergo gynecologic laparoscopic surgery under general anesthesia were randomly assigned to one of three groups: group 1, control (standard clinical practices); group 2, BIS guided; and group 3, AAI guided. Patients with known neurologic or psychiatric disorders, patients currently using anticonvulsants or other centrally active medications, and patients with clinically significant cardiovascular, respiratory, hepatic, renal or metabolic disease; long-term drug or alcohol abuse; or a body weight greater than 50% above their ideal body weight were excluded from participating in this study.

All patients received 2 mg intravenous midazolam for premedication, and the BIS and AEP electrodes were applied simultaneously in the preoperative holding area. On arrival in the operating room, routine hemodynamic and respiratory monitoring devices were also applied. Baseline BIS and AAI values were obtained with the patients' eyes closed for 1–2 min before induction of anesthesia. Anesthesia was induced with 1.5–2.5 mg/kg intravenous propofol and 1–1.5 μg/kg intravenous fentanyl injected over 15–30 s. Intravenous succinylcholine, 1–1.5 mg/kg, was administered to facilitate tracheal intubation. Desflurane, 3% inspired concentration, in combination with 60% nitrous oxide in oxygen (1.5 l $\cdot$ min^{-1}/1 l $\cdot$ min^{-1}) was administered for maintenance of anesthesia. Cisatracurium, in 10- to 20-mg intravenous boluses, was administered for neuromuscular blockade. All patients were mechanically ventilated to maintain an end-tidal carbon dioxide concentration of 35–40 mmHg. Esmolol, in 10-mg intravenous boluses, was administered to treat sustained increases in heart rate at the discretion of the anesthesiologist. The neuromuscular reversal drugs (0.05 mg/kg neostigmine and 0.01 mg/kg glycopyrrolate, intravenously) were administered, and the inhaled anesthetics were discontinued immediately on completion of skin closure. At the end of surgery, all patients received 30 mg intravenous ketorolac and 4 mg intravenous ondansetron to minimize postoperative pain and emesis, respectively.

Three investigators were involved in conducting each study case. In the control group, the staff anesthesiologist (R. H. W., A. S., or R. K.) was responsible for administering the anesthetic drugs and for monitoring the "depth of anesthesia" using standard clinical signs with the goal of maintaining hemodynamic stability while avoiding patient movement and achieving a rapid recovery after surgery. In the control group, both the BIS and AEP monitors were positioned out of the anesthesiologist's line of sight. A second investigator (H. M.) ensured proper functioning of the monitors during the operation and recorded physiologic data at specific time intervals during the perioperative period. In the BIS- and AAI-guided groups, the BIS® or AEP monitor, respectively, was positioned to enable the anesthesiologist to use the displayed index value to titrate the inspired concentration of desflurane to maintain the BIS or AAI value in the range of 50–60 or 15–25, respectively, during the operation.

Mean arterial pressure, heart rate, end-tidal concentrations of desflurane, and BIS and AAI values were recorded by the second investigator at 1-min intervals during the induction (for 10 min) and emergence (until orientation) periods, as well as at 5-min intervals during the maintenance period. Anesthesia (from induction of anesthesia until discontinuation of nitrous oxide) and surgery (from incision until placement of the surgical dressing) times were also recorded. After discontinuation of the inhaled anesthetics, the times at which patients were able to open their eyes, were able to follow simple commands (*e.g.*, squeeze the investigator's hand), and were oriented to person, place and time were assessed at 1-min intervals by a third investigator (J. T.), who was unaware of the monitoring group to which the patient had been assigned.

On arrival in the PACU, the White fast-track score[9] and the modified Aldrete score[10] were assessed. The times to sitting up, standing, ambulating, tolerating oral fluids ("fit for discharge"), as well as actual discharge times were assessed at 5- to 10-min intervals in the recovery room. Patients were discharged home directly from the PACU.[11] Before discharge home, all patients were asked to assess their quality of recovery score[12] using a nine-item checklist (Appendix). In addition, the use of desflurane (in milliliters) was calculated using the formula described by Dion.[13] At the time of discharge from the hospital and during the follow-up telephone interview at 24 h after surgery, patients were asked whether they recalled any events during the intraoperative period.

Statistical Analysis

An *a priori* power analysis based on a previous study[2] suggested that a sample size of 20 patients for each group should be adequate to detect a 30% or greater reduction in the times to eye opening with a power of 0.8 (α = 0.05). One-way analysis of variance was performed for normally distributed continuous variables, and when a significant difference was noted, a Newman-Keuls test was performed for *post hoc* comparisons be-

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Table 1. Demographic Characteristics, Durations of Anesthesia and Surgery, and Dosages of Anesthetic Drugs Administered during Intraoperative Period among the Three Study Groups

	Control	BIS Guided	AAI Guided
No.	20	20	20
Age, yr	48 ± 10	54 ± 14	50 ± 15
Weight, kg	72 ± 10	73 ± 12	72 ± 13
Height, cm	163 ± 5	162 ± 5	162 ± 7
ASA I/II/III, No.	9/11/0	9/10/1	7/12/1
Propofol, mg	195 ± 55	183 ± 35	187 ± 48
Fentanyl, μg	80 ± 30	86 ± 33	90 ± 30
Desflurane concentration, ET%	3.6 ± 1.5	2.7 ± 0.9*	2.6 ± 0.9*
Desflurane, ml	29 ± 9	21 ± 10*	21 ± 10*
Esmolol, No. (%)	2 (10)	4 (20)	3 (15)
Surgery time, min	49 ± 15	46 ± 20	40 ± 24
Anesthesia time, min	66 ± 16	58 ± 22	55 ± 27

Values are presented as mean ± SD, number, or percentage.

* $P < 0.05$ *vs.* control group.

AAI = auditory evoked index; ASA = American Society of Anesthesiologists (physical status); BIS = Bispectral Index; ET = end-tidal.

tween groups. Repeated-measures analysis of variance with *post hoc* Bonferroni correction for comparison of the recovery values of BIS or AAI *versus* baseline values, respectively. Continuous data not normally distributed were analyzed by Kruskal-Wallis test using the nonparametric analysis of variance. When a significant difference was found, the Mann–Whitney U test was used for *post hoc* comparisons between groups. Categorical data were analyzed using the chi-square test or the Fisher exact test where appropriate. The relation between BIS and AAI values during the induction, maintenance, and recovery periods was analyzed using linear regression to determine the correlation coefficients. A *P* value of less than 0.05 was considered statistically significant. Data are presented as mean ± SD, number, percentage, or median (with interquartile range).

Results

There were no significant differences among the three study groups with respect to demographic characteristics or the duration of surgery or anesthesia. In addition, the total dosages of propofol and fentanyl administered during the intraoperative period (and the usage of esmolol) were similar in all three study groups (table 1). The mean end-tidal concentrations of desflurane were significantly decreased in the BIS- and AAI-guided groups compared with the control group (table 1). The amounts of desflurane (in milliliters) were also reduced by 28% in both the BIS- and AAI-guided (*vs.* control) groups (table 1).

During the maintenance period, the average hemodynamic variables did not differ significantly among the three study groups (fig. 1). However, the mean BIS and AAI values were significantly lower in the control group (BIS, 41 ± 10; AAI, 11 ± 6) compared with the BIS-guided (BIS, 57 ± 14; AAI, 18 ± 11) and AAI-guided (BIS, 55 ± 12; AAI, 20 ± 10) groups, respectively. Even though the AAI values were consistently lower than the BIS values during the maintenance period (figs. 2 and 3), a positive correlation was found between these two indices ($r = 0.43$). Of interest, the AAI exhibited a better correlation with the BIS during the induction ($r = 0.78$) and emergence ($r = 0.75$) periods.

The times to eye opening, extubation, following commands, and orientation were consistently shorter in the BIS- and AAI-guided (*vs.* control) groups (table 2). In addition, significantly more patients achieved fast-track eligibility and modified Aldrete scores of 10 on arrival in the PACU in the BIS- and AAI-guided (*vs.* control) groups (table 2). The times to sitting up, tolerating oral fluid, standing, ambulating, home readiness, and actual discharge were also significantly decreased in the BIS- and AAI-guided (*vs.* control) groups (table 2). More importantly, median quality of recovery scores were significantly higher in the BIS- and AAI-guided (*vs.* control) groups at the time of discharge (table 2). None of the patients reported recall of intraoperative events when questioned at the time of discharge from the hospital or during the follow-up telephone interview at 24 h after surgery. Postoperative side effects (including nausea and vomiting) were similar in all three study groups (table 3).

Discussion

Clinical studies involving electroencephalographic-based cerebral monitors have demonstrated improved titration of both intravenous[1,3] and inhalational[2,4] anesthetics during general anesthesia. Although these clinical utility studies have consistently shown that the titration of anesthetics using these monitors can facilitate an earlier emergence from general anesthesia, improvements in later recovery endpoints have not been consistently reported. In this study, we further demonstrated that the use of either the BIS® or the AEP monitor not only resulted in a shorter stay in the hospital, but also led to an improved quality of recovery for the patient.

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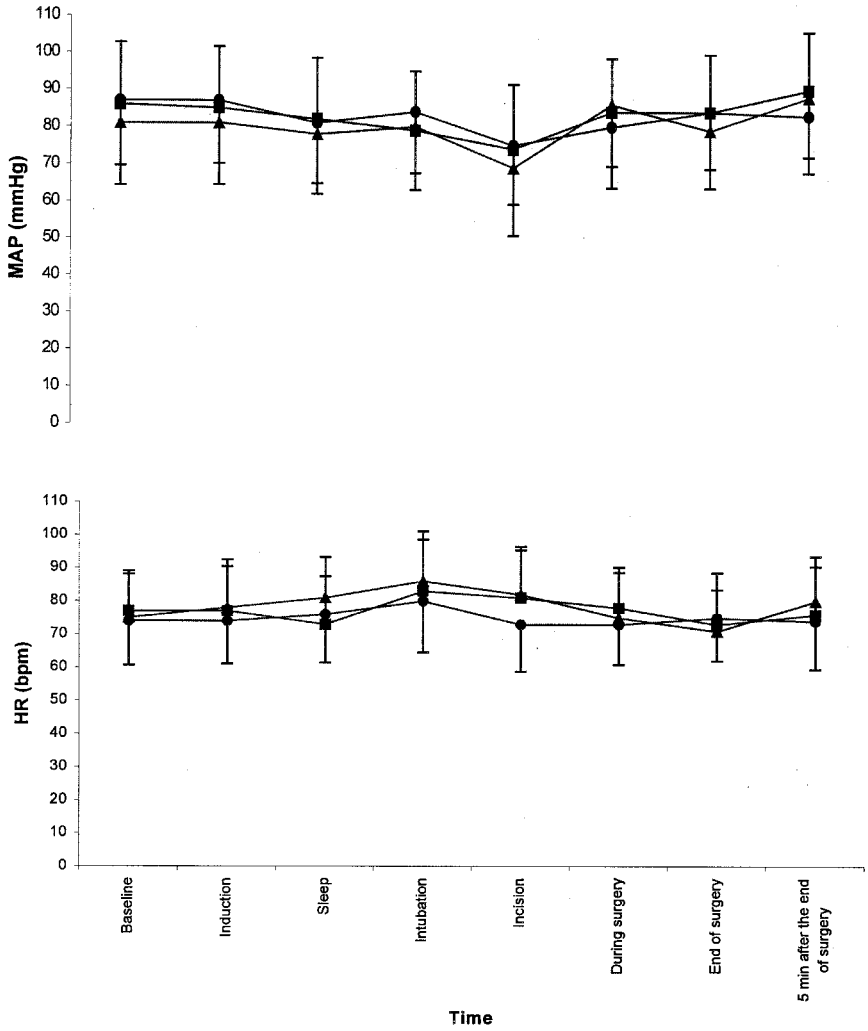

Fig. 1. Mean arterial pressure (MAP) and heart rate (HR) values in the three study groups. Values are presented as mean ± SD. -■- = AAI-guided group; -●- = Bispectral Index–guided group; -▲- = control group.

In their recent publication, Ahmad *et al.*[5] questioned the claim that the use of an electroencephalographic-based cerebral monitor can produce meaningful changes in the time to discharge after ambulatory surgery. However, the failure to find a difference in discharge times in their study may have been related to the fact that the anesthesiologists caring for these patients failed to use the displayed electroencephalographic index to make decisions regarding the use of anesthetic drugs, or the institutional PACU recovery protocols did not allow for an early discharge because of minimum duration of stay requirements.[6] Not surprisingly, the anesthetic, analgesic, and muscle relaxant dosage requirements were identical in both the BIS-guided and control groups in this earlier study.[5] Although sevoflurane was allegedly titrated to maintain the BIS value in the 50–60 range, the reported (mean ± SD) sevoflurane concentration (2.14 ± 0.25%) is simply not consistent with a BIS value greater than 50.[2,14]

Our current data support earlier studies[2–4] suggesting that practitioners use lower concentrations of volatile anesthetics when they have access to the information provided by these cerebral monitors. As a result of the anesthetic-sparing effect of using these electroencephalographic-based monitoring devices, the average BIS and AAI values during the maintenance period were significantly higher in the two cerebral-monitored groups compared with the control group. Even though the absolute magnitudes of the AAI and BIS values differed during the perioperative period (figs. 2 and 3), a positive correlation was found between these two electroencephalographic-based indices. We would speculate that all electroencephalographic-based cerebral monitors have similar potential benefits with respect to their anesthetic-sparing effects during surgery.[1–4]

Use of cerebral monitors to minimize the administration of anesthetic drugs and expedite the recovery process has raised concerns regarding the potentially deleterious effects of increased autonomic activity (*e.g.*, myocardial ischemia) as well as the possibility of intraoperative awareness.[15] In this study, the intraoperative hemodynamic variables were not significantly different despite the fact that the AAI- and BIS-guided (*vs.* control) groups received 28% less desflurane. Furthermore, there

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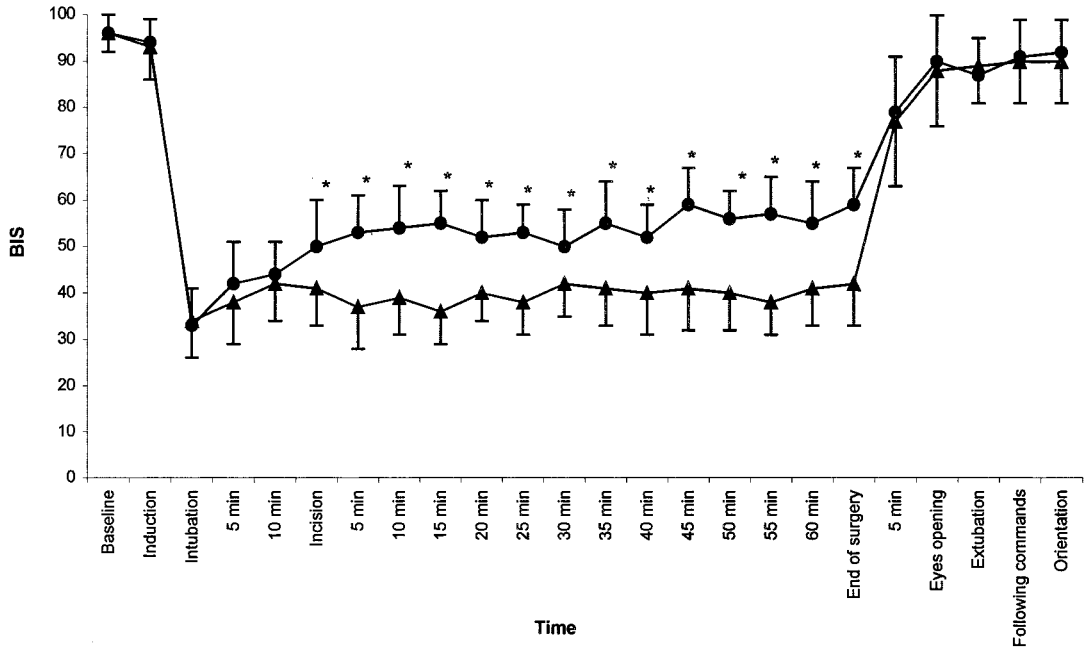

Fig. 2. Perioperative Bispectral Index (BIS) values in the control (-▲-) and BIS-guided (-●-) groups. Values are presented as mean ± SD. * $P \leq 0.05$ *versus* control group.

were no serious adverse events during or after surgery, and none of the patients reported recall of intraoperative events. Of interest, a recent study by Weldon *et al.*[16] suggested that by avoiding excessively deep levels of anesthesia, it may be possible to reduce postoperative morbidity in geriatric patients. Another recent study by White *et al.*[17] found that outpatients experienced a faster recovery and fewer side effects after ambulatory surgery when sympatholytic drugs were used to control acute autonomic responses compared with a volatile anesthetic alone, allowing patients to be maintained at a higher average BIS value during the operation.

This study can be criticized because of the possibility of investigator bias as a result of the anesthesiologists' previous experience using BIS monitoring. It is possible that the three anesthesiologists administering the anesthetic drugs were so accustomed to using the electroencephalographic-based monitor that the effect of removing the cerebral monitoring device may have lead them to inadvertently "overdose" patients in the control

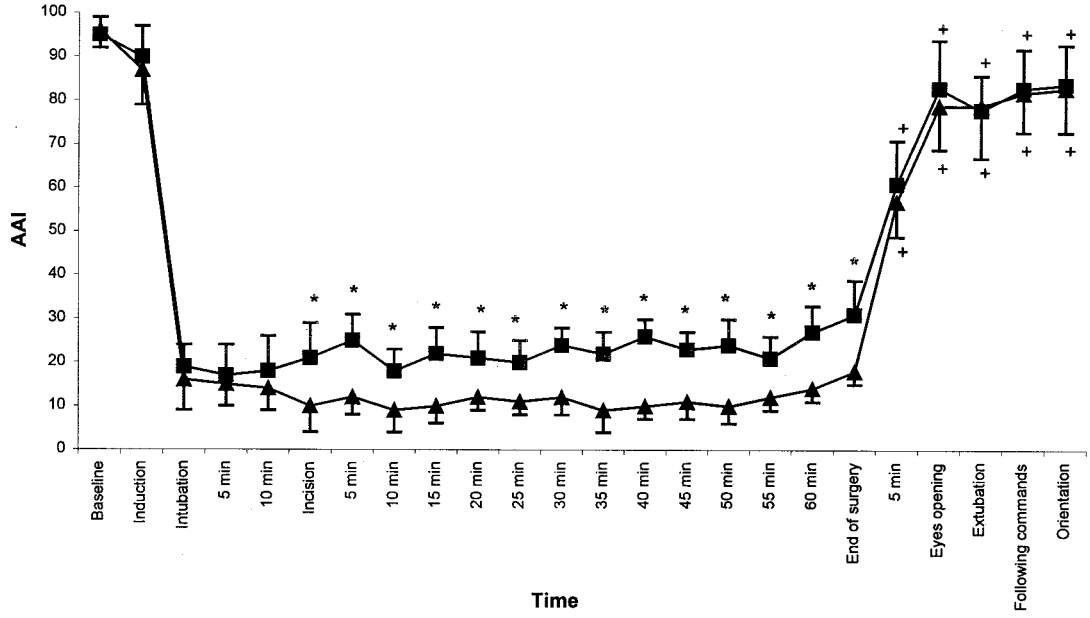

Fig. 3. Perioperative auditory evoked potential index (AAI) values in the control (-▲-) and AAI-guided (-■-) groups. Values are presented as mean ± SD. * $P < 0.05$ *versus* control group. † $P < 0.05$ *versus* baseline values.

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Table 2. Recovery Profiles after Ambulatory Anesthesia among the Three Study Groups

	Control	BIS Guided	AAI Guided
Opening eyes, min	9 ± 4	7 ± 3*	6 ± 2*
Extubation, min	9 ± 4	6 ± 3*	6 ± 2*
Following commands, min	10 ± 4	7 ± 3*	6 ± 2*
Orientation, min	10 ± 4	7 ± 3*	6 ± 2*
Fast-track score ≥ 12 on arrival in PACU, No. (%)	14 (70)	20 (100)*	20 (100)*
Modified Aldrete score of 10 on arrival in PACU, No. (%)	13 (65)	19 (95)*	19 (95)*
Sitting up, min	116 ± 51	68 ± 34*	57 ± 30*
Tolerating oral fluid, min	112 ± 45	82 ± 34*	80 ± 32*
Standing up, min	177 ± 56	113 ± 40*	110 ± 44*
Ambulation, min	177 ± 58	118 ± 40*	113 ± 43*
Fit for discharge, min	185 ± 56	116 ± 38*	120 ± 40*
Actual discharge, min	195 ± 57	132 ± 39*	128 ± 39*
Quality of recovery score at discharge (0–18), No. (IQR)	16 (10–18)	18 (17–18)*	18 (17–18)*

Values are presented as mean ± SD, number, percentage, or median (with interquartile range [IQR]).

* $P < 0.05$ *vs.* control group.

AAI = auditory evoked index; BIS = Bispectral Index.

group. Because this clinical investigation was conducted in the context of standard clinical practice, more vigorous blinding procedures would not have been appropriate. Even though none of the patients reported recall of intraoperative events, the power of the study was clearly inadequate to detect a difference between the groups with respect to this particular complication. Of interest, the AAI values displayed a slower return to the preoperative (baseline) values after discontinuing the anesthetic drugs. This finding is consistent with the suggestion that the AAI may possess increased sensitivity to anesthetic drugs compared with the BIS.[15] Alternatively, the AAI may simply be a less stable signal over time. This observation is also similar to our findings in a recent study comparing the electroencephalographic-based patient state index to the BIS value.[18] Nevertheless, the current study showed that both electroencephalographic-based cerebral monitors facilitated the titration of the volatile anesthetic during the maintenance period and contributed to a faster emergence from general anesthesia and earlier discharge home.

In summary, the use of AEP and BIS monitoring was equally effective in reducing the desflurane requirement and in facilitating the recovery process after outpatient laparoscopic surgery procedures. Furthermore, use of these cerebral monitors led to an improvement in the patients' quality of recovery after ambulatory anesthesia.

Table 3. Incidence of Side Effects before Discharge Home in the Three Study Groups

	Control	BIS Guided	AAI Guided
No.	20	20	20
Nausea, No. (%)	7 (35)	8 (40)	6 (30)
Vomiting, No. (%)	3 (15)	3 (15)	4 (20)
Rescue antiemetic, No. (%)	6 (30)	6 (30)	5 (25)
Headache, No. (%)	1 (5)	0 (0)	1 (5)
Dizziness, No. (%)	2 (10)	1 (5)	1 (5)

Values are numbers or percentages. No significant differences were noted among the three study groups.

AAI = auditory evoked index; BIS = Bispectral Index.

Appendix

Quality of Recovery Score[11]

		Not at All	Some of the Time	Most of the Time
1	Had a feeling of general well-being	0	1	2
2	Had support from others (especially doctors and nurses)	0	1	2
3	Was able to understand instructions and advice; not confused	0	1	2
4	Was able to look after personal toilet and hygiene unaided	0	1	2
5	Was able to pass urine ("waterworks") and had no trouble with bowel function	0	1	2
6	Was able to breathe easily	0	1	2
7	Was free from headache, backache, and muscle pains	0	1	2
8	Was free from nausea, dry retching, and vomiting	0	1	2
9	Was free from severe pain and constant moderate pain	0	1	2

Summary score: 0–18.

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