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Titration of Volatile Anesthetics Using Bispectral Index Facilitates Recovery after Ambulatory Anesthesia

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Background: **The bispectral (BIS) index has previously been shown to be a quantifiable measure of the sedative and hypnotic effects of anesthetic drugs. This study was designed to assess the effect of BIS monitoring on the utilization of volatile anesthetics and their recovery profiles after ambulatory surgery.**

Methods: **Sixty consenting women undergoing outpatient laparoscopic tubal ligation procedures were randomly assigned to one of four treatment groups. After a standardized induction, anesthesia was maintained with either desflurane (Groups I and II) or sevoflurane (Groups III and IV) in combination with nitrous oxide, 65%, and fentanyl. In the control groups (Groups I and III), the anesthesiologists were blinded to the BIS value, and the volatile anesthetics were administered according to standard clinical practice. In Groups II and IV, the volatile anesthetics were titrated to maintain the BIS value at 60. The volatile anesthetic usage and the times from discontinuation of anesthesia to verbal response, orientation, and home-readiness were recorded.**

Results: **During the maintenance period, the BIS values were significantly lower in the control groups (mean, 42) compared with the BIS-titrated groups (mean, 60). The volatile anesthetic usage in the BIS-titrated groups was 30–38% lower ($P < 0.05$) compared with the control groups. Similarly, the times to verbal responsiveness were 30–55% shorter in the BIS-titrated (*vs.* control) groups.**

Conclusions: **Titrating desflurane and sevoflurane using the BIS monitor decreased their utilization and contributed to a faster emergence from anesthesia in outpatients undergoing laparoscopic tubal ligation procedures. (Key words: Anesthesia, general. Anesthetics, inhalation; desflurane; sevoflurane. Monitoring, electroencephalography; bispectral analysis. Anesthetic outcome, recovery.)**

The bispectral (BIS) index, a derived value from the electroencephalograph (EEG),[1] has been shown to be a quantifiable measure of the sedative and hypnotic effects of anesthetic drugs on the central nervous system (CNS).[2-4] Previously, it had been suggested that it may be possible to decrease the requirements for intravenous anesthetic drugs and thereby facilitate recovery by using the BIS value to guide the practitioner in the administration of propofol.[5]

This study was designed to test the hypothesis that titration of volatile anesthetics to a target BIS value would provide for a more rapid emergence in outpatients receiving desflurane or sevoflurane with nitrous oxide (N_2O) for maintenance of general anesthesia. A BIS value of 60 was chosen as the target for titrating the volatile anesthetics because BIS values of less than 60 have been reported to be associated with a low probability of recall and a high probability of unresponsiveness during surgery.[2-4]

A prospective, randomized, controlled study design was used to assess the differences in intraoperative hemodynamics and recovery profiles after desflurane or sevoflurane anesthesia when using either a BIS-titrated or a non-BIS-titrated (control) anesthetic technique in outpatients undergoing laparoscopic procedures.

Methods and Materials

After obtaining institutional review board approval and written informed consent, 60 healthy outpatients scheduled to undergo laparoscopic tubal ligation procedures were enrolled in this study. Patients were randomly assigned to one of four study groups according to

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a computer-generated random numbers table. Patients with known neurologic disease and with cardiovascular or metabolic diseases, impaired renal or hepatic function, body weight greater than 100% above the ideal, or a history of alcohol or drug abuse were excluded from participating in this study.

In addition to routine monitoring devices (heart rate [HR], noninvasive mean arterial pressure [MAP], pulse oximeter), the EEG signal was acquired using four electrodes (Zipprep™, Aspect Medical Systems, Natick, MA) applied to the forehead, with one on each outer malar bone, one at the center of the forehead, and one (ground) on the either side of the center electrode. The BIS (Rev 3.12 U) value was displayed using an Aspect EEG monitor (Model A-1050, Aspect Medical Systems, Natick, MA). After obtaining baseline values for the BIS index and hemodynamic variables, midazolam (2 mg) was administered intravenously, and anesthesia was subsequently induced with intravenous fentanyl, 1 μg/kg, and intravenous propofol, 2 mg/kg. Laryngoscopy and tracheal intubation were facilitated with intravenous succinylcholine, 1 mg/kg, and lidocaine, 4%, (4 ml) was administered intratracheally to provide topical anesthesia. Anesthesia was maintained with either desflurane, 2–5%, (Groups I and II) or sevoflurane, 0.7–2%, (Groups III and IV) in combination with N_2O, 1 l/min (65%), in oxygen, 0.7 l/min. In the control groups (Groups I and III), the anesthesiologists were blinded to the BIS index by facing the EEG monitor away from their sight, and the concentrations of the volatile anesthetics were adjusted according to standard clinical practice (*i.e.*, to maintain hemodynamic stability and avoid patient movement with the aim of achieving a rapid recovery after surgery). In the BIS-titrated groups (Groups II and IV), the volatile anesthetics were titrated to maintain a BIS index of 60.

All patients were mechanically ventilated to maintain an end-tidal carbon dioxide concentration of 32 to 36 mmHg. Intermittent bolus doses of intravenous mivacurium, 0.04 mg/kg, were administered to maintain stable peak inspiratory pressure values and to avoid coughing (or "bucking") with the aim of maintaining at least one twitch using the train-of-four monitor for assessing the degree of neuromuscular blockade. Supplemental doses of intravenous fentanyl, 25–50 μg, were administered to treat persistent elevations in HR (>100 beat/min) or MAP (>20% of the baseline) values despite maximal inspired concentrations of the volatile anesthetics (*i.e.*, desflurane, 5%, or sevoflurane, 2%) in Groups I and III, and increases in HR and MAP values occurring at the targeted BIS index value in Groups II and IV. All patients received intravenous ketorolac, 30 mg, and intravenous droperidol, 0.625 mg, approximately 10–15 min before the end of surgery, to reduce postoperative pain and emesis, respectively. All inhaled anesthetics were discontinued on completion of the skin closure.

The BIS, MAP, and HR values were recorded at 1-min intervals during induction of anesthesia and subsequently at 3- to 5-min intervals during the maintenance period. The average volatile anesthetic concentrations and age-adjusted fraction of agent-specific minimum alveolar concentration (MAC) over time (*i.e.*, MAC · hour = sum of end-tidal concentration divided by the MAC value multiplied by the duration [h] at that concentration) were determined. In addition, the usage (ml) of desflurane and sevoflurane was calculated using the formula described by Dion (usage of volatile anesthetic [ml] = dialed concentration × total fresh gas flow × duration at that concentration × molecular weight divided by 2,412 × density).[6] Recovery times were determined at 1-min intervals from discontinuation of the inhaled anesthetics to awakening (*e.g.*, opening eyes on verbal command), orientation to person, date, and place, and subsequently at 15-min intervals until the patient was judged "home-ready" (*i.e.*, achieving the criteria for discharge home).[7] At the time of discharge from the hospital and during the follow-up telephone interview 24 h after surgery, patients were asked whether they recalled any intraoperative events.

Before initiating the study, a power analysis based on a pilot study suggested that a sample size of 15 patients for each group should be adequate to detect a 30% reduction in the times to awakening and extubation with a power of 0.8 (alpha = 0.05). One-way analysis of variance (ANOVA) was performed for all continuous variables, and when a significant difference was noted, a Newman-Keuls test was performed for *post hoc* comparisons within and between groups. Nonparametric variables were analyzed using the chi-square test with Yates' continuity correction, as appropriate. Data are expressed as mean values ± SD, and P values of less than 0.05 were considered statistically significant.

Results

The four study groups were comparable with respect to age, weight, height, American Society of Anesthesiologists' (ASA) physical status, and duration of surgery and anesthesia (table 1). The HR values remained stable

Table 1. Demographic Data for the Four Anesthetic Treatment Groups

	Desflurane		Sevoflurane	
	Control	BIS-titrated	Control	BIS-titrated
Number (n)	15	15	15	15
Age (yr)	27 ± 6	28 ± 4	26 ± 7	26 ± 6
Weight (kg)	75 ± 10	76 ± 12	72 ± 13	70 ± 12
Height (cm)	162 ± 3	162 ± 4	163 ± 2	163 ± 2
ASA physical status (I/II)	11/4	10/5	10/5	11/4
Duration of surgery (min)	49 ± 20	46 ± 14	43 ± 22	45 ± 19
Duration of anesthesia (min)	78 ± 22	76 ± 20	75 ± 21	74 ± 21

Values are mean ± SD.

throughout the operation and did not differ among the four anesthetic treatment groups (fig. 1). The MAP decreased by 37 ± 5% below baseline values after induction of anesthesia with propofol and increased significantly in all four treatment groups after surgical incision (fig. 1). The MAP values were similar in the four groups except for the initial 15-min period after the surgical incision when the MAP values were found to be significantly lower in the control groups (fig. 1).

The mean baseline (preinduction) BIS index values were 97 ± 1, which decreased to a minimum of 37 ± 8 after induction of anesthesia with propofol (fig. 2). During the operation, the BIS index values (mean ± SD) were significantly lower in the control groups compared with the BIS-titrated groups (44 ± 11 and 42 ± 8 in Groups I and III *vs.* 60 ± 4 and 62 ± 3 in Groups II and IV, respectively). The BIS index values on awakening (eye opening) were similar in all four groups (93 ± 6).

During the maintenance period, the end-tidal concentrations of desflurane and sevoflurane were significantly lower ($P < 0.001$) in the two BIS-titrated groups compared with the control groups (4.2 ± 0.4% *vs.* 2.3 ± 0.5% in Groups I and II and 1.8 ± 0.3% *vs.* 0.9 ± 0.3% in Groups III and IV, respectively; fig. 2). Compared with the control groups, the volatile anesthetic requirements (MAC · h) and the usage (ml) of desflurane and sevoflurane were significantly lower in their respective BIS-titrated groups (table 2). Importantly, the number of supplemental boluses of fentanyl did not differ

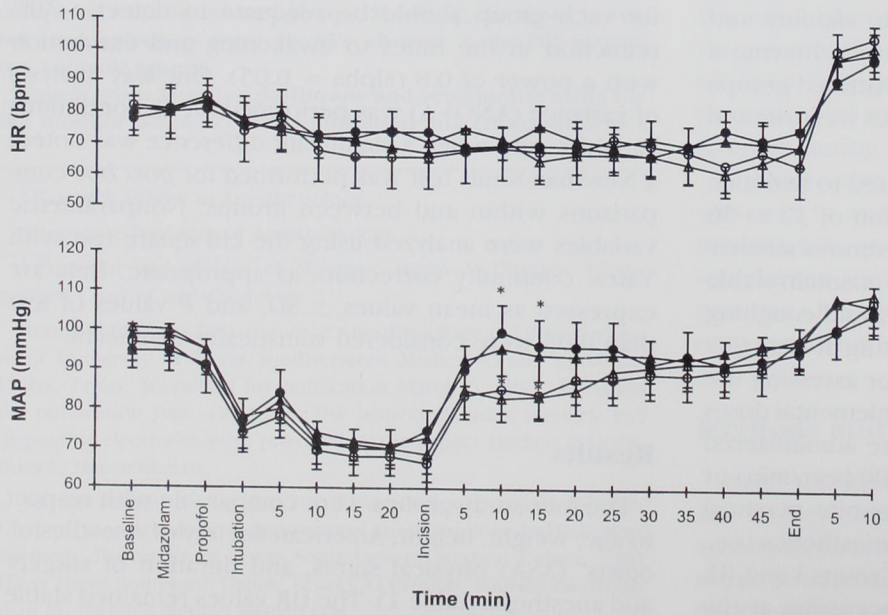

Fig. 1. Changes in the heart rate (HR) and mean arterial pressure (MAP) during surgery in the four study groups. -△-, Group I (desflurane-control); -▲-, Group II (desflurane-BIS-titrated); -○-, Group III (sevoflurane-control); -●-, Group IV (sevoflurane-BIS-titrated). Values are mean ± SD. * indicates $P < 0.05$ compared with the control groups.

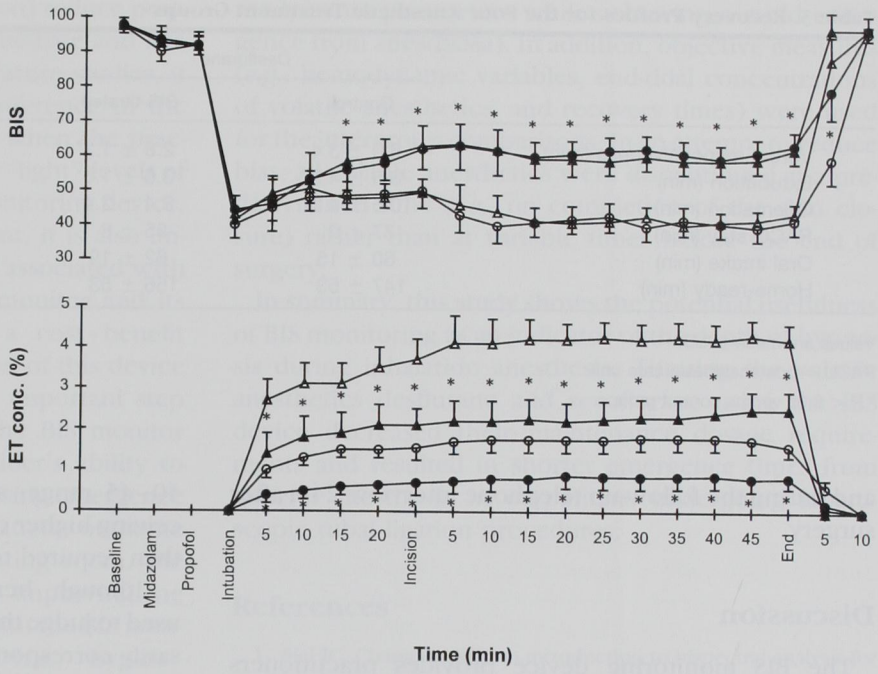

Fig. 2. Changes in the BIS values and end-tidal concentrations (ET conc.) of the volatile anesthetics during surgery in the four study groups. -△-, Group I (desflurane-control); -▲-, Group II (desflurane-BIS-titrated); -○-, Group III (sevoflurane-control); -●-, Group IV (sevoflurane-BIS-titrated). Values are mean ± SD. * indicates $P < 0.05$ compared with the control groups.

among the four groups (*e.g.*, 19, 20, 15, and 18 boluses in the Groups I, II, III, and IV, respectively), and total dosages of fentanyl in each group were also similar (table 2). However, the requirements for mivacurium were significantly higher in the BIS-titrated groups compared with the control groups (table 2). In the BIS-titrated groups, 17 patients (57%) had transient increases in peak airway pressure, and 7 patients (23%) had coughing or bucking, whereas in the control groups, only 9 patients (30%) had increases in peak airway pressure, and 3 patients (10%) had coughing or bucking. No patient required neuromuscular reversal drugs.

The times to awakening and extubation were significantly shorter in the BIS-titrated groups compared with the control groups (table 3). Within the BIS-titrated groups, the time to awakening was significantly shorter in Group II compared with Group IV. Times to orientation were similar in all patients receiving desflurane (Groups I and II), although orientation time was significantly decreased in Group IV compared with Group III (table 3). There were no differences between the groups with respect to the duration of the PACU stay and the times to home-readiness (table 3). None of the patients reported recall of intraoperative events when questioned at the time of discharge from the hospital

Table 2. The Dosage Requirements for the Anesthetic Drugs Used in the Four Anesthetic Treatment Groups

	Desflurane		Sevoflurane	
	Control	BIS-titrated	Control	BIS-titrated
MAC · hour (% · h)	1.2 ± 0.5	0.8 ± 0.3*	1.5 ± 0.5	0.7 ± 0.4*
Desflurane (ml)	25.0 ± 6.3	17.3 ± 4.9*	NA	NA
Sevoflurane (ml)	NA	NA	13.8 ± 2.1	8.5 ± 4.8*
Mivacurium (mg)	7.6 ± 3.1	13.3 ± 4.9*	8.5 ± 4.0	13.1 ± 6.9*
Fentanyl (μg)	146 ± 78	134 ± 81	123 ± 46	134 ± 59

Values are mean ± SD.

NA = not applicable.

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

Table 3. Recovery Profiles for the Four Anesthetic Treatment Groups

	Desflurane		Sevoflurane	
	Control	BIS-titrated	Control	BIS-titrated
Verbal responsiveness (min)	6.0 ± 3.4	2.8 ± 1.2*	7.6 ± 2.7	5.0 ± 2.0*
Extubation (min)	6.5 ± 4.3	3.6 ± 1.5*	7.7 ± 3.5	5.5 ± 2.2*
Orientation (min)	10.5 ± 4.2	8.4 ± 2.4	13.2 ± 4.0	10.2 ± 2.8*
PACU stay (min)	37 ± 9	35 ± 8	35 ± 8	37 ± 10
Oral intake (min)	60 ± 15	62 ± 19	58 ± 10	59 ± 14
Home-ready (min)	147 ± 53	156 ± 53	149 ± 41	148 ± 59

Values are mean ± SD.

PACU = postanesthesia care unit.

* $P < 0.05$ *versus* control groups.

and during the follow-up telephone interview 24 h after surgery.

Discussion

The BIS monitoring device provides practitioners with information regarding the hypnotic component of the anesthetic state.[2] The BIS index has been shown to be a significant predictor of patient response to skin incision when isoflurane was used as a primary anesthetic.[8] However, when opioid analgesics are administered as adjuncts during general anesthesia, the BIS index does not correlate with patient responses to skin incision.[8] A recent report demonstrated a good correlation between end-tidal isoflurane concentrations and BIS index values, suggesting a role for the device in monitoring isoflurane-induced sedation.[9] Further, the BIS monitor has been found to predict recovery of consciousness from general anesthesia.[10] This study demonstrated that titrating desflurane and sevoflurane to maintain a BIS index value of 60 during general anesthesia decreased the amount of the volatile anesthetic used during the maintenance period. In addition, the use of a BIS titration protocol resulted in a more rapid emergence and shorter times to extubation after anesthesia.

Analogous to these findings with desflurane and sevoflurane, preliminary studies with propofol have suggested that the addition of BIS monitoring to standard clinical practices can improve titration of propofol and may contribute to decreases in the maintenance dosage requirements.[5] Further, BIS monitoring provided for a more rapid emergence from propofol–alfentanil–nitrous oxide anesthesia and decreased the length of the postanesthesia care unit (PACU) stay.[11,12] In the control groups, the average BIS values were maintained in the 40–45 range, suggesting that these patients were receiving higher concentrations of the volatile anesthetics than required to maintain an unconscious state.

Although hemodynamic responses are commonly used to judge the depth of anesthesia, they do not necessarily correspond to purposeful motor responses to surgical stimuli.[13] Further, there is no solid basis for using hemodynamic variables as an indicator of anesthetic depth. Monitoring end-tidal concentrations of volatile anesthetics to judge the adequacy of depth of anesthesia also is questionable. Although the MAC concept is useful in comparing the relative potency of volatile anesthetics, multiple confounding factors can affect the MAC values of individual patients. In clinical practice, the use of MAC as a guide to titrate volatile anesthetics can result in either underdosing or overdosing with an volatile anesthetic. Further, end-tidal anesthetic monitoring does not improve intraoperative hemodynamic stability or decrease emergence times from general anesthesia.[14]

Because volatile anesthetics are known to enhance the clinical effects of nondepolarizing neuromuscular-blocking drugs,[15] the higher concentrations of volatile anesthetics used in the control groups may have contributed to the decreased need for mivacurium. In addition, the increased muscle relaxant requirements in the BIS-titrated groups was probably related to the "lighter" plane of anesthesia, which was maintained in these groups.

The availability of more rapid and shorter-acting intravenous (*e.g.*, propofol) and volatile (*e.g.*, desflurane and sevoflurane) anesthetics and muscle relaxants (*e.g.*, mivacurium) has clearly facilitated the early recovery process. In addition, the prophylactic use of nonopioid analgesics (*e.g.*, bupivacaine and ketorolac) and anti-

emetics (*e.g.*, droperidol and ondansetron) reduce postoperative side effects and enhance immediate and late recovery after ambulatory surgery. In future studies, it will be necessary to demonstrate a difference in the drug consumption and recovery times when the practitioner is incentized to maintain similar "light" levels of anesthesia with and without the BIS monitoring device.

In the present healthcare environment, it is also important to consider the increased costs associated with BIS monitoring (*e.g.*, the cost of the monitor and its disposable accessories).[16] Therefore, a cost-benefit analysis is important before introduction of this device into "routine" anesthesia practice. An important step in this process is to document that the BIS monitor actually improves the anesthesia provider's ability to administer anesthetic drugs (*e.g.*, decreasing emergence and turnover times) and improves patient outcome (*e.g.*, earlier discharge from the operating room, the PACU and the ambulatory facility). By improving the titration of desflurane and sevoflurane with the BIS monitor, it should be possible to fast-track (*i.e.*, "bypass" the PACU) the majority of outpatients receiving general anesthesia.[17] However, cost analysis of new medical devices are complex and the benefits are difficult to measure with accuracy.[18]

One of the major concerns when using the BIS monitor to titrate anesthetics is the possibility of intraoperative recall. In combination with 65% N_2O, the end-tidal concentrations of the volatile anesthetics used in the BIS-titrated groups were higher than those required to prevent learning and recall.[19,20] Further, the use of midazolam would be expected to decrease the concentration of volatile anesthetics required to prevent recall. Because none of the patients in the BIS-titrated groups experienced intraoperative recall, the lower concentrations of the volatile anesthetics administered in these groups appeared to provide an adequate hypnotic state. Nevertheless, the low incidence of intraoperative recall during general anesthesia would necessitate the use of a much larger sample size to find a difference if one actually existed between the BIS-treated and control groups.

One of the criticisms of this study is the possibility of bias as a result of the lack of a double-blind design. However, this clinical investigation was conducted in the context of standard clinical practice, and routine "blinding" procedures would not be appropriate. The anesthesia practitioners were instructed to maintain a minimally acceptable "depth of anesthesia" (*i.e.*, to prevent purposeful movement and maintain acceptable hemodynamic parameters while achieving a rapid emergence from anesthesia). In addition, objective measures (*e.g.*, hemodynamic variables, end-tidal concentrations of volatile anesthetics, and recovery times) were used for the intergroup comparisons. In an attempt to reduce bias, all volatile anesthetics were discontinued at a predetermined time (*i.e.*, on completion of the skin closure) rather than at variable times before the end of surgery.

In summary, this study shows the potential usefulness of BIS monitoring as an indicator of the depth of hypnosis during inhalation anesthesia. Titrating the volatile anesthetics desflurane and sevoflurane using the BIS device decreased their maintenance dosage requirements and resulted in shorter emergence times from general anesthesia in outpatients undergoing laparoscopic tubal ligation procedures.

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