Anesthesiology
1997; 87:808-15

Bispectral Index Monitoring Allows Faster Emergence and Improved Recovery from Propofol, Alfentanil, and Nitrous Oxide Anesthesia

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Background: **The bispectral index (BIS), a parameter derived from the electroencephalograph (EEG), has been shown to correlate with increasing sedation and loss of consciousness. This study determined whether addition of BIS monitoring to standard anesthetic practice results in improvements in the conduct of anesthesia or in patient outcomes.**

***Methods*: Three hundred two patients receiving a propofol–alfentanil–nitrous oxide anesthetic were studied at four institutions. Thirty-four patients were initially enrolled to determine preexisting anesthetic practice and patient outcomes at each institution. Subsequent patients were randomized to either standard clinical practice (SP group), or standard practice plus BIS monitoring (BIS group). In all patients, the anesthesiologist attempted to provide a stable anesthetic with the fastest possible recovery. BIS was recorded for all patients, but viewed only in the BIS group. In the BIS group, propofol infusions were adjusted to achieve a target BIS between 45–60, increasing to 60–75 during the final 15 min of the case. In the SP group, propofol dose adjustments were made based only on standard clinical signs. Drug use, intraoperative responses, and patient recovery parameters were recorded.**

***Results*: Demographics were similar between groups. Compared with the SP group, patients in the BIS group required lower normalized propofol infusion rates (134 *vs.* 116 $\mu g \cdot kg^{-1} \cdot min^{-1}$; $P < 0.001$), were extubated sooner (11.22 *vs.* 7.25 min; $P < 0.003$), had a higher percentage of patients oriented on arrival to PACU (43% *vs.* 23%; $P < 0.02$), had better postanesthesia care unit (PACU) nursing assessments ($P < 0.001$), and became eligible for discharge sooner (37.77 *vs.* 31.70 min; $P < 0.04$). There was no significant difference in the incidence of intraoperative responses between the groups.**

***Conclusions*: Titrating propofol with BIS monitoring during balanced anesthesia decreased propofol use and significantly improved recovery. Intraoperative course was not changed. These findings indicate that the use of BIS may be valuable in guiding the administration of propofol intraoperatively. (Key words: Anesthetics, intravenous: alfentanil; nitrous oxide; propofol; Measurement techniques: bispectral index. Outcome: anesthesia. Recovery: emergence time.)**

THE bispectral index (BIS) is a variable derived from the electroencephalograph (EEG) that has been reported to have the ability to measure the hypnotic component of the anesthetic state.[1-6] It is a dimensionless number from 0 to 100, and decreasing values indicate more sedation and hypnosis. In volunteer studies, BIS correlated strongly with the effects of propofol, isoflurane,

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Received from the Departments of Anesthesiology, Duke University, Durham, North Carolina; Grady Health System, Emory University, Atlanta Georgia; University of North Carolina, Chapel Hill, North Carolina; Massachusetts General Hospital, Harvard University, Boston, Massachusetts; and Aspect Medical Systems, Natick, Massachusetts. Submitted for publication December 17, 1996. Accepted for publication May 30, 1997. This study was presented in part at the American Society of Anesthesiologists meeting on October 19-23, 1996, in New Orleans, Louisiana. Supported in part by a grant from Aspect Medical Systems. Peter S. Glass, M.B., F.F.A(SA)., Fredrick Payne, M.D., Carl Rosow, M.D., Ph.D., and Peter Sebel, M.B., B.S., Ph.D., F.F.A.R.S.C.I., have received grant support and consulting fees from Aspect Medical Systems.

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and midazolam on level of sedation, recall, and learning tasks, and a BIS < 60 had a high probability of correctly predicting absence of consciousness.[2,7-11] In these studies, the level of sedation produced during propofol administration was more strongly correlated with BIS than measured or predicted propofol concentrations.[12] BIS has also been shown to predict the probability of recovery of consciousness after either a thiopental or propofol induction.[13] These findings demonstrated that BIS may be used to measure the effect of anesthetic agents on the level of consciousness.

The anesthetic state is achieved with a hypnotic or sedative and an analgesic to provide absence of consciousness, amnesia, and analgesia. The present study was designed to investigate whether using BIS to monitor consciousness would improve clinical anesthetic delivery compared with standard practice. The hypotheasis was that monitoring of the EEG response using BIS throughout surgery would allow accurate titration of propofol for each patient, thereby reducing the amount of drug administered and shortening recovery time. The primary objective of this clinical utility study was to show the efficacy of BIS monitoring as a pharmacodynamic measure of patient response to propofol during general anesthesia. A secondary objective was to show whether guiding drug administration by BIS changes the number of unwanted somatic and hemodynamic responses intraoperatively.

Methods and Materials

This multicenter, prospective, randomized clinical utility study compared "standard practice (SP)" with "standard practice plus BIS monitoring (BIS)" treatment groups. Institutional Review Board approval and written informed patient consent were obtained at each site. During a preliminary baseline phase, each site collected relevant outcome results from a series of patients receiving propofol-alfentanil-N_2O anesthesia to study preexisting clinical practice. This group formed the historical control, and the data were used to test for potential learning bias or changing clinical practice during the course of the trial. Anesthesia in all patients was supervised by a faculty anesthesiologist.

Once the historical control subjects were collected, subsequent patients were randomized to one of the two treatment groups (SP or BIS). Assignment to the study condition was determined using sequential coded envelopes after patients' informed consent had been obtained. The sequence of treatments was determined in blocks of 10 (5 SP and 5 BIS) using a random number generator.

Men and women, aged 18-80 yr, American Society of Anesthesiologists' (ASA) physical status I, II, or III, scheduled for general surgical procedures expected to last at least 1 h were studied. Subjects with known neurologic disorders, uncontrolled hypertension, baseline systolic blood pressure (BP) < 106, heart rate (HR) < 55, or any serious medical conditions that would interfere with cardiovascular response assessment were excluded. Cases lasting less than 30 min were also excluded from analysis. Each of four sites was to enroll 50-80 patients.

All subjects in both groups had EEGs and vital signs recorded throughout each case. The EEG signal was acquired using Zipprep™ electrodes (Aspect Medical Systems Inc., Natick, MA; all impedances < 5 kOhms) applied to the forehead and temple using a frontal-temporal montage. BIS (Rev 3.0U) was calculated and displayed in real time using an A-1000 EEG monitor (Aspect Medical Systems Inc.). The EEG was recorded continuously beginning before the induction of anesthesia until patients were awake and responding to verbal commands at the conclusion of surgery. The anesthesiologist viewed the monitor in the BIS treatment group and adjusted the dose of propofol to achieve a target BIS range of 45-60. Processed EEG parameters (*i.e.*, BIS) were not displayed (the monitor screen was covered over with an opaque card) in the SP group, so dosage adjustments of propofol were made at the discretion of the primary anesthesiologist based only on standard clinical signs and to provide a rapid recovery. A trained research coordinator also was present in the operating room (OR) to record data from all patients.

All subjects received intravenous midazolam, 1-2 mg, fluid load (500 ml), and induction regimens consisting of propofol, 1-2 mg/kg, and alfentanil ≤ 30 μg/kg. After loss of consciousness, infusions of propofol at 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and alfentanil, 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, with 50% N_2O were started, and if necessary, a neuromuscular-blocking agent was administered to facilitate intubation of the trachea. After intubation or insertion of a laryngeal mask, additional neuromuscular blocking agents were only administered as surgically indicated, and at least two twitches (monitored by train-of-four) were present whenever possible.

During the intraoperative maintenance phase, all patients were assessed for signs of inadequate anesthesia and hypotension or bradycardia, as defined in table 1.

Table 1. Definition of "Unwanted Patient Responses"

Criteria for inadequate anesthesia
Hypertension: blood pressure >20% increase from baseline
Relative tachycardia: heart rate >90 bpm
Somatic: movement, grimacing, eye opening, coughing
Criteria for significant hypotension/bradycardia
Blood pressure: >20% decrease from baseline
Heart rate: >20% decrease from baseline

In the SP group, episodes of inadequate anesthesia were managed with increases in the doses of either alfentanil, propofol, or an antihypertensive at the discretion of the primary anesthesiologist. Hypotension and bradycardia were managed with appropriate dose reductions, adjustment of fluid status, or other pharmacologic agents as needed based on the judgment of the anesthesiologist. Patients in the BIS group received a variable dose propofol infusion adjusted to maintain a BIS in the 45–60 range whenever possible. Signs of inadequate analgesia or hypotension were to be managed with increased or decreased alfentanil, respectively, if BIS was within the recommended range. The administration of other medications was otherwise the same as SP.

About 15 min before the end of surgery, anesthesia was reduced in both groups to facilitate rapid recovery. In the BIS group, alfentanil infusions were discontinued, and propofol was adjusted to achieve a BIS in the 60–75 range. This range was to be maintained to within 5 min before the end of surgery, when the propofol infusion and nitrous oxide were discontinued and when the patient was allowed to awaken.

Intermittent noninvasive BP and HR were recorded every 5 min, as was continuous EEG, in time-synchronized computer files. Descriptions of all important intraoperative events, including all episodes of inadequate anesthesia (as defined in table 1) or hypotension or bradycardia requiring intervention, were recorded, along with all medications administered (bolus doses, infusion rates, total amounts used) and times of key intraoperative points (intubation, start of procedure, end of surgical stimulation, dressing completed). The time when propofol anesthesia was discontinued was identified as the starting point (time = 0) of patient recovery.

Patient recovery was observed continuously after the termination of anesthesia. Times of initial wake-up events (open eyes, response to simple command, extubation, move to postanesthesia care unit [PACU]) were recorded in the OR by the anesthesiologist. After transfer to the recovery area, patients were assessed continuously by a recovery room nurse who was blinded to the intraoperative treatment group assignment.

Table 2. Clinical Global Impression Scales

Rating	Description
Anesthetic assessment	
1	Excellent; no "unwanted responses"
2	Good; 1 or 2 minor responses
3	Fair; several significant responses
4	Poor; hard to manage case
5	Most dificult
Recovery assessment	
1	Excellent; fully oriented on arrival
2	Good; fast, smooth recovery
3	Fair; slow recovery from anesthetic
4	Poor; prolonged sedation and recovery
5	Very poor; extended recovery delay or unanticipated admission

The anesthesiologist and the blinded recovery room nurse independently provided an overall rating of each case using a 5-point categorical "Clinical Global Impression" scale (table 2). Patients were discharged from the recovery room when they met a standard set of discharge criteria (table 3).

Descriptive statistics were used to characterize demographic variables of each of the study groups. Comparisons between treatment groups were conducted using either a chi-square test, Mann-Whitney U test (nonpara-

Table 3. Standard Criteria for Discharge

Pulse	>50 and ±20% baseline
BP, systolic/MAP	>90 and ± 20% baseline/+20% baseline
Respiratory rate	8–30
O_2 saturation	>90%
Temperature	>96°F oral/95°F axillary or (>35.5°C oral/35°C axillary)
Alert	Yes
Arousable, oriented	Responsive to name or with light touch. No delay in answer to "Do you know your name, . . . the time, . . . where you are?"
Nausea	Patient self-rating: non to mild
Vomited	Not currently vomiting
Pain	Patient self-rating: none to moderate
Airway	No obstruction
Breath sounds	Postsurgery best
Cardiac rhythm	Acceptable rhythm

BP = blood pressure; MAP = mean arterial pressure.

metric data), Student's t tests, analysis of variance (ANOVA), or repeated measures ANOVA as appropriate. The distributions of emergence times in the BIS and SP treatment groups were also compared using Kaplan-Meier log-rank survival analysis.

Data are displayed as mean (95% confidence intervals) with P values < 0.05 considered statistically significant. Normalized drug infusion data, which considers induction and maintenance doses, are presented. In this study protocol, an improvement of $> 20\%$ in any recovery endpoint was defined, *a priori,* to be clinically significant. This study was designed to allow sufficient statistical power (80%, with alpha = 0.05) to detect a 20% reduction in recovery times or a 20% reduction in the incidence of intraoperative events.

Results

Thirty-four control and 268 randomized patients were enrolled at the four study sites participating in this study. Twenty-eight patients had protocol violations for various reasons (case duration < 30 min, eight patients; extended surgeries, five patients; improper timing of agent administration, five patients; equipment failure and lack of critical recorded endpoints, eight patients; and delayed administration of neuromuscular reversal agents, four patients) and were therefore excluded from efficacy analysis. Therefore, the evaluable study population consisted of 34 control subjects, 125 SP, and 115 BIS group patients. The demographic distribution in each study group is presented in table 4. An ANOVA comparison of the recovery times in the SP groups revealed no significant differences between sites in the outcome parameters. Although several isolated recovery times for the BIS group were different between sites, there was no consistent evidence of site related differences in the overall outcome. Therefore, results from the pooled data from all sites combined for the SP and BIS groups are presented.

A comparison between the SP and BIS groups of the average actual propofol infusion rates (fig. 1), BIS levels (fig. 2), mean BPs (fig. 3) and HRs (fig. 4) at various milestones during surgery are presented. The average normalized propofol infusion (induction and maintenance doses) in the BIS group was lower than the SP group (134 *vs.* 116 $\mu g \cdot kg^{-1} \cdot min^{-1}$; $P < 0.001$). The mean amounts of propofol (induction and maintenance) used were 1,253 mg and 964 mg for the SP and BIS groups, respectively, $P < 0.001$. Overall, the rate of reduction of normalized propofol infusion rates was faster in the BIS group, and BIS levels were correspondingly higher, but mean BP and HR remained stable and indistinguishable from the SP group.

Table 4. Demographic Data for the BIS and SP Groups

Demographic	SP	BIS
No. of patients	125	115
Males/females	41/84	37/78
Age (yr)*	41 (39–43)	40 (37–43)
Weight (kg)*	77.5 (74.3–80.7)	80.0 (76.4–83.7)
ASA Physical Status 1/2/3 (no. of patients)	45/72/8	45/65/5
Total duration of anesthesia (min)*	125 (114–135)	108† (99–119)
Laryngeal mask airway	15	16
Endotracheal tube	110	99
Normalized alfentanil infusion rate (μg/kg/min)	0.67 ± 0.25	0.66 ± 0.21

Alfentanil infusion rate was calculated as total alfentanil administered divided by weight and case duration.

* Means (95% confidence intervals).

† $P < 0.05$ *versus* SP.

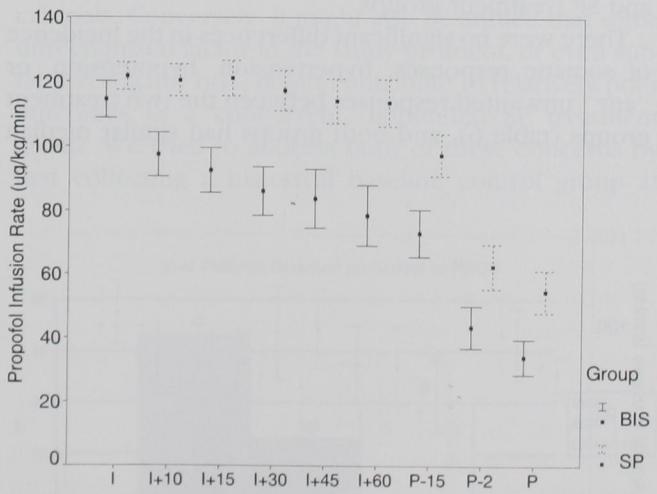

Fig. 1. Plot of propofol infusion rates (mean ± 95% confidence interval, in $\mu g \cdot kg^{-1} \cdot min^{-1}$) at various milestones during surgery. *Dotted lines*, standard Practice (SP) group; *solid lines*, BIS group. The endpoints are abbreviated in figures 1–4 as: *B,* a preinduction baseline; *Ind,* the time of induction; *I,* the start of the procedure; *P,* the time of propofol off; and *OE,* the time of open eyes. The numbers accompanying these abbreviations refer to min before or after the respective endpoint.

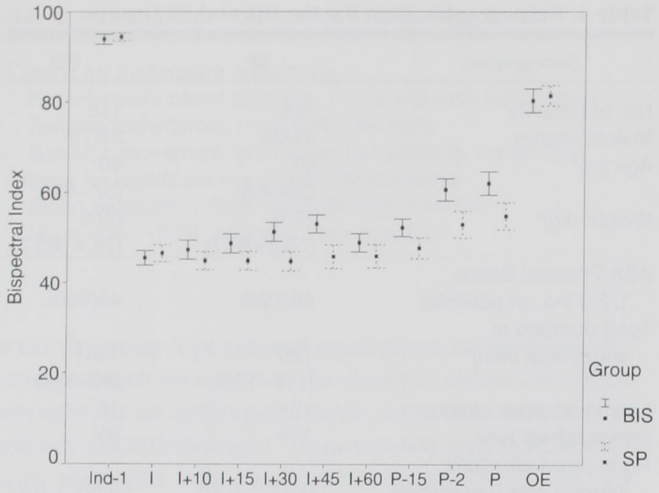

Fig. 2. Plot of BIS levels (mean ± 95% confidence interval) at various milestones during surgery. *Dotted lines*, standard practice (SP) group; *solid lines* = BIS group.

Results for the primary recovery interval endpoints of "opens eyes," "responds to command," "extubation," and "eligibility for discharge" are summarized in table 5. All of these indices of recovery were significantly more rapid in the BIS group than in the SP group. Figure 5 shows a survival analysis comparison of the cumulative probability of patients remaining unconscious after discontinuation of propofol administration in the BIS and SP treatment groups.

There were no significant differences in the incidence of somatic responses, hypertension, hypotension, or "any" unwanted responses between the two treatment groups (table 6), and both groups had similar median

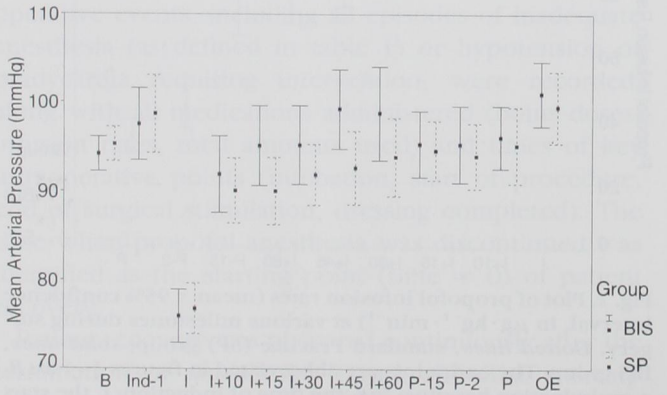

Fig. 3. Plot of mean blood pressures (mean ± 95% confidence interval, in mmHg) at various milestones during surgery. *Dotted lines*, standard practice (SP) group; *solid lines*, BIS group.

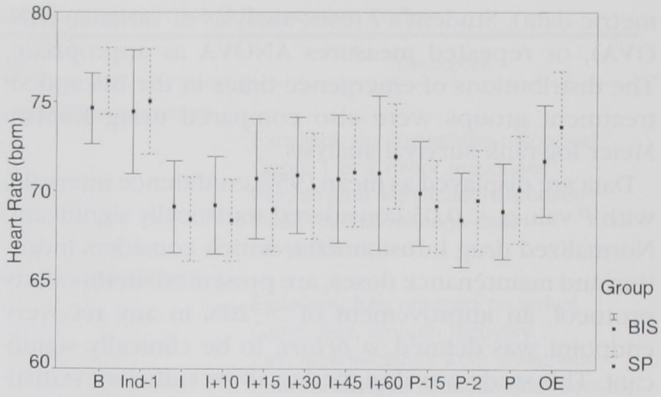

Fig. 4. Plot of heart rates (mean ± 95% confidence interval, in beats/min) at various milestones during surgery. *Dotted lines*, standard practice (SP) group; *solid lines*, BIS group.

intraoperative global assessment scores (BIS = 2 *vs.* SP = 2, not significant).

More patients in the BIS treatment group arrived fully oriented on admission to the PACU (BIS 43% *vs.* SP 23%; $P < 0.02$; fig. 6), and overall global nursing impression scores are shown in table 7. Although the median scores are similar (BIS = 2 *vs.* SP = 2), the difference between the two groups was statistically significant, with the BIS group achieving better scores than the SP group ($P < 0.001$, Mann-Whitney test). Patients in the SP group emerged from anesthesia faster than those in the historical control population, suggesting that standard practice techniques improved during the study period.

Table 5. Time Needed to Achieve the Primary Recovery Endpoints for the BIS, SP, and Control Groups

Recovery Endpoint	Controls	SP	BIS
No. of patients		125	115
Opens eyes	12.43 (10.00–14.87)	9.52* (8.2–10.83)	6.25† (5.28–7.25)
Responds to commands	14.34 (11.25–17.50)	10.47* (9.13–11.80)	6.65† (5.65–7.65)
Extubated	13.28 (10.88–15.68)	11.22 (8.51–13.60)	7.27‡ (6.23–8.28)
Eligible for discharge	43.85 (35.70–52.00)	37.78 (33.66–41.90)	31.70§ (28.03–35.38)

Values are mean (95% confidence interval).

* $P < 0.05$, SP *versus* controls.

† $P < 0.001$ *versus* SP.

‡ $P < 0.01$ *versus* SP.

§ $P < 0.05$ *versus* SP.

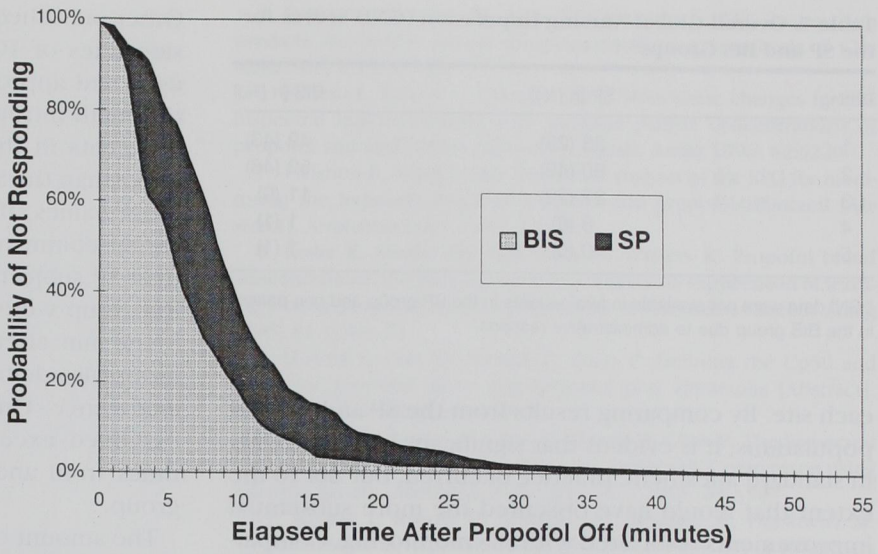

Fig. 5. Comparison of the cumulative probability of patients remaining unconscious after the discontinuation of propofol anesthesia in the BIS (*light hatched area*) and standard practice (SP, *solid dark area*) groups. Cumulative probabilities were determined using Kaplan-Meier survival analysis. Log-rank differences between the two distributions (BIS *vs.* SP) were highly significant ($P < 0.0001$).

Discussion

Results from this clinical utility trial show that the BIS may be used to measure the pharmacodynamic effect of propofol and thereby facilitate its titration to improve recovery from anesthesia. In the group wherein BIS was not used, patients were consistently administered more propofol throughout the anesthetic. This holds true in all study centers and probably reflects current clinical practice in general. On the other hand, titration of propofol based on the BIS resulted in reduced propofol infusion rates, reduced total amount of propofol used, faster wake-up, and improved recovery from anesthesia. No significant increase in the incidence of unwanted reactions such as movement or hypertensive responses occurred, thereby indicating that the benefits of improved recovery times obtained using BIS monitoring were not obtained at the expense of an increase in events associated with inadequate anesthesia.

Table 6. Incidence of Intraoperative "Unwanted Patient Responses" for the BIS, SP and Control Groups

Event	Controls	SP	BIS
No. of patients	34	125	115
Any	59	78	82
Somatic	21	31	39
Hypertension	21	30	37
Hypotension	21	38	32

Values are % of total patients in each treatment group.

Several important study design issues should be considered when evaluating the results from this trial. In a recent editorial, Roizen and Toledano discussed the problem of "learning contamination bias" that can be associated with the introduction and incorporation of new monitoring technologies.[14] They suggested that as new information is gained from use of a device, standard clinical practice patterns may improve, making it more difficult to show a difference in randomized device clinical trials. Conversely, it might also be argued that some unrecognized factor in the study protocol, or even subtle investigator bias, might contribute to relatively poor outcomes in a concurrent, unblinded SP treatment group. We tried to address both of these concerns by first collecting a historical baseline control group at

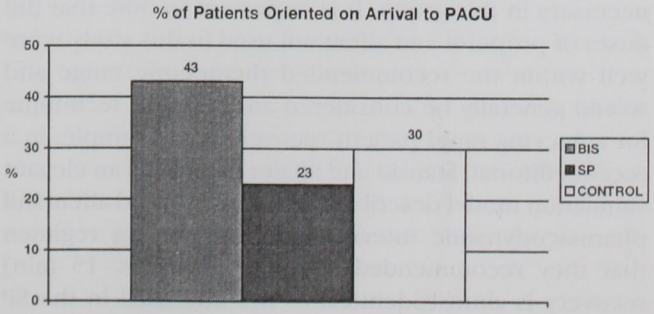

Fig. 6. Comparison of the percent of patients who were alert and oriented on arrival to the PACU in the BIS, standard practice (SP), and control groups. The difference between BIS and SP groups is statistically significant ($P < 0.001$, chi-square test).

Table 7. Overall Global Nursing Impression (GNI) Scores for the SP and BIS Groups*

Rating	SP [n (%)]	BIS [n (%)]
1	28 (23)	49 (43)
2	60 (49)	52 (46)
3	27 (22)	11 (9)
4	8 (6)	1 (1)
5	0 (0)	1 (1)

* GNI data were not available in two patients in the SP group and one patient in the BIS group due to administrative reasons.

each site. By comparing results from the SP and control populations, it is evident that significant improvements in standard anesthetic practice occurred, but not to the extent that would have obscured the more substantial improvements associated with BIS monitoring. Comparison of the BIS group results with those of the historical control subjects, rather than the SP group, suggests stronger improvements associated with BIS monitoring.

Intraoperatively, we were not able to use a double-blind study design, so some potential for investigator bias existed. The primary anesthesiologists were instructed to deliver the best possible anesthetic that would allow a rapid recovery in the SP group. As shown in figures 1 and 2, it is evident that, consistent with good clinical practice, propofol infusions were reduced during the course of surgery in anticipation of the end of surgery. Mean BP and HR were also similar in both groups, indicating that vital signs were also managed similarly and appropriately in both groups. Therefore, we are unable to detect obvious evidence of significant investigator bias.

In retrospect, most SP patients were maintained at a BIS level below 50 for much of the case, so according to BIS criteria, more propofol was being used than was necessary in this group. It is important to note that the doses of propofol and alfentanil used in this study were well within the recommended therapeutic range and would generally be considered an excellent technique for achieving rapid patient recovery. For example, in a recent editorial, Stanski and Shafer presented an elegant simulation model describing the propofol and alfentanil pharmacodynamic interaction.[15] The dosing regimen that they recommended to achieve fast (< 15 min) recovery is almost identical to the one used in the SP group in the present study. Consequently, it is not surprising that the emergence times that were obtained in the SP group in this study are consistent with the outcomes predicted by the Stanski and Shafer models. Other published reports also suggest that propofol infusion rates of 100–150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ are commonly used and appropriate when administered in combination with nitrous oxide and an opioid analgesic.[16,17]

Patients in the BIS group emerged from anesthesia faster than the SP or control patients. When comparing mean values, BIS patients opened eyes, responded to verbal command, and were extubated 34–38% faster than SP subjects. As shown in figure 5, patients in the BIS group were more likely to wake-up within the first 5–10 min after discontinuation of propofol. The BIS group also demonstrated greater predictability of rapid emergence. Only 5% of the patients in the BIS group exhibited exceptionally long (> 15 min) emergence times from anesthesia compared with 16% in the SP group.

The amount of propofol used was significantly less in the BIS group compared with the SP group (1,253 mg for SP group *vs.* 964 mg for BIS group). If potential indirect cost savings associated with faster OR and PACU turnover are also considered, it is possible that BIS monitoring may facilitate cost-effective anesthetic delivery, although direct study of this issue is required. No significant differences between treatment groups were noted in intraoperative events or in intraoperative global assessment scores. This may be in part a result of the relatively low statistical power associated with analysis of this endpoint. During the design of this study, we only anticipated sufficient power to detect a true difference of greater than 20% in the incidence of intraoperative events. No differences of this magnitude were observed. Nevertheless, our results indicate that titration of propofol based on BIS response does not change the incidence of somatic movements or hypertensive episodes. Another potentially important inference that can be made based on these findings is that somatic and cardiovascular responses are not closely related to either the amount of propofol given or the hypnotic state. It has been suggested that such responses may instead reflect the amount of stimulation or analgesic state and thus be influenced most by the amount of opioid used.[18] Because similar amounts of alfentanil were used in the SP and BIS treatment groups, no difference in response rates would be expected under these circumstances.

Patient assessment during the PACU recovery phase was conducted in a "blinded" manner. On arrival to the PACU, a significantly higher percentage of BIS patients were already alert and fully oriented. As nearly 50% of patients were awake and oriented at 5 min (fig. 6), this

may allow these patients in an ambulatory setting to bypass PACU I. This needs to be confirmed in further studies. Although most patients in both groups experienced smooth and uneventful recoveries, BIS patients nevertheless also received significantly better PACU global assessment scores and became eligible for discharge sooner.

In conclusion, these results demonstrate the safety and efficacy of BIS monitoring as a pharmacodynamic measure of patient response to propofol during propofol-alfentanil-N_2O anesthesia. Addition of routine BIS monitoring to standard anesthetic care resulted in reduced use of propofol and faster recovery compared with standard clinical practice, and this may result in potential economic benefits.

The authors thank Michael Bazaral, M.D., and Steven Shafer, M.D., for their advice on development of study protocol.

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