Preserved Memory Function during Bispectral Index–guided Anesthesia with Sevoflurane for Major Orthopedic Surgery

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Background: Memory function under anesthesia is undesired but may arise from light hypnosis as well as stress-enhanced learning during surgery. The bispectral index (BIS, Aspect Medical Systems, Norwood, MA) is a monitor of hypnotic state that can help to avoid light hypnosis (*i.e.*, BIS above 60). This study tested the hypothesis that BIS-guided anesthesia maintaining BIS 50–60 reduces the likelihood of memory function under anesthesia.

Methods: After obtaining informed consent, 128 patients scheduled for joint replacement surgery under general anesthesia with sevoflurane were randomly assigned to BIS-guided anesthesia, titrating drugs to BIS 50–60 (BIS group), or a standard practice group in which BIS was recorded but did not guide drug administration. After induction, all patients were repeatedly played a list of 15 words. After recovery from anesthesia, all were interviewed about recall and completed a recognition memory test containing the presented words (targets, 33.3%) and new words (distractors). Preoperatively, patients filled out a stress questionnaire (Spielberger State-Trait Anxiety Inventory).

Results: BIS values above 60 were recorded in both groups, but no patient recalled the presented words postoperatively. Only patients in the BIS group selected targets more often than distractors (37.1% *vs.* 31.5% hit rate, $P = 0.001$). Target hit rates correlated poorly to stress scores ($P > 0.9$), but were associated with the amount of fentanyl received preoperatively ($P = 0.01$) and pain management technique ($P < 0.01$).

Conclusions: BIS titration to BIS 50–60 does not necessarily curb memory function under anesthesia when BIS values higher than 60 occur. Preoperative analgesia attenuated the likelihood of memory function under anesthesia.

WE have limited understanding of the brain's ability to process complex, meaningful information that is not consciously perceived. This raises the question whether patients under general anesthesia form memories, even if they are deeply anesthetized. The question is not easily answered in the absence of a gold standard for consciousness.[1] For clinical purposes, monitors of "hypnotic state" were developed based on detectable differences in the electroencephalogram of human subjects who responded, or did not respond, to verbal commands or other forms of stimulation. We have used electroencephalogram bispectral index (BIS, Aspect Medical Systems, Norwood, MA) as a measure of hypnotic state to address the question of memory function under anesthesia, especially when the patient is deemed to be unconscious (*i.e.*, BIS below 60).[2,3]

Anesthesia clearly impairs basic elements of memory function, as evident from neuroimaging[4] and impaired memory performance for words presented at lower *versus* higher BIS levels in human surgical patients.[5–7] This is consistent with the notion that memory function depends on attentional resources, which falter rapidly when anesthesia is given. However, memory for verbal stimuli presented during general anesthesia as measured by BIS < 60 has been reported,[5,8–11] and suggests that the human brain processes and stores information unconsciously.

Two explanations are commonly given for spared memory function under anesthesia: The anesthetic was not as deep as it appeared, and therefore consciousness facilitated memory function; and stress-induced learning mechanisms supported the formation of memory during unconsciousness.[10] This study intended to address the controversy over memory function under anesthesia by investigating the occurrence of memory function in a group of surgical patients in whom hypnotic state was controlled within a narrow range as measured by BIS 50–60. We compared memory function in these patients to a group in which BIS did not guide anesthetic management (standard practice [SP]) and hypothesized less memory in the BIS-guided group, provided that BIS monitoring explicitly avoided light hypnosis. The comparison to an SP group is suboptimal, given that BIS is typically low during routine care, but patients with consistently high BIS values are rarely encountered or left untreated, nor can such studies be staged experimentally in an ethical way. The comparison to SP has merit when BIS varies widely during routine care and values above 60 occur, which is not uncommon.[11–13]

In addition to memory function, patients' subjective stress levels were assessed and perioperative fentanyl doses recorded to address claims that stress and analgesic interventions affect memory function by altering the physiologic stress response to surgery.[9]

Materials and Methods

After institutional review board approval (Emory University, Atlanta, Georgia), 167 patients gave written informed consent to participate in this study that was part

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of a larger project investigating inflammatory outcome after major orthopedic surgery under general anesthesia with and without BIS monitoring.[14] The sample size was arbitrarily determined to yield at least 100 analyzable cases overall (roughly 50 data points per treatment group). Patients 18 yr of age or older scheduled for hip or knee replacement surgery, primary or revision, under general anesthesia were eligible to participate. Because our primary intervention involved brain function (electroencephalogram) monitoring, patients with a medical history or status that could compromise or skew electroencephalogram recordings were excluded from participation. Specific exclusion criteria were a history of illicit drug abuse, antipsychotic medication treatment, head trauma resulting in the loss of consciousness, or central nervous system disorders (*e.g.*, epilepsy). To further eliminate possible neurologic dysfunction, persons scoring below 24 on the Mini-Mental State Examination,[15] administered preoperatively, were excluded. Lastly, individuals with severe visual or auditory handicaps and illiterate individuals or nonfluent English speakers were excluded from participation.

Anesthetic Management

Patients were randomly assigned to one of two anesthetic management groups using a computer-generated list linking subject study numbers to group assignment. In one group, a BIS monitor (XP, algorithm 3.4) was used to guide anesthetic administration and titrate drugs to values between 50 and 60 (BIS-guided group). In the other group, BIS was recorded but not available to the attending clinician for drug dosing. Instead, standard clinical signs such as heart rate and blood pressure guided anesthetic management in this group (standard practice). None of the patients received benzodiazepines pre- or intraoperatively, but fentanyl (50–100 μg) was given at the discretion of the anesthesiologist/pain service to ease discomfort or anxiety over epidural or patient-controlled analgesia (PCA) placement. For induction, all patients were given 2 mg/kg propofol and 3 μg/kg fentanyl. Vecuronium bromide (0.1 mg/kg) was given to facilitate tracheal intubation, with additional doses as necessary. During anesthesia maintenance, sevoflurane in oxygen was given using standard ventilation parameters in addition to 50–100 μg fentanyl for analgesia, 0.5 mg/kg esmolol for hypertension, and 100 μg phenylephrine for hypotension on an as-needed basis. Physiologic parameters were automatically recorded to a computer throughout the study using Rugloop (Demed, Belgium), including BIS, end-tidal gas concentrations (every 5 s) and vital signs (every 3 min). Postoperative pain was managed with epidural (with meperidine/bupivacaine or liposomal morphine) or PCA (with hydromorphone or morphine) based on individual patient demands.

Memory Assessments

Outcome assessors (JRG and CK) were blinded to study group allocation and tested patients postoperatively for recall and recognition memory. Recall was assessed approximately 6 h after surgery with five questions[16,17]: What is the last thing you remember before falling asleep? What is the first thing you remember after waking up? Do you remember anything in between? Did you dream? What is the worst thing about your operation? As necessary, additional questions were asked. For instance, when a patient reported recall for events that occurred between falling asleep and waking up from anesthesia, he or she was asked to describe the event.

The recognition memory test was administered after the recall assessment and consisted of an auditory test. For this part of the study, 45 words had been selected from the Toronto Noun Pool§ to create a homogenous set of words with comparable lexical word frequency and other language characteristics that affect memory. The average (±SD) Kucera-Francis word frequency for this set was 40.3 (15.9), and concreteness was 5.2 (1.4). Words were emotionally bland (*e.g.*, sister, planet, painting). The set was split into three 15-word lists of comparable word frequency and concreteness, one of which was played to patients during surgery in a counterbalanced fashion. For this presentation, audio files of individual words were uploaded in a sound editor∥ and separated by short periods of silence (2 s) to create a digital audio sequence. The sequence was recorded 60 times onto compact disc and played to patients during anesthesia at a set volume using a compact disc player and headphones. Word presentation typically started 15 min after induction and lasted approximately 42 min in all. For the recognition test, 15 test items were created, each consisting of 1 word played during anesthesia (target) and 2 new words not played earlier (distractors). The position of targets was counterbalanced across items. Within test items, the word frequency was matched. To create the items, audio files of individual words were uploaded in the sound editor and separated by 1 s of silence. The sequence was then repeated to enhance stimulus audibility and understanding. Items were recorded onto compact disc in three different orders to create test versions that were counterbalanced between patients. Upon testing, the patients were instructed to listen to each test sequence and select the word played during surgery, or to guess if necessary (three-alternative forced choice).

Psychological Stress Assessments

Patient completed the State-Trait Anxiety Inventory (STAI) to assess subjective psychological stress levels.[18]

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§ Available at http://memory.psych.upenn.edu/wordpools.php. Accessed July 20, 2009.
∥ Available at http://audacity.sourceforge.net. Accessed May 18, 2009.

Both forms of the STAI were administered to obtain transient (state) as well as more permanent (trait) anxiety estimates. Composite scores are obtained similarly for both forms, and may range from 20 (minimum) to 80 (maximum). The inventory was administered once preoperatively (baseline) and twice postoperatively (48 h and 1 month). The results of the baseline assessment are reported here. The results of the two other measurements can be found elsewhere, as well as the results of a depression questionnaire that was filled out at similar intervals.

Statistical Analysis

Physiologic data recorded intraoperatively were extracted to obtain individual data for steady-state anesthesia, defined as the period between 10 min after intubation and 10 min before extubation. Specifically, data were extracted for the time period during which words were presented. Data were statistically analyzed using SPSS 14.0 (SPSS, Chicago, IL) and Microsoft Excel 2000 (Microsoft Corp., Redmond, WA).

The main analyses focused on an effect of study group assignment on recognition memory test performance. Given the low incidence of explicit recall (awareness) after general anesthesia,[16,17] this study was not powered to detect differences between study groups in explicit recall. The prevalence of explicit recall was therefore not statistically addressed. Differences in recognition memory performance were statistically tested by comparing observed hit rates in the two study groups. Because stimuli had been presented during anesthesia in a counterbalanced fashion, meaning that some patients were exposed to a set of words while others were not, the probability of selecting a word at test when it had been presented during anesthesia (target hit rate) could be compared to the probability of selecting the same word when it had not been presented during anesthesia (distractor hit rate). The distractor hit rate established chance performance, and any upward deviation from this probability in the absence of word recall suggests evidence of implicit memory for words presented during anesthesia. Target hit rates were compared within groups to distractor hit rates using one-sample t tests. A similar comparison was made using the distractor hit rate observed over all patients, rather than within treatment groups. Demographics and treatment characteristics were compared between groups using independent sample t tests, chi-square tests, or Fisher exact tests.

Secondary analyses explored recognition memory performance in relation to stress mechanisms by relating individual hit probabilities to individual baseline STAI scores using a nonparametric correlation measure, Spearman's *rho*; by relating observed hit probabilities to the extent of surgical stimulation during word presentation, as expressed in the number of surgical minutes and tested parametrically using Pearson's r measure of correlation, based on the assumption that surgical stress creates a neuromodulatory response that facilitates memory function; and by relating observed hit probabilities and the incidence of memory to fentanyl administration, using ANOVA and chi-square tests, based on the assumption that analgesic interventions suppress the stress response and, thereby, the likelihood of memory function.

$P < 0.05$ was considered statistically significant, and all reported P values are for two-sided tests (uncorrected for multiple comparisons).

Results

Of 167 consented patients, 39 were excluded because intraoperative monitoring could not be accomplished (n = 17), the surgery or anesthetic was cancelled or changed (n = 10), inclusion criteria were not met (n = 7), or the patient was lost to follow-up (n = 5). The remaining 128 patients were interviewed for recall after recovery from anesthesia, and were presented with a recognition test to assess memory for words played during anesthesia. From this latter data set, the responses of 19 patients were excluded for one of the following reasons: The patient was wearing a hearing aid that was removed during surgery, which rendered the auditory stimulus presentation unreliable (n = 10); it could not be

Table 1. Characteristics of Patients Assessed for Recognition Memory

	BIS Group (n = 62)	SP Group (n = 47)
Age (y)	61.2 ± 11.4	63.9 ± 11.8
Female, n (%)	34 (55)	31 (66)
Weight (kg)	87.9 ± 18.9	84.4 ± 14.8
BMI	30.2 ± 5.6	28.9 ± 3.7
MMSE score	28.2 ± 1.8	28.5 ± 1.3
STAI state score	36 ± 11	33 ± 9
STAI trait score	32 ± 9	32 ± 8
BIS maintenance*	52.7 ± 5.0	45.1 ± 8.7
BIS word presentation*	50.8 ± 5.5	44.0 ± 8.4
BIS higher than 60 (% word presentation)	13.4 ± 13.9	8.3 ± 16.0
End-tidal gas maintenance (%)*	1.31 ± 0.29	1.56 ± 0.29
End-tidal gas word presentation (%)*	1.30 ± 0.31	1.60 ± 0.37
Duration of anesthesia (min)	126 ± 51	112 ± 48
Fentanyl preoperative (µg/kg)	0.27 ± 0.43	0.40 ± 0.47
Fentanyl intraoperative (µg · kg^{-1}· hr^{-1})†	2.83 ± 1.04	2.70 ± 1.18
Fentanyl postoperative (µg/kg)	0.47 ± 0.66	0.55 ± 1.10
Epidurals (*vs.* PCA), n (%)	19 (31)	17 (37)
Days in hospital (recovery) (n)	4.1 ± 1.1	4.0 ± 1.2

Data are mean ± SD unless otherwise noted.

* $P < 0.001$ between-group comparisons.   † Includes the induction dose.

BIS = bispectral index; BMI = body mass index; Maintenance = time period between 10 min after intubation to 10 min before extubation; MMSE = Mini-Mental State Examination;[12] PCA = patient-controlled analgesia; SP = standard practice group; STAI= Spielberger State-Trait Anxiety Inventory;[17] Word Presentation = time period during which an audio compact disc with words was played.

Table 2. Data of Patients Reporting Postoperative Recall

	Patient 1 (F, 76, SP)	Patient 2 (F, 59, BIS)	Patient 3 (M, 53, BIS)
Verbatim recollection*	Heard clanging of pots and pans after being put to sleep	Woke up and heard hammering; felt pain during surgery	Heard music, a particular song (Not independently confirmed)
Word recollection†	Believes she heard one particular test word during anesthesia, which was incorrect (false memory)	Believes she heard one particular test word during anesthesia, which was correct (true memory)	No recollection
Recognition Target Hit Score (% correct)‡	4 (27)	9 (60)	10 (67)
BIS @ words, mean (max–min)	55.3 (70.5–41.8)	48.0 (70.2–37.3)	51.2 (61.3–39.0)
BIS @ maintenance, mean (max–min)§	53.9 (70.5–41.6)	48.3 (92.5–32.1)	52.1 (61.0–39.0)
BIS > 60 during words (% of time)	21	9	1.2
BIS > 60 during maintenance (% of time)§	14	8	0.4
End-tidal gas concentration (mean %)‖	1.41	0.99	1.81
Duration of anesthesia (min)	72	88	77
Anesthesia records	No complications reported	Difficulty controlling BIS noted	No complications reported

Patients' sex, age, and group assignment are shown in brackets at the top.

* Elicited during the postoperative recall interview.   † Established during or after the recognition memory test, when patients volunteered information based on hearing test items.   ‡ The number of items presented during anesthesia that were correctly recognized at test (maximum = 15, chance performance = 5, or 33%).   § Maintenance was defined as the time period between 10 min after intubation and 10 min before extubation.   ‖ End-tidal concentrations are shown for the maintenance period, and were largely the same during the period of word presentation.

BIS = bispectral index–guided group; F = female; M = male; SP = standard practice group.

determined when stimuli had been presented, which precluded extraction of physiologic data during that time (n = 6); or the patient heard more or fewer cycles of critical stimuli than the protocol stipulated (n = 3). The recognition memory part of this study, therefore, included data of 109 patients.

Demographics and other characteristics of patients tested for recognition memory are presented in table 1. Sixty-two patients were randomly assigned to the BIS-guided group and 47 to the SP group. About 50% of patients were classified as American Society of Anesthesiologists Class I-II and 50% as American Society of Anesthesiologists Class III, with no differences between study groups. During anesthesia maintenance, patients in the SP group received more hypnotic agent and their BIS was on average lower than in patients in the BIS-guided group (table 1, P < 0.001). Coinciding with a lower BIS average, the percentage of BIS below 45 was significantly larger in the SP group, while the percentage of BIS exceeding 60 was smaller (table 1). However, BIS values and averages varied more in the SP group, as the standard deviations for BIS measurements in table 1 demonstrate. In three patients in the SP group, BIS averaged above 60 during anesthesia maintenance, whereas such averages were not recorded in BIS-guided patients.

Recall and Dreaming

Characteristics of the larger sample assessed for recall (n = 128) were similar to those reported in table 1.

Sixty-seven patients were randomly assigned to the BIS-guided group and 61 to the SP group. When interviewed postoperatively, three patients (2.3%) reported recall of the time period between falling asleep and waking up from anesthesia. Their recollections and other pertinent data are reported in table 2. These patients did not report dreaming, nor did their recollection prompt an emotional response. When asked what had been worst thing about their operation, all three reported medical events such as drug-induced nausea, dry mouth, or chills.

Seven patients (5.5%) reported dreams, which were generally vague but pleasant (*e.g.*, playing golf, being with family). Nothing in the reports alluded to possible awareness episodes.

Recognition Memory

Consistent with the trend seen during anesthetic maintenance, the average BIS during word presentation was lower in the SP than in the BIS-guided group (table 1). Observed hit probabilities for words presented during anesthesia are shown in table 3. The overall target and distractor hit probabilities (0.350 *vs.* 0.325) differed significantly (P < 0.05), suggesting memory of words presented during anesthesia. As table 3 shows, however, this effect should be attributed to patients in the BIS group who were more likely, when tested postoperatively, to select words presented during anesthesia (target hit rate = 0.371) than words not presented during anesthesia (distractor hit rate = 0.315, P = 0.001). The

Table 3. Observed Mean ± SD Hit Probabilities for Target and Distractor Words per Treatment Group and the Overall Sample

	Target	Distractor
BIS group (n = 62)*	0.371 ± 0.132	0.315 ± 0.117
SP group (n = 47)	0.323 ± 0.132	0.338 ± 0.119
Overall (n = 109)†	0.350 ± 0.133	0.325 ± 0.118

* $P = 0.001$ and † $P < 0.05$ for within-group comparisons of target *versus* distractor hit probabilities.

BIS = bispectral index-guided; SP = standard practice (not bispectral-index-guided).

SP group performed no better than chance, and overall showed no evidence of memory function.

Overall, and in each treatment group, the target hit probability related poorly to the percentage of recorded BIS values above 60 (Pearson correlation, $r = 0.05$, $P = 0.58$), the mean BIS during word presentation ($r = 0.09$, $P = 0.33$), or other measures such as mean heart rate, arterial blood pressure, or end-tidal gas concentration during word presentation.

Stress Modulation of Memory

Baseline questionnaires suggested that groups experienced comparable and appropriate levels of anxiety in anticipation of major surgery (table 1). Compared with normative data,[18] above-average state anxiety was noted in 31% of patients in the BIS group *versus* 21% of patients in the SP group ($P = 0.27$). Trait-related anxiety was less common but likewise comparable between groups (16% *vs.* 13% BIS-guided *vs.* SP-groups, respectively, $P = 0.79$). Observed hit probabilities correlated poorly to scores on either STAI measure (n = 101, $rho_{STAI-state} = -0.009$, $P = 0.93$; $rho_{STAI-trait} = -0.006$, $P = 0.95$).

Words were presented exclusively during surgery in 26% of patients in both study groups. In the remaining patients, word presentation started before surgery, but nobody heard the entire set before surgical incision. The number of surgical minutes during word presentation correlated positively with observed target hit probabilities, but not significantly (n = 107, $r = 0.14$, $P = 0.17$). This time index did not differ between study groups ($P = 0.81$).

Significant recognition memory, defined as a target hit probability higher than chance (*i.e.*, ≥ 40% correct, n = 46, 48% BIS group *vs.* 36% SP group, $P = 0.24$), related to the amount of fentanyl received in preoperative holding but not to intraoperative or postoperative fentanyl interventions. Patients with significant recognition memory were less likely to having received fentanyl preoperatively (49%) than patients not showing evidence of memory (74%) (Fisher exact test, $P = 0.01$). In addition, they had a higher incidence of PCA as opposed to epidural pain management (80% *vs.* 56% PCA incidence in memory *vs.* no memory groups, $P = 0.008$), but the two

analgesic techniques were not associated with systematic differences in preoperative fentanyl dosing (or intra- and postoperative differences, for that matter). The incidence (nor dose) of preoperative fentanyl administration or postoperative pain management techniques did not differ between anesthesia treatment groups (table 1).

Discussion

This study demonstrated reliable implicit memory for words presented on average during adequate general anesthesia as measured by BIS < 60. Memory took the form of a priming effect that facilitated patients to pick words presented during anesthesia rather than words not presented during anesthesia when tested postoperatively. None of the patients explicitly recalled presented words when first interviewed after surgery, including the three patients who reported recall of other events. Contrary to our hypothesis, priming was observed in the BIS-guided rather than SP group. This seems to contradict the notion that tight control of hypnotic state obliterates memory function, as we have argued.[19]

Two of our early BIS titration studies did not find evidence of memory function when depth of hypnosis was tightly controlled and moments of light anesthesia were avoided.[19,20] In one study, the evidence for implicit memory function in trauma patients[5] was not replicated when drugs were titrated to maintain BIS values between 50 and 55.[19] In another,[20] BIS-guided anesthetic management to BIS 40–60 failed to induce priming of category exemplars that was observed repeatedly in the absence of hypnotic state monitoring.[21,22] The null findings in the BIS-titrated replication studies confirmed the hypothesis that inadequate hypnosis contributed to memory function under anesthesia. Struys *et al.* reached a similar conclusion when comparing BIS-guided anesthesia to SP not using BIS.[12] They observed implicit memory in the SP group alongside a wider range of BIS values that included a significant portion above BIS 60. These early studies indicated that hypnotic state titration to adequate levels curbed memory function.

More recently, however, Stonell *et al.* titrated anesthetics to BIS 55–60, and found reliable implicit memory for a word series presented around BIS 50 on average.[8] The authors related levels of anesthesia (categorized BIS) to subsequent memory performance and confirmed lack of evidence for memory function below BIS 40, as we and others have noted.[5,11] In addition, BIS values above 50 were identified as a significant predictor of memory. This latter finding is instructive and may help to explain why priming-related memory for meaningful stimuli presented at BIS planes below 60 (but not 50) occurs.

In the current study, BIS during critical word presentation averaged above 50 in the BIS-guided group,

whereas it remained well below 50 in the SP group. This divide provides one possible explanation why we observed reliable implicit memory in BIS-guided patients. Consistent with the notion that BIS > 50 facilitates memory function, BIS averaged above 50 (54 ± 14) during word presentation in the trauma study referenced earlier[5] and in a significant portion of patients in the Stonell study discussed above.[8] Both these studies reported evidence of memory function. Conversely, our early titration studies averaged BIS < 50 during word presentation (closer to the SP group in the current investigation) and did not observe memory.[19,20] Each of these findings is consistent with the notion that BIS above 50, but not below, facilitates memory function under anesthesia. It may coincide with an increased probability of return of higher cognitive function (*i.e.*, response to verbal command), which is uncommon but occasionally occurs between BIS 55–60.[6]

Another explanation for memory function under anesthesia is the actual control of hypnotic state attained. Contrary to our early titration studies,[19,20] we were less successful in maintaining BIS below 60 during word presentation this time. In 2005,[19] we registered a handful of words (1%) presented at BIS above 60, and in 2001,[20] BIS averaged between 60 and 70 in less than a handful of patients (5%) at some point during word presentation. Neither study established evidence of memory function. In the present study, BIS was above 60 more than 13% of recorded case time in the BIS-guided group on average (table 1). This translates to at least 5 min of recorded case time. Although this count reflects instances of elevated BIS (5 s epochs) and does not imply that BIS was elevated for more than 5 min consecutively, hypnotic state as measured by BIS was less tightly controlled in the current investigation. In addition to a higher BIS average, therefore, the higher percentage of BIS above 60 in BIS-guided patients may also explain why reliable memory was observed in this, but not the SP group. The implication is that BIS values above 60 affect memory function.

To test this hypothesis, it would be critical to avoid BIS over 60 altogether and keep hypnotic variation at a minimum. Merely excluding lighter levels from the analyses or categorizing hypnotic states into deeper *versus* lighter levels may prove instructive, but would not suffice. With these stringent criteria in mind, only one study to date demonstrated memory for words presented at low BIS (< 50) levels.[9] These investigators altogether excluded 25 patients with BIS values above 60 from data analyses, yet observed a small priming effect for seven words repeatedly presented to patients during orthopedic same-day surgery. However, using a similar approach to hypnotic adequacy as well as probing memory, we did not observe memory function at comparable BIS levels in the two early titration studies already mentioned.[19,20]

Andrade *et al.* have argued that the physiologic stress response to surgery is an important modulator of memory function under anesthesia,[9,10] and reported tentative evidence for an effect of surgical stimulation on implicit memory.[10] We were unable to replicate this finding in the present study but note that all our patients, unlike Andrade's, were surgically stimulated to some degree. Preoperative fentanyl, on the other hand, was associated with a lower incidence of memory function. This finding is consistent with the hypothesis that analgesics indirectly attenuate memory function by suppressing the stress response.[9] However, in contrast to prior studies that focused on intraoperative analgesic interventions,[9] our findings suggest that a benefit may be found at an earlier, preoperative stage. At the same time, it remains to be seen how the relatively small doses of fentanyl (50–100 μg) patients received in this study before surgery could subsequently affect the physiologic stress response to surgery or intraoperative memory function. We note that the difference in memory performance between pain management techniques (PCA *vs.* epidural) might be the result of using an anesthetic test dose in patients with epidurals, and consequently, reduced nociception in this group of patients.

We conclude that BIS-guided anesthesia, titrating drugs to maintain BIS values between 50 and 60, is not necessarily associated with a lower probability of memory function, as compared with not using BIS to guide anesthetic management. Variation in BIS is reduced by BIS-guided anesthesia, but if BIS values higher than 60 occur, memory function may be preserved. Preoperative fentanyl may curb the stress response to surgery, and therefore, the likelihood of memory function during surgery.

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