

Speed of Recovery and Side-effect Profile of Sevoflurane Sedation Compared with Midazolam

Andra E. Ibrahim, M.D.,* Mohamed M. Ghoneim, M.D.,† Evan D. Kharasch, M.D., Ph.D.,‡ Richard H. Epstein, M.D.,§ Scott B. Groudine, M.D.,|| Thomas J. Ebert, M.D., Ph.D.,# Wendy B. Binstock, M.D.,** Beverly K. Philip, M.D.,†† the Sevoflurane Sedation Study Group‡‡

Background: Sedation for surgical procedures performed with regional or local anesthesia has usually been achieved with intravenous medications, whereas the use of volatile anesthetics has been limited. The use of sevoflurane for sedation has been suggested because of its characteristics of nonpungency, rapid induction, and quick elimination. The purpose of this investigation was to assess the quality, recovery, and side effects of sevoflurane sedation compared with midazolam.

Methods: One hundred seventy-three patients undergoing surgery with local or regional anesthesia were enrolled in a multicenter, open-label, randomized investigation comparing sedation with sevoflurane *versus* midazolam. Sedation level was titrated to an Observer's Assessment of Alertness-Sedation score of 3 (responds slowly to voice). Recovery was assessed objectively by Observer's Assessment of Alertness-Sedation, Digit Symbol Substitution Test (DSST), and memory scores, and subjectively by visual analog scales.

Results: Significantly more patients in the sevoflurane group had to be converted to general anesthesia because of excessive movement (18 sevoflurane and 2 midazolam; $P = 0.043$). Of remaining patients, 141 were assessable for efficacy and recovery data (93 sevoflurane and 48 midazolam). Sevoflurane and midazolam produced dose-related sedation. Sevoflurane patients had higher DSST and memory scores during recovery. Seventy-six percent (sevoflurane) compared with 35% (midazolam) returned to baseline DSST at 30 min postoperatively ($P < 0.05$). More frequent excitement-disinhibition was observed with sevoflurane (15 [16%] *vs.* midazolam; $P = 0.008$).

Conclusions: Sevoflurane for sedation produces faster recovery of cognitive function as measured by DSST and memory scores compared with midazolam. However, sevoflurane for sedation is complicated by a high incidence of intraoperative excitement.

* Assistant Professor, Department of Anesthesiology, ‡ Professor, Department of Anesthesiology and Medicinal Chemistry (Adjunct), University of Washington. † Professor, Department of Anesthesiology, University of Iowa. § Associate Professor, Department of Anesthesiology, Jefferson Medical College. || Associate Professor, Department of Anesthesiology, Albany Medical College. # Professor, Department of Anesthesiology, and Adjunct Professor, Department of Physiology, Medical College of Wisconsin. **Assistant Professor, Department of Anesthesiology, University of Chicago. †† Associate Professor, Department of Anesthesia, Harvard Medical School. ‡‡ Members of the Sevoflurane Sedation Study Group are listed in the appendix.

Received from the Department of Anesthesia, University of Washington, Seattle, Washington; the Department of Anesthesia, University of Iowa College of Medicine, Iowa City, Iowa; the Department of Anesthesiology, Jefferson Medical College, Philadelphia, Pennsylvania; the Department of Anesthesiology, Albany Medical College, Albany, New York; the Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin; the Department of Anesthesia and Critical Care, University of Chicago, Chicago, Illinois; and the Department of Anesthesia, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Submitted for publication November 12, 1999. Accepted for publication August 3, 2000. Supported by Abbott Laboratories, Abbott Park, Illinois. Drs. Apfelbaum, Ebert, Epstein, Kharasch, and Philip have received speaking honoraria from Abbott Laboratories. Presented in part at the annual meetings of the American Society of Anesthesiologists, Orlando, Florida, October 21, 1998, and Dallas, Texas, October 11, 1999. Dr. Mervyn Maze was acting Editor-in-Chief for this article.

Address reprint requests to Dr. Ibrahim: Department of Anesthesiology, University of Washington, Box 356540, 1959 NE Pacific, Seattle, Washington 98195-6540. Address electronic mail to: aei@u.washington.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

SEDATION for surgical procedures performed with regional or local anesthesia has usually been achieved with a variety of intravenous medications, such as benzodiazepines, barbiturates, and propofol. Midazolam, a benzodiazepine, is widely used for conscious sedation because it produces dose-related sedation as well as amnesia and anxiolysis. Inhaled agents, *e.g.*, nitrous oxide, have been used for conscious sedation in obstetrics, dental, and ambulatory surgery. Except for limited use for analgesia during labor and delivery,¹ volatile anesthetics have seldom been used because of airway irritation and pungency.

Sevoflurane, a fluorinated methyl isopropyl ether, has been used frequently for inhalation induction of anesthesia because of nonpungency and low incidence of respiratory irritability. Sevoflurane provides for a smooth induction with decreased incidence of cough, breath-holding, laryngospasm, and bronchospasm compared with halothane² and particularly desflurane.³⁻⁵ Sevoflurane is useful for short procedures and facilitates quick recovery. Sevoflurane exhibits a low blood-gas partition coefficient, which is associated with both a rapid induction of anesthesia and quick emergence. General anesthesia with sevoflurane results in faster emergence and response to commands compared with isoflurane^{6,7} and propofol.^{8,9} Because of nonpungency, rapid induction, and quick elimination, sevoflurane may theoretically be useful for sedation. Indeed, Philip *et al.*¹⁰ anecdotally reported successful sedation with sevoflurane in ambulatory surgery patients. The purpose of this investigation was to assess the quality, clinical feasibility, recovery, and side effects of sevoflurane sedation compared with intravenous midazolam.

Methods

Participants

One hundred seventy-three patients (American Society of Anesthesiologists physical status I-III, aged 18-81 yr) were enrolled in a multicenter, open-label, randomized investigation involving a single protocol approved by each institutional review board. Written informed consent was obtained from all patients. Patients were scheduled for elective surgery of anticipated duration 0.5-2 h and requested either local or regional anesthesia with sedation. Individuals were excluded from the study if they were pregnant, taking opioids or sedatives within 24 h before enrollment, or at risk for aspiration. All patients fasted for a minimum of 6 h before surgery. No

Table 1. Observer's Assessment of Alertness/Sedation (OAAS)¹¹

Responsiveness	Speech	Facial Expression	Eyes	Score
Responds readily to name	Normal	Normal	Clear, no ptosis	5
Lethargic response to name	Mild slowing	Mild relaxation	Glazed or mild ptosis	4
Responds to name only if called repeatedly	Slurring	Marked relaxation	Glazed or marked ptosis	3
Responds only after mild prodding	Not recognizable			2
No response to prodding or shaking				1

OAAS is the lowest score in any of the four categories.

preoperative sedation, opioids, or prophylactic antiemetics were given. Remifentanyl infusion was permitted for analgesia during regional block placement.

Study Design and Anesthetic Technique

Subjects were randomized to sevoflurane (n = 117) or midazolam (n = 56) in a 2:1 ratio as determined by permuted block. The block size was six (four sevoflurane and two midazolam). A 2:1 randomization ratio of sevoflurane to midazolam was chosen to increase the experience level with sevoflurane for sedation. Patient treatment assignments were contained in sequentially ordered individually sealed envelopes, which were opened immediately before entering the operating room. *A priori* power calculations were based on the assumption that 75% of the sevoflurane patients and 50% of the midazolam patients would attain an Observer's Assessment of Alertness-Sedation (OAAS) score of 5, 5 min after the procedure. A sample size of 49 patients in the midazolam treatment group and 97 patients in the sevoflurane treatment group would be required to achieve an 80% power with an α level of 0.05. All patients received an air-oxygen mixture at 2 l/min *via* circle system (face mask connected to a semiclosed anesthetic circuit) and were monitored with an electrocardiograph, noninvasive blood pressure, pulse oximetry, capnograph, and oxygen analyzer. A face mask was applied before administration of any study drug and was held manually or fixed with a rubber head strap to achieve a tight seal. Blood pressure, heart rate, oxygen saturation, end-expired carbon dioxide, and end-expired sevoflurane concentration were assessed every 1-2 min for the first 10 min of study drug administration or until maintenance was reached, whichever was later, then every 5 min. An observer who was not blinded to the identity of the study drug was present for frequent clinical assessment of depth of sedation. Sedation level was assessed every minute using the OAAS scale¹¹ and titrated to an OAAS score of 3 (table 1). This open-label investigation has theoretical potential for interpretive bias. However, clinical assessment of sedation depth (data obtained by the unblinded observer) was used to adjust drug dose (clinical end point) and was not a primary or secondary outcome measure. Maintenance level was defined as three consecutive OAAS scores of 3; subsequent assessments were then made every 5 min.

Sevoflurane concentration was increased slowly to a maximum of 1.0 minimum alveolar concentration (MAC; 2.05% end tidal). Inadequate (or excessive) sedation was treated by increasing (or decreasing) the concentration by 0.2-0.6% (vaporizer settings) until the desired effect was reached. Midazolam was titrated slowly to the desired effect. Within a 2-min period, no more than 2.5 mg was to be given to patients younger than 60 yr, and no more than 1.5 mg in patients aged 60 yr or older. Inadequate sedation was treated by further administration of drug given by slow titration in increments judged by the investigator to reach the desired effect. Excessive sedation was treated by holding midazolam doses until the patient returned to an OAAS score of 3. Every midazolam dose administered was recorded. The level of sedation was maintained at an OAAS score of 3 throughout the procedure until the last suture or procedure equivalent.

Patients underwent local or regional anesthesia (spinal, epidural, axillary, ulnar, ankle, sciatic, femoral, interscalene, and Bier blocks). Block placement occurred before the administration of the study drug. If analgesia during block placement was necessary, a remifentanyl infusion ($0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was administered and discontinued after the block placement was completed (n = 28). Induction of sedation with sevoflurane or midazolam was not begun until the patient returned to an OAAS score of 5.

Administration of other sedating agents was prohibited and resulted in patient removal from data analysis. However, fentanyl administration was allowed in the event of pain, as a treatment for excitation and excessive patient movement, or prophylaxis of painful surgical stimuli. Fentanyl 25-50 μg was administered intravenously as needed to supplement sedation-analgesia. Every dose of fentanyl and the reason for administration was recorded. The incidence of side effects (*e.g.*, apnea, airway obstruction, headache, excitation) was recorded by the observer. Severe excitation-disinhibition was defined as when, in the investigator's opinion, agitation and uncontrollable patient movement resulted in difficult or unsafe operating conditions and conversion to general anesthesia was considered necessary. Moderate excitation-disinhibition was defined as agitation and uncontrollable movement that was not believed to compromise surgical operating conditions or patient safety or did not require

the discontinuation of the technique or induction of general anesthesia.

Postprocedure milestones included the times that the procedure ended (last suture or procedure equivalent), study drug was stopped, arrival to designated recovery area (phase 1 or 2), time to first OAAS score of 5, when the patient met discharge eligibility defined below, and actual discharge from phase 1 recovery. Discharge eligibility criteria were defined as when the patient was awake, alert, and oriented equivalent to baseline, experiencing minimal nausea without vomiting, pain was well controlled, and room air oxygen saturation was at least 94% or at baseline or higher. If a patient bypassed phase I recovery and went directly to phase II, the actual discharge time from phase 1 recovery was recorded as 0 min.

Evaluation of Recovery

The speed of awakening and return of preoperative baseline cognitive functions were assessed by OAAS score, Digit Symbol Substitution Test (DSST),^{12,13} and memory tests. A second observer who was blinded to the identity of the study drug obtained baseline test scores preoperatively and repeated these tests at the end of the procedure in the operating room and several times postoperatively. To ensure the blinding of the observer in the operating room, all drug syringes were concealed under a cloth, and a nose clip was worn to avert any scent of sevoflurane. The OAAS score was measured every minute during the first 5 min during recovery and then at 10 min and again at 30 min. The DSST was given at baseline (before entering the operating room) and at 5, 10, and 30 min of recovery. The DSST score represents the number of correct substitutions completed in 90 s. The memory tests included immediate and delayed recall tests. The immediate recall test was given at baseline and 10 and 60 min of recovery. The delayed recall test was given at 60 min and 24 h after the end of the procedure. The immediate recall test involved using tape recordings to administer lists of 16 different words balanced on word frequency and normative free recall at a rate of one word every 5 s.¹⁴⁻¹⁶ One of three different word lists was used for the administration of each immediate recall test (baseline, 10 min, and 60 min). Immediately after the list was completed, patients were asked to recall in any order as many of the words as possible from the list. The score of the immediate recall test was the number of correct words recalled. The delayed recall test involved asking the patients to recall the words from any previously presented list in any order.¹⁷ The 60-min delayed recall test was given before the presentation of the 60-min immediate recall test and tested the recall of words from the baseline test and the 10-min word list. The 24-h delayed recall test tested recall from all three word lists. (Separate word lists were not used for the delayed recall test.)

Subjective self-assessment of quality of recovery was measured by visual analog scales (VAS) determined at baseline and 5, 10, and 30 min of recovery. Attributes assessed (and scored from 0 to 100) included level of alertness-sedation (0-100; almost asleep to wide awake), energy level (no energy to full of energy), clear-headedness-confusion (confused to clear-headed), coordination-clumsiness (extremely clumsy to well coordinated), anxiety (calm-relaxed to extremely nervous), and nausea (no nausea to worst nausea).

Patient satisfaction was determined by a questionnaire given to the patients before discharge. The patients were asked whether they were pleased with their anesthetic experience and whether they would accept the same anesthetic in the future.

Statistical Analysis

Analysis of study drug administration, recovery data (OAAS, DSST, and memory scores, time to anesthesia events) included only patients who successfully completed the study. The analysis of complications and side effect data included all enrolled patients. One-way analysis of variance was used to compare age, height, and weight between treatment groups. Gender and race was compared with 2 × 2 Fisher exact test, and the Cochran Mantel-Haenszel test was used to compare American Society of Anesthesiologists physical status between treatment groups. Duration of study drug administration, time to anesthesia events, and deviation from target level of sedation were compared with a two-way analysis of variance model using treatment groups and sites as factors and their interactions. Raw test scores (DSST, memory, and VAS) were compared with a two-way analysis of variance model using treatment groups and sites as factors and their interactions, with application of the Bonferroni correction. Return to preoperative DSST and OAAS levels, fentanyl administration, side effects, and patient satisfaction survey responses were compared with the 2 × 2 Fisher exact test. Chi-square analysis was used to compare the incidence of excitation and antiemetic requirements. *P* values less than 0.05 were considered significant. Results are presented as mean ± SD.

Results

Patient Characteristics

One hundred seventy-three patients at seven clinical centers were enrolled and received the study drug (117 sevoflurane and 56 midazolam). Twenty patients were prematurely withdrawn during the intraoperative period because of severe disinhibition or excessive movement requiring the induction of general anesthesia (18 sevoflurane and 2 midazolam; *P* = 0.043). Eight patients (4 sevoflurane, 4 midazolam) were excluded because they received less than 20 min of anesthesia. Two

Table 2. Demographic Data*

Variable	Total (N = 141)	Sevoflurane (N = 93)	Midazolam (N = 48)
Age	48 ± 15	49 ± 15	48 ± 16
Male:Female [No. of patients (%)]	42 (30%):99 (70%)	30 (32%):63 (68%)	12 (25%):36 (75%)
Weight (kg)	74 ± 17	74 ± 17	76 ± 17
Height (cm)	168 ± 10	167 ± 11	169 ± 9
ASA physical status I, II, III [No. of patients (%)]	64 (45%), 68 (48%), 9 (6%)	42 (45%), 44 (47%), 7 (8%)	22 (46%), 24 (50%), 2 (4%)

* No significant differences between groups.

ASA = American Society of Anesthesiologists.

(sevoflurane) were excluded because the surgical procedure required a sedation depth approaching the level of general anesthesia; these procedures were not appropriate for local anesthesia with sedation, constituting a protocol violation. Two patients (midazolam) were excluded because they received midazolam before baseline measurements. One hundred forty-one patients (93 sevoflurane, 48 midazolam) were assessable for efficacy and quality-cognitive recovery of the sedation technique (table 2). Analysis of complications and side effect data was performed as an intent-to-treat analysis, which included all enrolled patients (117 sevoflurane and 56 midazolam).

The duration and dose of sevoflurane and midazolam administered were 55 ± 3 and 49 ± 4 min ($P = 0.199$), and 0.40 ± 0.02 MAC-hours and 8.3 ± 0.6 mg, respectively. The average end-tidal sevoflurane concentration used from induction to end of sedation was $0.81 \pm 0.03\%$ (0.39 ± 0.01 MAC). Induction (time from study drug start to the first of three consecutive OAAS readings of 3) was not significantly different between sevoflurane and midazolam (9.1 ± 6.6 vs. 7.5 ± 6.4 min, respectively). The average sevoflurane and midazolam dose administered during induction was $0.88 \pm 0.04\%$ (0.43 ± 0.04 MAC) and 5.4 ± 2.7 mg, respectively. Maintenance (time from the first of three consecutive OAAS scores = 3 until discontinuation of study drug) was also not significantly different between both drugs (45.9 ± 33.5 min sevoflurane vs. 57.2 ± 32.6 min midazolam). Local anesthesia was administered to 92 patients, and regional anesthesia (spinal, epidural, axillary, ulnar, ankle, sciatic, femoral, interscalene and Bier blocks) was administered to 49. Forty-six (94%) and three (6%) of 49 regional blocks were evaluated as providing "good" and "fair" anesthesia, respectively. Fentanyl administration was more frequent in patients who received local anesthesia (84 of 92 [91%] total: 55 of 60 [92%] sevoflurane and 29 of 32 [91%] midazolam) than regional anesthesia (24 of 49 (49%) total: 18 of 33 [55%] sevoflurane and 6 of 16 [38%] midazolam). In patients undergoing local and regional anesthesia, fentanyl was administered 2.4 ± 1.6 times (32 ± 26 μ g) and 2.3 ± 2.0 times (37 ± 13 μ g), respectively. Fentanyl was administered for analgesia, prophylaxis of painful stimuli, or

excitation, and for excessive movement 35%, 44%, and 21% of the time, respectively.

The percentage of time that sedation deviated from the desired depth during maintenance (OAAS = 3) was similar in both groups ($35 \pm 27\%$ sevoflurane vs. $37 \pm 26\%$ midazolam). The percentages of time each OAAS score occurred throughout the procedure is shown in figure 1.

Objective Recovery

Patients who required conversion to general anesthesia or who were maintained at a sedation level approaching general anesthesia were not included in the analysis of recovery data. Return to an OAAS score of 5 after study drug was discontinued was determined (fig. 2). No significant difference was observed between the groups in the first 10 min after drug administration. However, after 30 min, all sevoflurane patients (93 of 93) and 45 of 48 midazolam patients (94%) had returned to an OAAS score of 5 ($P = 0.038$).

Cognitive recovery was measured by DSST and memory scores. Cognitive recovery measured by DSST was faster with sevoflurane (18 [19%], 47 [51%], and 77 [76%] returned to their baseline scores at 5, 10, and 30 min postoperatively, respectively) versus midazolam (2 [4%], 9 [19%], and 17 [35%]; $P < 0.05$ at all three time

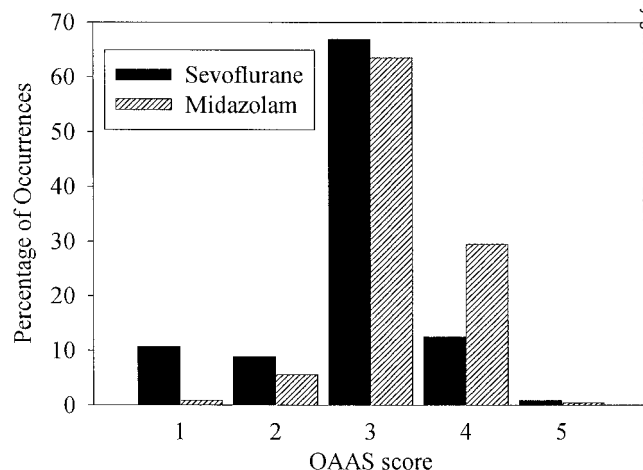


Fig. 1. Depth of sedation during maintenance. The distribution of Observer's Assessment of Alertness-Sedation (OAAS) scores as expressed as a percentage of all evaluations made during maintenance.

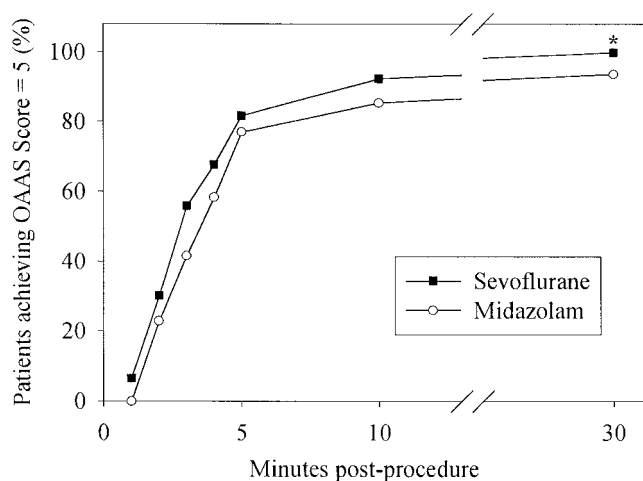


Fig. 2. The percentage of patients who achieved an Observer's Assessment of Alertness-Sedation (OAAS) score of 5 during the first 30 min of recovery after sevoflurane or midazolam (* $P < 0.05$).

points). DSST scores were also analyzed as the deviation from baseline score (fig. 3). Patients who received sevoflurane had scores that were closer to baseline at 5, 10, and 30 min after the procedure compared with midazolam ($P < 0.05$).

Cognitive recovery measured by memory scores was also faster with sevoflurane. Baseline scores on the immediate recall test (number of words recalled) were not significantly different between sevoflurane (5 ± 2) and midazolam (5 ± 2). However, scores at 10 min (4 ± 2 vs. 3 ± 1 ; $P < 0.05$) and at 60 min (5 ± 2 vs. 4 ± 2 ; $P < 0.05$) after the discontinuation of the study drug were significantly better in the sevoflurane group (fig. 4). No difference was observed on the delayed recall tests after 60 min (4 ± 3 vs. 4 ± 3) or at 24 h (4 ± 3 vs. 4 ± 2).

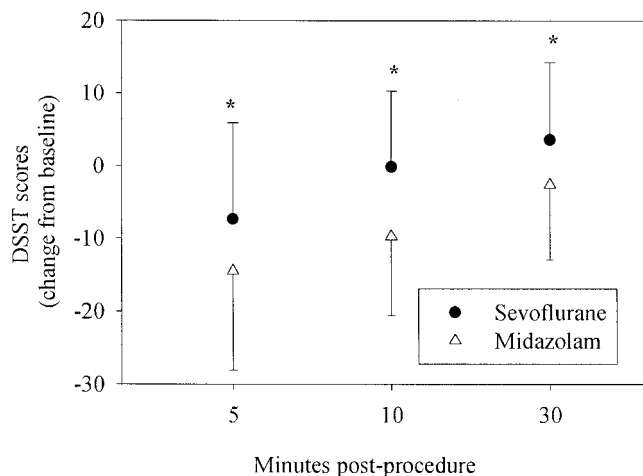


Fig. 3. Digit Symbol Substitution Test scores (DSST; mean \pm SD) at 5, 10, and 30 min after the procedure, calculated as change from baseline (* $P \leq 0.05$).

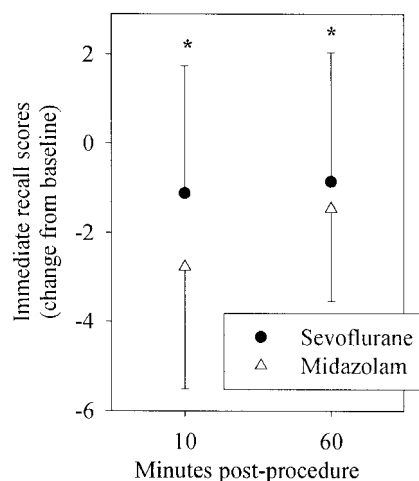


Fig. 4. Immediate recall scores (mean \pm SD) at 10 and 60 min after the procedure, calculated as change from baseline (* $P < 0.05$).

Self-assessment Recovery

Quality of recovery was assessed by VAS scores. Sevoflurane patients were significantly more awake at 10 and 30 min after the procedure. No significant difference was observed in the level of energy, confusion, excitement, clumsiness, or nausea after the procedure (table 3).

Nearly all of the patients were pleased with the anesthetic technique provided (99% sevoflurane, 100% midazolam; $P =$ not significant) and would accept the same anesthetic in the future (99% sevoflurane, 100% midazolam; $P =$ not significant). This data was not collected on the patients who were withdrawn from the study because of failure of the sedation technique.

Time to Anesthesia Events

The time to anesthesia events was compared between both groups. Time to induction, incision, and maintenance was similar between both groups. Recovery, defined as time from last suture or procedure equivalent to first OAAS score of 5, was not different between sevoflurane and midazolam (7 ± 9 min vs. 7 ± 9 min). Times to arrival to recovery area (18 ± 19 vs. 16 ± 31 min), actual discharge from phase 1 recovery (39 ± 36 vs. 38 ± 35) and eligibility for discharge (57 ± 111 vs. 76 ± 108) were not significantly different between groups.

Complications and Side Effects

All enrolled patients were included in this analysis (117 sevoflurane and 56 midazolam). The incidence of severe excitation-disinhibition (defined as agitation or uncontrollable patient movement that resulted in difficult or unsafe operating conditions and required induction of general anesthesia) was significantly higher in the sevoflurane group (18 of 117 [15%] sevoflurane vs. 2 of 56 [4%] midazolam; $P = 0.043$). These patients were

Table 3. VAS Scores

Variable or Evaluation Time	Sevoflurane (N = 93)		Midazolam (N = 48)	
	Raw Score (Mean ± SD)	Change from Baseline (Mean ± SD)	Raw Score (Mean ± SD)	Change from Baseline (Mean ± SD)
Alertness or sedation				
Baseline	88 ± 19		85 ± 19	
5 min after procedure	53 ± 30	-37 ± 39	50 ± 31	-33 ± 38
10 min after procedure	67 ± 27*	-23 ± 37	55 ± 29	-27 ± 36
30 min after procedure	79 ± 24*	-11 ± 32	65 ± 27	-19 ± 31
No energy or full of energy				
Baseline	74 ± 23		73 ± 24	
5 min after procedure	45 ± 30	-31 ± 38	40 ± 28	-31 ± 36
10 min after procedure	52 ± 30	-24 ± 36	41 ± 25	-29 ± 36
30 min after procedure	61 ± 30	-16 ± 35	52 ± 25	-20 ± 34
Confused or clear-headed				
Baseline	92 ± 15		88 ± 20	
5 min after procedure	67 ± 28	-25 ± 34	60 ± 27	-28 ± 32
10 min after procedure	73 ± 29	-22 ± 34	61 ± 29	-25 ± 34
30 min after procedure	82 ± 23	-13 ± 30	72 ± 23	-16 ± 29
Calm or excited				
Baseline	47 ± 29		54 ± 28	
5 min after procedure	24 ± 25	-17 ± 39	24 ± 26	-33 ± 37
10 min after procedure	22 ± 24	-22 ± 36	20 ± 21	-34 ± 35
30 min after procedure	25 ± 28	-19 ± 41	31 ± 28	-26 ± 39
Clumsy or well-coordinated				
Baseline	83 ± 24		80 ± 24	
5 min after procedure	51 ± 33	-34 ± 39	46 ± 28	-31 ± 37
10 min after procedure	58 ± 32	-26 ± 38	50 ± 30	-27 ± 37
30 min after procedure	67 ± 32	-17 ± 35	56 ± 25	-21 ± 34
No nausea or severe nausea				
5 min after procedure	14 ± 25		8 ± 18	
10 min after procedure	12 ± 22		5 ± 10	
30 min after procedure	13 ± 24		8 ± 19	

Optimal score for categories in alertness, energy level, clear-headedness, excitement, and coordination is 100. Optimal score for nausea category is 0.

* Sevoflurane versus midazolam scores, $P < 0.05$.

VAS = Visual Analogue Scale.

withdrawn from the study and assessment of recovery, but not from assessment of side-effect and complication data. Moderate excitation-disinhibition (defined as agitation and uncontrollable movement, which was not believed to compromise surgical operating conditions or patient safety or did not require the discontinuation of the technique or induction of general anesthesia) was also more frequent with sevoflurane than midazolam (15 [16%] vs. 0; $P = 0.008$). The incidence of moderate disinhibition-excitement in sevoflurane patients was 11 of 33 (30%) who received regional and 4 of 60 (7%) who received local anesthesia ($P = 0.002$). All of the regional blocks in the patients who experienced moderate disinhibition-excitement were considered to be "good" quality blocks. None of the patients who received "fair" regional blocks experienced disinhibition-excitement. Including all enrolled patients in the intent-to-treat analysis, 15 of 39 patients (38%) who received sevoflurane sedation and regional anesthesia experienced moderate or severe disinhibition, whereas 18 of 78 patients (23%) who received sevoflurane sedation and local anesthesia experienced moderate or severe disinhibition ($P =$ not significant).

The incidence of excitement and disinhibition was greater in patients who did not receive fentanyl. Of the patients who experienced moderate or severe excitement, 23 received fentanyl and 12 did not. Of those who did not experience moderate or severe excitement, 11 received fentanyl and 24 did not ($P = 0.049$). The incidence of excitement and disinhibition did not differ between patients who did and did not receive remifentanyl for analgesia during block placement. Of all enrolled regional patients, 9 of 28 (32%) who received remifentanyl experienced excitement, compared with 10 of 31 (32%) who did not receive remifentanyl.

No significant difference was observed in the incidence of coughing, laryngospasm, apnea, and other complications between the two groups (table 4). Antiemetic requirements and incidence of vomiting were compared in patients who received only the sedation technique. Seventeen sevoflurane patients (18%) and six midazolam patients (13%) required anti-emetics during or after the procedure ($P =$ not significant). Two sevoflurane patients (2%) vomited at 5 min postoperatively, and one midazolam patient (2%) vomited at 30 min postoperatively ($P =$ not significant).

Table 4. Incidence of Side Effects

Side Effect	Sevoflurane (N = 117)	Midazolam (N = 56)
Excitement or disinhibition	35 (30%)*	2 (3.6%)
Coughing	6 (5.1%)	0
Laryngospasm	1 (0.9%)	0
Breath holding	4 (3.4%)	2 (3.5%)
Secretions	2 (1.7%)	0
Shivering	8 (6.8%)	1 (1.8%)
Apnea	6 (5.1%)	4 (7.1%)
Bradycardia	1 (0.9%)	0
Tachycardia	1 (0.9%)	0
Hypertension	1 (0.9%)	1 (1.8%)
Anxiety	1 (0.9%)	0
Dizziness	4 (3.4%)	1 (1.8%)
Hiccups	0	2 (3.6%)
Diplopia	0	1 (1.8%)
Tinnitus	1 (0.9%)	0

All enrolled patients are included in this analysis.

* $P = < 0.001$.

Discussion

The purpose of this investigation was to determine whether inhaled sevoflurane is an effective agent for sedation for patients undergoing surgery with regional or local anesthesia, and to compare the quality of recovery and rate of return of baseline cognitive function between sevoflurane and midazolam. Sevoflurane did produce dose-related sedation. Recovery to baseline cognitive function was faster with sevoflurane, and patients felt more awake as measured by VAS scores compared with patients who received midazolam for sedation. However, the occurrence of excitement-disinhibition with sevoflurane sedation was significant and may limit the usefulness of this technique. Further studies of sevoflurane sedation designed to diminish the incidence of excitement, such as the addition of fentanyl or other drugs, might improve this technique. Consequently, only a well-trained anesthesia provider who is equipped to deal with the potential complications of excitement (which include the requirement for induction of general anesthesia) should perform this sedation technique. Furthermore, sevoflurane administration requires the use of a face mask, anesthetic machine and agent analyzer, scavenging system, *etc.*, whereas the midazolam technique requires intravenous access, supplemental oxygen, and basic monitoring.

Midazolam was chosen as a comparator because it is widely used for sedation for surgical procedures performed with local or regional anesthesia, especially when the desired sedation level is responsiveness to voice. Midazolam produces dose-related sedation, as well as amnesia and anxiolysis. Midazolam sedation is simple to use, and, unlike propofol, does not require an infusion pump set-up. Additional studies are needed to compare the quality of sedation and emergence times of sevoflurane with other sedative agents such as propofol.

Anticipated benefits of an improved subjective quality of recovery with faster return of preoperative cognitive function might theoretically include shorter time in the recovery room and improved patient satisfaction. Although sevoflurane provided a more rapid recovery of cognitive function as measured by postoperative DSST and memory scores, these sensitive measures of cognitive function play no role in determining discharge eligibility. Moreover, although subjective recovery of alertness (measured by VAS) was improved after sevoflurane, objective recovery as measured by OAA scores revealed no difference in speed of awakening during the first 10 min postoperatively. Although the difference in OAA scores at 30 min after the procedure (100% *vs.* 94%) was found to be statistically significant, the clinical significance of this difference may not be appreciated. Finally, no difference was observed in time to discharge from the recovery room or eligibility to discharge. Admittedly, contributions to discharge times are multifactorial and usually do not reflect faster recovery, regardless of the drug used.^{18,19} However, these benefits also did not translate into improved patient satisfaction. And patients who required general anesthesia because of failure of the sedation technique were not queried for patient satisfaction.

The most serious limitation of sevoflurane for sedation was the development of excitement-disinhibition characterized by agitation and excessive uncontrollable movement, which sometimes caused serious disruption to operating conditions. The incidence of intraoperative excitement-disinhibition and excessive uncontrollable movement was high and clinically significant and may limit the usefulness of this technique. The incidence of moderate (not requiring conversion to general anesthesia) and severe (requiring conversion to general anesthesia) disinhibition was significantly greater with sevoflurane than midazolam. We tested the hypothesis that disinhibition was related to inadequate analgesia with local anesthesia because the sevoflurane sedation technique provides primarily sedation, and if analgesia is also needed, other analgesics need to be given. However, the data revealed that excitement-disinhibition occurred more frequently in patients receiving regional anesthesia, suggesting that inadequate analgesia with local sedation was not the cause of greater excitement with sevoflurane. Furthermore, the quality of the regional blocks in all of the patients who experienced moderate excitement was considered to be good; thus, an inadequate regional anesthetic was not the cause of excitement. In addition, fentanyl was administered more frequently to patients receiving local anesthesia, and it is conceivable that the administration of fentanyl decreased the incidence of excitement. Indeed, although the data were not captured in such a way that would provide objective evidence, it was the clinical impression that fentanyl decreased the incidence or severity of excitement. Further investigation is necessary.

Excitement has been reported to occur in adult patients undergoing mask induction with sevoflurane^{9,20} and other volatile anesthetics, but the reason for the development of agitation and excessive uncontrollable movement with sevoflurane sedation is unclear. Because the face mask was worn by all patients, anxiety or claustrophobia from wearing the face mask does not explain the increased incidence of excitement observed in sevoflurane patients. The incidence of other symptoms of airway irritation (e.g., breath-holding, cough, laryngospasm, bronchospasm) were not individually significantly greater in sevoflurane patients than in midazolam patients. Some investigators have suggested that the development of excessive uncontrollable movement may be a manifestation of seizures. Yli-Hankala *et al.*²¹ reported epileptiform electroencephalogram patterns during sevoflurane mask induction, yet other investigators found no evidence of seizures.²² The addition of nitrous oxide²³ and the vital-capacity rapid-inhalation technique²⁰ have reduced the incidence of excitement during sevoflurane induction of general anesthesia. Effects of nitrous oxide and a more rapid induction of inhalation sedation on excitement during sevoflurane sedation remain to be determined.

Nausea may be the single most important factor that adversely affects discharge after day-care surgery²⁴; thus, a low incidence of nausea is crucial to promote early discharge from the recovery room. Because potent volatile anesthetics are known to be associated with nausea,^{6,25} this possibility is recognized in patients who receive sevoflurane. Subject self-assessment (VAS) did not reveal significantly higher incidence of nausea post-operatively, and the number of patients who required anti-emetics and the incidence of vomiting were also similar between both groups. However, these data was not collected for the patients who failed the sedation technique.

In summary, although inhaled sevoflurane does produce dose-related sedation, the incidence of excitement-disinhibition is high and clinically significant and may seriously impact on operating conditions. Further studies of sevoflurane sedation designed to diminish the incidence of excitement might improve this technique. However, return of cognitive function measured by DSST and memory scores after sevoflurane sedation is faster than after midazolam sedation.

The authors thank Robert I. Block, Ph.D. (Associate Professor, Department of Anesthesia, University of Iowa), for the supply of the word lists used in this investigation.

References

1. Abboud TK, Gangolly J, Mosaad P, Crowell D: Isoflurane in obstetrics. *Anesth Analg* 1989; 68:388-91
2. Kataria B, Epstein R, Bailey A, Schmitz M, Backus WW, Schoeck D, Hackl W, Govaerts MJ, Rouge JC, Kern C, Van Ackern K, Hatch DJ: A comparison of

sevoflurane to halothane in paediatric surgical patients: Results of a multicentre international study. *Paediatr Anaesth* 1996; 6:283-92

3. Van Hemelrijck J, Smith I, White PF: Use of desflurane for outpatient anesthesia: A comparison with propofol and nitrous oxide. *ANESTHESIOLOGY* 1991; 75:197-203
4. Smiley RM: An overview of induction and emergence characteristics of desflurane in pediatric, adult, and geriatric patients. *Anesth Analg* 1992; 75:S38-44
5. Bunting HE, Kelly MC, Milligan KR: Effect of nebulized lignocaine on airway irritation and haemodynamic changes during induction of anaesthesia with desflurane. *Br J Anaesth* 1995; 75:631-3
6. Ebert TJ, Robinson BJ, Uhrich TD, Mackenthun A, Pichotta PJ: Recovery from sevoflurane anesthesia: A comparison to isoflurane and propofol anesthesia. *ANESTHESIOLOGY* 1998; 89:1524-31
7. Philip BK, Kallar SK, Bogetz MS, Scheller MS, Wetchler BV: A multicenter comparison of maintenance and recovery with sevoflurane or isoflurane for adult ambulatory anesthesia. *Anesth Analg* 1996; 83:314-9
8. Raeder J, Gupta A, Pedersen FM: Recovery characteristics of sevoflurane- or propofol-based anaesthesia for day-care surgery. *Acta Anaesthesiol Scand* 1997; 41:988-94
9. Jellish WS, Lien CA, Fontenot J, Hall R: The comparative effects of sevoflurane versus propofol in the induction and maintenance of anesthesia in adult patients. *Anesth Analg* 1996; 82:479-85
10. Philip JH, Myers TP, Philip BK: Inhalation sedation/analgesia with sevoflurane [letter]. *J Clin Anesth* 1997; 9:608-9
11. Chernik DA, Gillings D, Laine H, Hender J, Silver J, Davidson AB, Schwartz EM, Siegel JL: Validity and reliability of the observer's assessment of alertness/sedation scale: Study with intravenous midazolam. *J Clin Psychopharmacol* 1990; 10:244-51
12. Salthouse TA: What do adult age differences in the digit symbol substitution test reflect? *J Gerontol* 1992; 47:121-8
13. Wechsler D: Manual for the Wechsler Adult Intelligence Scale-Revised. New York, Psychological Corporation, 1981
14. Thorndike EL, Lorge I: The Teacher's Word Book of 30,000 Words. New York, Teacher's College Bureau of Publications, Columbia University, 1944
15. Paivio A, Yuille JC, Madigan SA: Concreteness, imagery, and meaningfulness values for 925 nouns. *J Exp Psychol* 1968; 76:1-25
16. Christian J, Bickley W, Tarka M, Clayton K: Measures of free recall of 900 English nouns: Correlation with imagery concreteness, meaningfulness, and frequency. *Mem Cogn* 1978; 6:379-90
17. Ghoneim MM, Block RL, Sum Ping ST, El-Zahaby HM, Hinrichs JV: The interactions of midazolam and flumazenil on human memory and cognition. *ANESTHESIOLOGY* 1993; 79:1183-92
18. Pavlin DJ, Rapp SE, Polissar NL, Malmgren JA, Koerschgen M, Keyes H: Factors affecting discharge time in adult outpatients. *Anesth Analg* 1998; 87:816-26
19. Hession MC: Factors influencing successful discharge after outpatient laparoscopic cholecystectomy. *J Perioper Nurs* 1998; 13:11-5
20. Yurino M, Kimura H: Induction of anesthesia with sevoflurane, nitrous oxide, and oxygen: A comparison of spontaneous ventilation and vital capacity rapid inhalation induction techniques. *Anesth Analg* 1993; 76:598-601
21. Yli-Hankala A, Vakkuri A, Sarkela M, Lindgren L, Korttila K, Jantti: Epileptiform electroencephalogram during mask induction of anesthesia with sevoflurane. *ANESTHESIOLOGY* 1999; 91:1596-1603
22. Constant I, Dubois M-C, Piat V, Moutard M-L, McCue M, Murat I: Changes in electroencephalogram and autonomic cardiovascular activity during induction of anesthesia with sevoflurane compared with halothane in children. *ANESTHESIOLOGY* 1999; 91:1604-15
23. Sarner JB, Levine M, Davis PJ, Lerman J, Cook DR, Motoyama EK: Clinical characteristics of sevoflurane in children. *ANESTHESIOLOGY* 1995; 82:38-46
24. Green G, Jonsson L: Nausea: The most important factor determining length of stay after ambulatory anaesthesia. A comparative study of isoflurane and/or propofol techniques. *Acta Anaesthesiol Scand* 1993; 37:742-6
25. Fleischmann E, Akca O, Wallner T, Arkilic CF, Kurz A, Hickler RS, Zimpfer M, Sessler DI: Onset time, recovery duration, and drug cost with four different methods of inducing general anesthesia. *Anesth Analg* 1999; 88:930-5

Appendix: The Sevoflurane Sedation Study Group

W. A. Barcellos (Department of Anesthesia, University of Iowa, Iowa City, Iowa); A. Crnkovic, L. Linneman (Department of Anesthesiology, Albany Medical College, Albany, New York); J. L. Apfelbaum (Department of Anesthesiology, University of Chicago, Chicago, Illinois); J. Philip, E. Roaf, J. Mandel (Department of Anesthesiology, University of California Davis Medical Center, Davis, California); D. Culley, L. Drager (Department of Anesthesia, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts).