

# Sevoflurane versus Halothane: Postoperative Maladaptive Behavioral Changes

## A Randomized, Controlled Trial

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**Background:** The authors conducted a double-blind, randomized, controlled trial to determine whether the use of sevoflurane in children undergoing anesthesia and surgery results in a higher incidence of postoperative maladaptive behavioral changes as compared with halothane.

**Methods:** Children and their parents ( $n = 102$ ) were randomly assigned to either a halothane group ( $n = 50$ ) or a sevoflurane group ( $n = 52$ ). The intraoperative anesthetic protocol was strictly controlled, and the postoperative analgesic consumption and pain levels were recorded. The effect of the group assignment on emergence status and maladaptive postoperative behavioral changes was assessed both by validated psychological measures and physiologic instruments (actigraphy) on postoperative days 1–7. Anxiety of the parent and child was also assessed, as was the child's postoperative recovery (Recovery Inventory).

**Results:** There were no group differences in preoperative state anxiety, postoperative analgesic requirements, postoperative pain, or the incidence of emergence delirium ( $P =$  not significant). Two-way repeated-measures analysis of variance showed no group differences in the incidence of postoperative maladaptive behaviors ( $F_{4,72} = 0.60$ ,  $P = 0.701$ ) or actigraphic variables such as percent sleep, number of night awakenings, and night awakenings that lasted for more than 5 min ( $P =$  not significant).

**Conclusion:** The authors found no increased incidence of emergence delirium, maladaptive postoperative behavior changes, or sleep disturbances in children undergoing anesthesia with sevoflurane as compared with halothane.

THE issue of emergence delirium after sevoflurane anesthesia is controversial.<sup>1–9</sup> When sevoflurane is compared to halothane, some reports indicate an increased incidence of emergence delirium,<sup>1,2,4,5,7,8</sup> whereas other studies report no difference between the two anesthetics

in incidence of emergence delirium.<sup>2,9</sup> Interestingly, a recent report by Foesel and Reisch<sup>10</sup> indicates that children who underwent anesthesia using sevoflurane were also more likely to have postoperative, maladaptive behavioral changes as compared with children who underwent anesthesia using halothane.

The occurrence of new-onset, maladaptive, postoperative behavioral changes has been described in a large number of children undergoing anesthesia and surgery.<sup>11–13</sup> These postoperative behavior changes can include new-onset separation anxiety, apathy and withdrawal, eating problems, and sleep problems. Postoperative sleep problems in children undergoing anesthesia and surgery are of particular concern, and their existence has been confirmed by both behavioral instruments and physiologic instruments such as actigraphy.<sup>12,14</sup> A recent study by Kain *et al.*<sup>15</sup> suggested that emergence delirium and new-onset postoperative maladaptive behavior are closely associated. The investigators found that children who have emergence delirium after anesthesia and surgery are seven times more likely to have postoperative maladaptive behavioral changes.<sup>15</sup> Considering the reported association between emergence delirium and postoperative behavioral changes and reports regarding sevoflurane and emergence delirium, the preliminary findings by Foesel and Reisch regarding postoperative behavioral changes and sevoflurane are not surprising.

Because sevoflurane is widely used to anesthetize children, we strongly believe that it is imperative to examine a possible cause–effect relation between sevoflurane and postoperative maladaptive behavioral changes. This is of particular importance because the study by Foesel and Reisch<sup>10</sup> was a nonrandomized, retrospective investigation and therefore was subject to multiple biases. Therefore, we designed a double-blind, randomized, controlled study to examine whether the use of sevoflurane in children undergoing anesthesia and elective outpatient surgery resulted in a higher incidence of postoperative maladaptive behavioral changes as assessed by both behavioral and physiologic instruments.

## Materials and Methods

Participants of this double-blind, randomized, controlled trial consisted of children aged 3–10 yr, with an American Society of Anesthesiologists physical status I or

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II, who were undergoing anesthesia and elective outpatient surgery at Yale-New Haven Children's Hospital. To avoid confounding variables, children with a history of chronic illness, prematurity (< 36 weeks' gestation), or reported developmental delay were not recruited for this study. Sedative premedication such as midazolam was not offered to children in this trial, and all parents were present while their children underwent induction of anesthesia. The Yale Institutional Review Board (New Haven, Connecticut) reviewed and approved the experimental protocol of the study; all parents provided written informed consent, and all children provided assent (when appropriate).

### Primary Outcome and Measure

The primary outcome, maladaptive postoperative behavioral changes in children after outpatient surgery, was assessed with the Post Hospitalization Behavioral Questionnaire (PHBQ).<sup>16,17</sup> This parental self-report questionnaire, originally designed by Vernon, is used to evaluate maladaptive (negative) behavioral responses in children after anesthesia and surgery. We have used this instrument with more than 1,000 patients during the past 10 yr, and thus our study group has extensive experience with the PHBQ. The instrument consists of 27 items in six domains: general anxiety, separation anxiety, sleep anxiety, eating disturbances, aggression against authority, and apathy/withdrawal. Ample data in the literature attest to the good reliability and validity of this instrument, as does a principal components factor analysis with varimax rotation performed recently by our study group on a sample of 1,492 PHBQ questionnaires.<sup>14</sup> Therefore, we conclude that the PHBQ can be reliably used in the perioperative setting to assess postoperative behavioral changes as a valid outcome.

### Secondary Outcomes and Measures

**Postoperative Sleep.** Postoperative sleep, a secondary outcome, was objectively assessed *via* actigraphic techniques. Actigraphy is a well-established method for assessing sleep in infants, children, and adults in a variety of settings.<sup>14,18,19</sup> The device used in this investigation (MiniMotionlogger Basic, MotionLogger Actigraph; Ambulatory Monitoring, Inc., Ardsley, NY) is a miniaturized motion detection system the size of a wristwatch that is worn on the wrist *via* a watchband; data are downloaded through a computer interface. We have used this device successfully in previous perioperative investigations involving both adults and children.<sup>14</sup> In this investigation, raw actigraphic data were translated to sleep variables using the Actigraphic Scoring Analysis program for IBM-compatible personal computers (ACTME; Ambulatory Monitoring, Inc.) and then scored using a validated algorithm.<sup>20</sup> Actigraphic sleep variables resulting from these calculations included (1) total sleep period (from sleep onset time to morning awakening), (2) per-

centage sleep (percentage of actual sleep time during total sleep period), (3) true sleep time (total minutes actually in sleep during entire sleep period), (4) number of night awakenings (*i.e.*, how many times the child awoke during the night), and (5) number of night awakenings that lasted for at least 5 min.

Detailed daily sleep logs that were completed by parents included information about children's sleep schedule (bedtime, waking time), sleep quality (night waking, sleep latency), and tiredness during the day. These logs were used to help score the data and resolve any questions regarding the actigraphic data.

**Emergence Behavior.** Trained observers assessed emergence behavior when each participant arrived in the recovery room after surgery. The emergence behavior was rated based on a scale developed and validated by Keegan *et al.*<sup>21</sup>

### Other Measures

The reader is referred, for more detailed psychometric data regarding the instruments used in this investigation, to previous publications by our study group.<sup>22,23</sup> All instruments and scales used in this investigation were administered under the direct supervision of a trained psychologist experienced in perioperative research.

**Modified Yale Preoperative Anxiety Scale.** The Modified Yale Preoperative Anxiety Scale is an observational state anxiety measure for young children that contains 27 items in five categories (Activity, Emotional Expressivity, State of Arousal, Vocalization, and Use of Parents). The Modified Yale Preoperative Anxiety Scale has good to excellent reliability and validity for measuring children's anxiety in the preoperative holding area and during induction of anesthesia.<sup>24,25</sup>

**Induction Compliance Checklist.** The Induction Compliance Checklist is an observational checklist, previously developed by our laboratory, that describes the child's compliance during induction of anesthesia. The Induction Compliance Checklist has a very high interclass *r* both within (0.998) and between observers (0.978).<sup>26</sup>

**State-Trait Anxiety Inventory.** The State-Trait Anxiety Inventory (STAI) is a self-report anxiety behavioral instrument that consists of two separate 20-item subscales that measure trait (baseline) and state (situational) anxiety. The STAI shows good validity and reliability and has been used to date in more than 1,000 scientific publications.<sup>27,28</sup>

**EASI Temperament Scale.** The EASI Temperament Scale is a parental report instrument that assesses four temperament categories (Emotionality, Activity, Sociability, and Impulsivity) in children and is widely used in the literature.<sup>29</sup> Good reliability and validity data are available for this instrument.

**Recovery Inventory.** The Recovery Inventory is a scale that assesses postoperative recovery. Items include

sleep, appetite, strength and energy, self-assistance, and movement. Individual ratings are summed for a Total Recovery Inventory Score.<sup>30</sup>

**Pediatric Pain Measure for Parents.** The Pediatric Pain Measure for Parents is a 15-item measure that assesses a child's postoperative pain. Items are drawn from parental reports of the cues that parents use to assess pain in their children; the measure aggregates these cues to provide systematic and reliable pain assessment. The measure shows good internal consistency and validity.<sup>31</sup>

### Study Protocol

Parents and their children were recruited at least 5 days before the child's surgery while undergoing a voluntary behavioral preoperative preparation program, or by telephone if the parents elected to not undergo the preparation program. This voluntary program is attended by approximately 40–50% of children undergoing elective outpatient surgery and provides information to both children and parents through an orientation tour of the operating room and interviews by a nurse, an anesthesiologist, and child-life specialist. After consent was obtained, parents received a packet containing an actigraph, baseline questionnaires (EASI Temperament Scale, STAI-Trait), and a sleep diary with which to record sleep and wake times. The child wore the actigraph at night for each of the five nights before the surgery to obtain valid baseline data. Parents completed the sleep diary on each of these nights, as well as demographic and baseline measures, and returned them on the day of surgery or *via* mail.

**Preoperative Holding Area.** On the day of surgery, when they arrived at the hospital, parents completed the STAI-State (one parent per child) and a trained observer rated the child's state anxiety in the holding area and after separation to the operating room using the Modified Yale Preoperative Anxiety Scale.

**Induction Period.** All parents accompanied their child into the operating room for induction of anesthesia. As soon as anesthesia was induced, a research assistant escorted parents to the perioperative waiting area. State anxiety (Modified Yale Preoperative Anxiety Scale) of children was evaluated after entrance to the operating room and after introduction of the anesthesia mask. On randomization, groups were matched for surgery type (see Randomization); attending anesthesiologists then followed a detailed, standardized protocol that was uniform for each type of surgery (appendix). Therefore, the only variation in care that each child received was the assignment of sevoflurane or halothane as the anesthetic agent.

**Postanesthesia Care Unit.** Incidence of emergence delirium was assessed both upon arrival to the postanesthesia care unit (PACU) and throughout the PACU stay. While in the PACU, patients were medicated with fentanyl and metoclopramide as needed (see appendix).

Based on the surgical procedure, some children received acetaminophen with codeine (one dose just before being discharged). Children were discharged to return home approximately 1–2 h after the conclusion of their surgery. The research assistants who were blinded to group assignment observed and collected all data in the PACU.

**At Home, Postoperative Days 1–5 and Week 1.** Parents were instructed to follow the surgeon's medication instructions, which included acetaminophen with codeine or acetaminophen; these instructions included taking no ibuprofen or any other analgesics or sedatives. Parents attached the actigraph to their child 1 h before bedtime each night and completed a sleep diary for their child on postoperative days 1–5. The daily sleep logs included information about the child's sleep schedule (bedtime, waking time), sleep quality (night waking, sleep latency), and tiredness during the day. Families were contacted by telephone on each of five nights after the surgery as well as at 1 week to assess behavioral recovery and pain. Parents completed the PHBQ and the Pediatric Pain Measure for Parents on each of these postoperative days. The purpose of the telephone conversation by the research assistants who were blinded to group assignment was to collect this data on a day-by-day basis, thereby avoiding recall bias. These researchers reminded the parents to have their child wear the actigraph at night.

### Statistic and Analytic Approaches

**Randomization.** Based on a computer-generated list, children were randomly assigned to receive either sevoflurane (sevoflurane group) or halothane (halothane group). Having realized *a priori* that postoperative behavioral changes may be the result of variables such as age of the child, preoperative anxiety, use of midazolam, type of surgical procedure, and postoperative pain, we therefore strictly controlled variables such as use of midazolam, anesthetic protocols, and postoperative pain management (see appendix). To best control for other confounding variables, the randomization process was stratified based on the child's age as well as the type of surgical procedure. Children in this study underwent the following procedures: herniorrhaphy, hydrocele, orchiopexy (38%); pressure-equalizing tube placement (19%); adenoidectomy (15%); endoscopy (12%); and strabismus repair (15%). Of importance is that all children and their parents, as well as all research assistants who gathered outcome data, were blinded to group assignment.

**Sample Size and Power.** The primary outcome of this study was the incidence of maladaptive postoperative behavioral changes during the week after surgery. Sample size was computed *a priori* for the two groups.<sup>32</sup> Given a moderate effect size of 0.66 and an  $\alpha$  of 0.05 (two tailed), 50 participants in each of the two



Table 1. Baseline Characteristics

	Group		P Value
	Sevoflurane (n = 52)	Halothane (n = 50)	
Parents			
Trait Anxiety (STAI)	39.23 ± 7.7	38.94 ± 7.5	0.61
State Anxiety—holding (STAI)	40.23 ± 10.8	41.4 ± 12.8	0.85
Children			
Age, yr	6.9 ± 2.1	7.1 ± 1.9	0.59
Sex, F/M, %	40/60	44/56	0.69
Temperament (EASI)			
Emotionality	10.98 ± 3.6	11.45 ± 3.8	0.54
Activity	15.15 ± 4.6	14.17 ± 3.7	0.26
Sociability	18.69 ± 2.7	18.79 ± 2.8	0.86
Impulsivity	11.69 ± 3.8	11.02 ± 3.1	0.35
Previous medical experiences (VAS)	89.2 ± 11.6	84.8 ± 18.5	0.17
State Anxiety—holding (mYPAS)	37.2 ± 13.2	35.3 ± 13.5	0.49
State Anxiety—OR doors (mYPAS)	40.2 ± 15.3	39.7 ± 20.7	0.91
State Anxiety—induction 1 (mYPAS)	42.6 ± 18.1	42.5 ± 21.8	0.98
State Anxiety—induction 2 (mYPAS)	46.3 ± 21.0	46.0 ± 21.0	0.94
Voluntary preparation program, yes/no, %	54/46	48/52	0.69

Data are presented as mean ± SD.

EASI = EASI Temperament scale; Holding = mYPAS measurement taken in the preoperative holding area; induction 1 = mYPAS measurement taken after child enters the operating room; induction 2 = mYPAS measurement taken on introduction of the anesthesia mask; MBSS = Miller Behavioral Style Scale; mYPAS = Modified Yale Preoperative Anxiety Scale; OR doors = mYPAS measurement taken at entrance to the operating room; STAI = Spielberger State-Trait Anxiety Inventory; VAS = visual analog scale measuring how well child handled previous medical visits.

groups yielded a power of 0.91, sufficient to identify group differences using an independent *t* test.

**Overall Statistics.** Data are presented as mean ± SD. Differences between groups were examined using inferential statistics, including *t* tests and one-way repeated-measures analysis of variance (ANOVA). Descriptive statistics demonstrate relations between parent variables and anxiety levels. *P* values of less than 0.05 were considered statistically significant.

**PHBQ Analysis.** The PHBQ scores were transformed so that 1, 2, and 3 = 0, a 4 = 1, and 5 = 2. In this manner, only the incidence of maladaptive behaviors was included in the analysis. PHBQ subscales were calculated after data were transformed. A repeated-measures ANOVA was then performed on these PHBQ scores. Bonferroni corrections were used for multiple comparisons. To assess the proportion of behavior changes occurring in each group, the presence or absence of any maladaptive behavior changes was calculated without regard to severity (*i.e.*, scores were transformed so that 1, 2, or 3 = 0 and 4 or 5 = 1).

**Actigraphy Analysis.** The raw actigraphic activity data were carefully inspected against the sleep diaries for accuracy of reported bedtimes and rise times, monitor removal periods, and reliability. Any discrepancies between the sleep diary and the actigraphic data (*e.g.*, diary indicated child woke up twice but actigraphic data showed no movement after 8:00 PM) were resolved with the parents. A minimum of four nights of preoperative and postoperative sleep were averaged to provide mean sleep actigraphic measures per subject, well in accordance with reliability estimates for previously published

data for pediatric surgery patients.<sup>14</sup> Sleep variables were assessed both preoperatively and postoperatively. We used an independent-samples *t* test to examine average sleep measures by group assignment. Because we expected there to be some change over time in sleep variables postoperatively, we also examined postoperative sleep measures using one-way repeated-measures ANOVA to investigate group differences in postoperative sleep changes over time.

**Induction Compliance Checklist Analysis.** Children who scored 0 (perfect compliance) or 1 (1 noncompliant behavior) were compared using a chi-square test to children who scored 2 (2 noncompliant behaviors) or higher (up to 10 noncompliant behaviors).

## Results

We enrolled 102 subjects in this double-blind, randomized, controlled trial. The sevoflurane group (n = 52) was similar to the halothane group (n = 50) with regard to variables such as age, sex, temperament, surgical procedure, parental trait anxiety, and parents' rating of their child's behavior during previous medical visits (table 1). Repeated-measures ANOVA revealed an expected increase in state anxiety as children moved from the holding area to induction of anesthesia ( $F_{3,66} = 3.88$ ,  $P = 0.013$ ). Analysis of anxiety by group assignment indicated that there were no group differences in state anxiety changes over the preoperative period ( $F_{3,66} = 0.18$ ,  $P = 0.904$ ). Also, no group difference between the sevoflurane and halothane groups for compliance during induction were found (sevoflurane group: 81% perfect

**Table 2. Proportion of Behavior Changes in Each Group for All Postoperative Days**

	Group						P Value
	Halothane Number of Behavior Changes			Sevoflurane Number of Behavior Changes			
	None	1 or 2	3 or More	None	1 or 2	3 or More	
POD 1	32.00	40.00	28.00	42.30	32.70	25.00	0.55
POD 2	53.10	26.50	20.40	65.40	21.20	13.50	0.43
POD 3	71.40	18.40	10.20	72.50	15.70	11.80	0.92
POD 4	76.60	14.90	8.50	80.00	8.00	12.00	0.51
POD 5	83.00	14.90	2.10	87.80	8.20	4.10	0.52
POD 7	85.40	12.20	2.40	86.00	14.00	0.00	0.53
Total	35.90	41.00	23.10	31.90	48.90	19.10	0.76

POD = postoperative day; total = total number of behavior changes on all postoperative days assessed.

or near-perfect induction *vs.* 19% noncompliance; halothane group: 84% *vs.* 16%, respectively;  $P = 0.67$ ).

Because the level of postoperative pain significantly influences postoperative behavioral recovery, we first examined postoperative analgesic consumption to ensure that the two groups were similar. An independent  $t$  test showed no differences between the sevoflurane and halothane groups in the total amount of codeine (any fentanyl was converted to codeine units) or acetaminophen consumed postoperatively in the hospital (codeine:  $2.3 \pm 1.9$  *vs.*  $2.4 \pm 3.5$  mg/kg;  $P = 0.92$ ; acetaminophen:  $10.7 \pm 6.3$  *vs.*  $12.3 \pm 3.8$  mg/kg;  $P = 0.36$ ). Similarly, there were no group differences in total analgesic consumption at home (codeine:  $0.13 \pm 0.36$  *vs.*  $0.13 \pm 0.45$  mg/kg;  $P = 0.94$ ; acetaminophen:  $22.2 \pm 34.3$  *vs.*  $30.9 \pm 49.8$  mg/kg;  $P = 0.32$ , for the sevoflurane and halothane groups, respectively). When data were analyzed over time (postoperative days 1–7), repeated-measures ANOVA found no group differences between the two groups (codeine:  $P = 0.98$ ; acetaminophen:  $P = 0.66$ ) and no group-times-time interaction.

Parents rated postoperative pain using the Pediatric Pain Measure for Parents. Repeated-measures ANOVA showed that pain scores decreased from the time of surgery to postoperative day 7, as expected ( $F_{5,70} = 13.47$ ,  $P = 0.0001$ ). Analysis by group showed no difference in postoperative pain between the sevoflurane and halothane groups ( $F_{5,70} = 0.97$ ,  $P = 0.441$ ).

### Primary Outcome

We next examined behavioral recovery as assessed by the PHBQ. We first examined the proportion of behavior changes occurring in each of the groups on each postoperative day (table 2). Chi-square analyses showed no differences between the groups in number of postoperative behavior changes either overall or on any of the individual postoperative days 1–5 and week 1 (table 2). Repeated-measures analysis was next used to examine this data because it eliminates the influence of individual differences, thereby reducing error variance, and is thus a more powerful test. When analyzed over time, a two-

way repeated-measures ANOVA showed an expected significant improvement for all participants over the postoperative assessment period ( $F_{5,71} = 9.75$ ,  $P = 0.0001$ ); however, there were no group differences in the number of new-onset maladaptive behaviors occurring after surgery ( $F_{4,72} = 0.60$ ,  $P = 0.701$ ). Next, we examined each of the six PHBQ subscales over postoperative days 1–7 using two-way repeated-measures ANOVA, with Bonferroni corrections for multiple comparisons. We found no group differences in General Anxiety ( $F_{5,72} = 0.43$ ,  $P = 0.826$ ), Eating ( $F_{5,72} = 0.52$ ,  $P = 0.76$ ), Apathy and Withdrawal ( $F_{5,72} = 1.06$ ,  $P = 0.389$ ), Sleep ( $F_{4,73} = 1.6$ ,  $P = 0.167$ ), Social Anxiety ( $F_{5,72} = 0.283$ ,  $P = 0.921$ ), or Aggression against Authority ( $F_{4,73} = 1.273$ ,  $P = 0.29$ ). Finally, we found no group-based differences in the incidence of behavioral changes based on the age of the child ( $P = 0.43$ ).

### Secondary Outcome: Emergence Delirium

Emergence delirium was assessed at the time of arrival at the postoperative care unit as well as throughout the PACU stay. Chi-square analysis showed that there were no group differences in the incidence of emergence delirium (no emergence symptoms: 52.1% *vs.* 52.0% for the sevoflurane and halothane groups, respectively; marked emergence symptoms: 16.7% *vs.* 10.0%;  $P = 0.57$ ).

### Secondary Outcome: Actigraphy

Sleep variables were assessed both preoperatively and postoperatively. We first examined preoperative sleep measures by group assignment to ensure that groups were equal on this baseline measure. Independent  $t$  tests using the average of all sleep variables for the preoperative period showed no group differences (table 3). Next, we examined postoperative sleep measures using three two-way repeated-measures ANOVAs to investigate change over time as a function of group assignment in percentage sleep, number of night awakenings, and night awakenings that lasted for more than 5 min. All three repeated-measures ANOVA analyses showed no group differences for any of the sleep variables (table 3),

Table 3. Sleep Variables as Measured by Actigraphy

	Group		<i>t</i> Test <i>P</i>	RM ANOVA, <i>F</i> ( <i>df</i> )	RM ANOVA, <i>P</i>
	Sevoflurane ( <i>n</i> = 52)	Halothane ( <i>n</i> = 50)			
Preoperative sleep					
Percentage sleep	85.7 ± 8.9	86.8 ± 7.9	0.58	NA	NA
Number of night awakenings	16.1 ± 7.9	15.1 ± 7.3	0.56	NA	NA
Night awakenings > 5 min	4.9 ± 3.3	4.8 ± 3.2	0.9	NA	NA
Postoperative sleep					
Percentage sleep	84.2 ± 9.9	85.3 ± 9.9	0.59	0.34 (4,52)	0.85
Number of night awakenings	16.3 ± 8.6	15.2 ± 7.8	0.57	0.79 (4,52)	0.54
Night awakenings > 5 min	5.6 ± 3.4	4.9 ± 2.9	0.32	0.21 (4,52)	0.93

*df* = degrees of freedom; NA = not applicable; RM ANOVA = repeated-measures analysis of variance.

indicating that type of anesthetic agent had no impact on postoperative sleep. Independent *t* tests using the average of all sleep variables for the postoperative period also showed no differences by group (table 3).

#### Secondary Outcome: Recovery Inventory

We found no differences in recovery as measured by the composite of Recovery Inventory (e.g., sleep, appetite, strength and energy, self-assistance, movement) as assessed by a two-way repeated-measures ANOVA ( $F_{5,69} = 0.914$ ,  $P = 0.477$ ). Individual-items repeated-measures ANOVAs over the 6-day period were also not different between the two study groups: Sleep:  $F_{5,69} = 0.513$ ,  $P = 0.76$ ; Appetite:  $F_{5,70} = 2.73$ ,  $P = 0.26$ ; Self-Assistance:  $F_{5,70} = 0.978$ ,  $P = 0.43$ ; Strength and Energy:  $F_{5,70} = 1.06$ ,  $P = 0.38$ ; and Movement:  $F_{5,70} = 1.738$ ,  $P = 0.13$ .

## Discussion

Under the conditions of this double-blind, randomized trial, we found that the use of sevoflurane is not associated with a higher incidence of emergence delirium, maladaptive postoperative behavioral changes, or sleeping problems as compared with halothane. Therefore, clinicians should not be concerned about increased risk of postoperative behavioral changes and sleeping problems after anesthesia using sevoflurane.

The results of this study are contradictory to the results by Foesel and Reisch,<sup>10</sup> who reported increased postoperative behavioral changes in children undergoing sevoflurane anesthesia. One should interpret the study by Foesel and Reisch carefully because it was not a randomized, controlled trial but rather an anesthesia record review with the potential for multiple biases and methodologic errors, including reporting bias, uncontrolled anesthetic technique, and the use of preoperative sedatives.<sup>10</sup> There was also a time lag of 6 and 24 months between the date of the anesthesia and when parents answered questions regarding their child's postoperative behavior in the study by Foesel and Reisch. The lack of

increased incidence of both emergence delirium and postoperative behavioral changes in patients who received sevoflurane that we found in this study is consistent with a recent publication reporting an association between these two clinical phenomena.<sup>15</sup> This lack of increased incidence of emergence delirium in children undergoing anesthesia with sevoflurane is also in line with some previous reports<sup>2,9</sup> and contradictory to others.<sup>2,4,5,7,8</sup> The ambiguity in this research may be mediated by the lack of a comprehensive and validated instrument to assess emergence delirium. The recent publication of an emergence delirium instrument by Sikich and Lerman<sup>33</sup> is expected to add substantially to research methodology in this area.

Maladaptive postoperative behavioral changes have been reported to occur in up to 65% of all children undergoing anesthesia and surgery.<sup>12</sup> Variables such as young age, anxiety of the child and of the parent in the holding area, anxiety of the child during induction of anesthesia, type of surgery, and level of postoperative pain have been reported to predict the occurrence of these behavioral changes.<sup>12</sup> Because of these potentially confounding variables, we did not simply rely on the randomization process but rather controlled for some of the variables (anesthetic technique) and stratified for other (age and procedure). Therefore, we believe that our experimental protocol was methodologically sound.

We also did not find any group differences in any of the actigraphic sleep variables in this study. We included actigraphy as an outcome instrument because it is an objective cutting-edge technology. In addition, we had found an association between the PHBQ sleep variables and the actigraphic variables in a previous study.<sup>14</sup>

In conclusion, we have found that children undergoing anesthesia with sevoflurane, as compared with halothane, are not at increased risk for development of new-onset postoperative behavioral changes or sleep disturbances.

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## Appendix

The anesthetic chart of each participant included an attached study protocol; a research assistant assured adherence to these protocols by the anesthesia attending and resident staff. All anesthetic inductions were performed as follows: scent mask with nitrous oxide-oxygen for 1 min (measured by a research assistant), then addition of sevoflurane or halothane titrated slowly over a 1- to 2-min period (halothane max, 2.5%; sevoflurane max, 6%). Attending anesthesiologists had the option to use 0.1 mg/kg vecuronium to facilitate intubation and reverse with neostigmine and glycopyrrolate (except pressure-equalizing tubes). Pain for all below procedures (except pressure-equalizing tubes) was managed in the postanesthesia care unit with 0.5-1  $\mu$ g/kg fentanyl as needed for pain (score of 3 or more on OPS). Postoperative nausea and vomiting was managed in the postanesthesia care unit using 0.1 mg/kg metoclopramide (all subjects received 0.1 mg/kg ondansetron during the surgical procedure).

### Placement of Pressure-equalizing Tubes

Preoperatively: 20 mg/kg oral acetaminophen. When the surgeon finished with the first ear, nitrous oxide was turned off, and the study drug and oxygen were continued until the end of the case. Postoperative: acetaminophen.

### Adenoidectomy

Maintenance: nitrous oxide-oxygen plus study drug, 1  $\mu$ g/kg fentanyl; home: acetaminophen or acetaminophen and codeine

### Strabismus

Maintenance: nitrous oxide-oxygen plus study drug, 3  $\mu$ g/kg fentanyl; postanesthesia care unit: 0.2 mg/kg dexamethasone; home: acetaminophen

### Herniorrhaphy/Endoscopy/Hydrocele/Orcchiopexy

Maintenance: nitrous oxide-oxygen plus study drug, 2  $\mu$ g/kg fentanyl; home: acetaminophen

### Circumcision

Maintenance: nitrous oxide-oxygen plus study drug, 2  $\mu$ g/kg fentanyl; home: acetaminophen and codeine