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Postoperative Behavioral Outcomes in Children

Effects of Sedative Premedication

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Background: **Although multiple studies document the effect of sedative premedication on preoperative anxiety in children, there is a paucity of data regarding its effect on postoperative behavioral outcomes.**

Methods: **After screening for recent stressful life events, children undergoing anesthesia and surgery were assigned randomly to receive either 0.5 mg/kg midazolam in 15 mg/kg acetaminophen orally (n = 43) or 15 mg/kg acetaminophen orally (n = 43). Using validated measures of anxiety, children were evaluated before and after administration of the intervention and during induction of anesthesia. On postoperative days 1, 2, 3, 7, and 14, the behavioral recovery of the children was assessed using the Post Hospitalization Behavior Questionnaire.**

Results: **The intervention group demonstrated significantly lower anxiety levels compared with the placebo group on separation to the operating room and during induction of anesthesia ($F[1,77] = 3.95$, $P = 0.041$). Using a multivariate logistic regression model, the authors found that the presence or absence of postoperative behavioral changes was dependent on the group assignment ($R = 0.18$, $P = 0.0001$) and days after operation ($R = -0.20$, $P = 0.0001$). *Post hoc* analysis demonstrated that during postoperative days 1–7, a significantly smaller number of children in the midazolam group manifested negative behavioral changes. At week 2 postoperatively, however, there were no significant differences between the midazolam and placebo groups.**

Conclusions: **Children who are premedicated with midazolam before surgery have fewer negative behavioral changes during the first postoperative week. (Key words: Anesthesia; behavior; midazolam; surgery.)**

PREVIOUSLY, we reported[1] that 54% of all children undergoing general anesthesia and surgery exhibit negative behavioral responses 2 weeks after operation. Twenty percent of these children continue to demonstrate negative behavior changes 6 months after operation, and in 7% these behaviors persisted 1 yr after operation. Nightmares, separation anxiety, eating problems, and increased fear of doctors are the most common problems 2 weeks after surgery.[1] It is noteworthy that increased anxiety of the child and parent in the preoperative holding area predicts the increased incidence of these negative postoperative behavioral problems.[1]

Based on these findings, we hypothesized that decreased preoperative anxiety may be associated with a decreased incidence of postoperative negative behavioral changes. Further, it can be hypothesized that because sedative premedicants are reported to lower children's anxiety in the preoperative holding area,[2] they also may reduce the incidence of postoperative negative behavioral changes. A recently published survey, however, reports that most anesthesiologists in the United States do not administer sedative premedicants to young children undergoing general anesthesia and surgery.[3] A possible reason may be that, although multiple studies have documented the effects of sedative premedicants on preoperative anxiety,[2,4–6] there is a paucity of data regarding the effects of sedative premedicants on postoperative outcomes. The purpose of this investigation, therefore, was to determine whether preoperative administration of sedative medications decreases the incidence of postoperative negative behavioral changes.

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Materials and Methods

Study Design and Patients

This was a randomized, double-blind, controlled study conducted with children undergoing general anesthesia and outpatient surgery. Consecutive outpatients aged 2–7 yr with American Society of Anesthesiologists physical status I–II scheduled to undergo general anesthesia and elective surgery (herniorrhaphy, orchiopexy, hydrocelectomy, tonsillectomy or adenoidectomy, and circumcision) were considered for enrollment. Patients were excluded from participation if they had a recent stressful life event (see study protocol: recruitment phase), had a history of prematurity or chronic illness, had a history of developmental delay, or were consuming medication that could interact with midazolam (*i.e.,* sedatives, anticonvulsants, erythromycin).

Ninety-eight children were screened for the study (see protocol). Eight children were found to have major life changes (*i.e.,* serious illness or death in the family, new house, new sibling, new job for parent, new nursery school) and were not recruited for the study (fig. 1). Two children refused to take their premedication and were excluded from the study. One child was admitted to the hospital immediately after the surgery, and one child was diagnosed with pneumonia on postoperative day (POD) 2; both were eliminated from further analysis. Thus, data from a total of 86 patients were analyzed.

A repeated-measures design was used in which each patient's behavior was evaluated throughout the perioperative period. The Institutional Review Board approved the study protocol, and informed consent was obtained from the parents of each child.

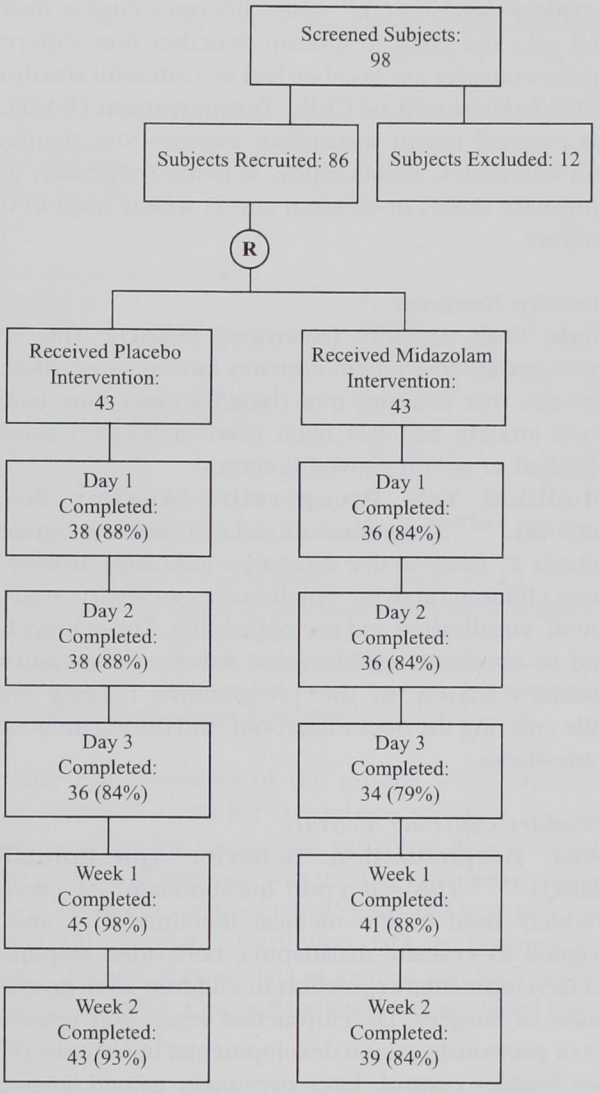

Fig. 1. Study profile.

Treatment Regimens

Patients were assigned randomly to receive either (1) 0.5 mg/kg midazolam (Roche Laboratories, Inc., Nutley, NJ) mixed in 15 mg/kg acetaminophen (Tylenol; McNeil-PPC, Inc., Fort Washington, PA) administered orally (intervention group) or 15 mg/kg Tylenol administered orally (control group). The patients, parents, anesthesiologists, assessors, and the research nurses who performed any of the postoperative outcome measures were blind to group assignment. For each patient, treatment was given 20–30 min before separation to the operating room. If the child was noncompliant and refused to take the premedication, midazolam or placebo, he/she was immediately excluded from the trial. Parental presence during induction of anesthesia was not allowed during this study. Parental presence was used, however, as rescue therapy as detailed in the protocol.

Baseline and Outcome Measures

Detailed reliability and validity data regarding the following behavioral assessment tools were reported previously by our study group.[7,8]

Coping and Temperament Measures

Monitor Blunter Style Scale (MBSS).[9] This standardized instrument assesses coping style in adults through four scenarios of stressful situations. The instrument was developed specifically for patients undergoing medical procedures and identifies information seeking, information avoiding, and distraction coping styles.

Coping Cards (CC).[10] This children's coping instrument asks the child to indicate whether nine different coping strategies are good or bad in a stressful situation.

EASI Instrument of Child Temperament (EASI).[11] This parental report instrument assesses four temperament categories, emotionality, activity, sociability, and impulsivity (EASI) in children and is widely used in the literature.

Anxiety Measures

State Trait Anxiety Inventory (STAI).‖ This self-report anxiety instrument contains two separate 20-item subscales that measure trait (baseline) and state (situational) anxiety and has been used in >1,000 studies published in peer-reviewed literature.

Modified Yale Preoperative Anxiety Scale (mYPAS).[12,13] This observational instrument of anxiety contains 27 items in five categories indicating anxiety in young children (activity, emotional expressivity, state of arousal, vocalization and use of parents). The mYPAS has good to excellent reliability and validity for measuring children's anxiety in the preoperative holding area, while entering the operating room, and during induction of anesthesia.

Primary Outcome Measure

Post Hospitalization Behavior Questionnaire (PHBQ).[14,15] This self-report questionnaire for parents is widely used in the medical literature[1,15,16] and is designed to evaluate maladaptive behavioral responses and developmental regression in children after hospitalization or surgery. Developmental regression refers to loss of previously gained developmental milestones (*e.g.,* loses bladder control, loses previously gained language abilities or talks "baby talk"). The PHBQ consists of 27 items frequently cited in the literature as common behavioral responses of children after surgery or hospitalization. Six categories of anxiety are incorporated in this instrument, including general anxiety, separation anxiety, sleep anxiety, eating disturbances, aggression against authority, and apathy/withdrawal. For each item, parents rated the extent to which each behavior changed in frequency compared with before surgery. Response options for each of the 27 behaviors were as follows: much less than before surgery (−2), less than before surgery (−1), not changed (0), more than before surgery (+1), and much more than before surgery (+2). This instrument shows good agreement with psychiatric interviews with parents of preschool children (r = 0.47) and was used in several investigations to document behavioral changes as a function of preoperative interventions.[14,17,18]

Study Protocol

Recruitment Phase. All patients were screened for recent stressful life events. This was done with Sandler and Block's modified version of Coddington's Life Event Scale for Children.[19] Parents were asked to indicate if their child experienced any stressful life events in the month before surgery (*e.g.,* divorce of parent, family moved to new house, loss of job by parent). All children who had a recent stressful life event were not recruited to the study (fig. 1). Next, baseline anxiety of the parent (STAI) and temperament of the child (EASI) were evaluated using validated instruments.

Day of Surgery, Holding Area. Anxiety of the child and parent was evaluated before administration of the intervention (mYPAS, STAI). Twenty to thirty minutes before separation to the operating room, patients received their randomized intervention.

Separation to the Operating Room. Children were evaluated on separation to the operating room (mYPAS). If a child exhibited extreme anxiety (as determined by the attending anesthesiologist who was blind to group assignment), parental presence was offered as rescue therapy.

Induction and Maintenance of Anesthesia. Anesthesia was induced in all subjects using an O_2/N_2O/halothane technique. Behavior of the child during induction was evaluated by an independent blind assessor using the mYPAS. Once the child was anesthetized, an intravenous cannula was inserted, and 0.1 mg/kg vecuronium was administrated intravenously to facilitate the intubation. Anesthesia was maintained with O_2/N_2O and isoflurane. Fentanyl (1–3 μ/kg) was administered intravenously based on the decision of the individual attending anesthesiologist. At the conclusion of all herniorrhaphies, the surgeons infiltrated the wound locally with 2–3 ml of 0.25% bupivacaine. Regional anesthesia was not performed on any of the patients in the study, and drugs such as ketamine or droperidol were not used.

Postanesthesia Care Unit. Incidence of adverse effects, time to discharge, analgesic requirements, and the occurrence of postoperative excitement[20] were recorded. Pain was evaluated by the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)[21] every 15 min and was managed by intravenously administered fentanyl

‖ Spielberger CD: Manual for the State-Trait Anxiety Inventory (STAI: Form Y). Consulting Psychologists Press, Palo Alto CA, 1983.

(1–2 μg/kg). Nausea and vomiting were managed with ondansetron hydrochloride (0.1 mg/kg, up to 4 mg). The use of sedatives was not allowed. Fitness for discharge from the Postanesthesia Care Unit was assessed by Steward's recovery scale.[22] All parents were present in the Postanesthesia Care Unit during their children's recovery period.

Postoperative Period. After surgery, patients were monitored over 2 weeks, and each child's behavior was evaluated by the parents at several time points: PODs 1, 2, 3, 7, and 14. Parents were contacted at the respective time points over the telephone by a trained research nurse who was using a written script and who was blind to group assignment. Parents were asked about any behavioral changes in their child (PHBQ) and about their child's pain (visual analogue scale [VAS]) during the respective postoperative period.[23,24] It is important to emphasize that parents were specifically instructed to indicate only new behavioral changes that occurred since the surgery.

Statistical Analysis

The primary end point of this study was the postoperative behavior of the child as assessed by the PHBQ. The sample size was based on the ability to detect a 30% difference between the incidence of postoperative negative behavioral changes in the midazolam group and the placebo group 2 days after surgery. Given a projected rate of 70% in the placebo group[25] and based on a two-sided α level of 0.05 and a power of 0.80, 41 patients were needed for each group. Because the type of surgery, age of the child, and previous surgical experience are important determinants of postoperative behavioral changes in children,[1] patients were matched with a yoked design based on their age, type of surgery, and surgical history. For example, the first 5-yr-old child undergoing herniorrhaphy who had not had surgery in the past was randomized (using a randomization table generated from a random numbers table) to one of the two groups. The second 5-yr-old child undergoing herniorrhaphy with no previous surgical experience was automatically allocated to the other group. This ensured equal distribution of ages, surgical experience, and type of surgery in the two groups.

The primary outcome was analyzed using a multivariable logistic regression model in which the dependent variable was the presence or absence of postoperative negative behavioral changes and the independent variables were the group assignment (placebo/midazolam) and the time point after surgery (POD 1, 2, 3, 7, or 14).

Table 1. Characteristics of Study Subjects and Their Parents

	Premedication Group (n = 43)	Placebo Group (n = 43)
Child's age (yr)	4.8 ± 1.8	5.1 ± 1.7
Child's gender (F/M) (%)	28/72	39/61
Previous surgery (%)		
Yes	25	25
No	75	75
Child's temperament (EASI)		
Emotionality	10 ± 4	11 ± 4
Activity	16 ± 4	16 ± 4
Sociability	18 ± 3	17 ± 3
Impulsivity	12 ± 3	13 ± 3
Parent's temperament (STAI-T)	37 ± 8	37 ± 7
Parent's coping style (MBSS)		
Blunter score	4 ± 2	4 ± 2
Monitor score	9 ± 3	9 ± 4
Child's coping style (CC)		
Information seeking	6 ± 1	6 ± 0.5
Avoiding	2 ± 1	1 ± 0.5

Data are mean ± SD. Ranges of instruments are reported in Appendix 1. There were no statistically significant differences.

EASI = Emotionality, Activity, Sociability and Impulsivity Instrument of Child Temperament; STAI-T = State Trait Anxiety Inventory, Trait anxiety subscore; MBSS = Monitor Blunter Style Scale; CC = Coping Cards.

Baseline characteristics of the groups were examined using Student's *t* test for continuous variables and chi-square analysis for categorical variables. Repeated-measures analysis of variance was used to compare variables such as preoperative anxiety (mYPAS) and postoperative pain (VAS). Normally distributed data are presented as mean ± SD and skewed data as median and interquartile range (25%–75%). Comparisons were considered significant if $P < 0.05$.

Results

There were no significant differences between the two groups regarding baseline demographics, surgical procedures, or anxiety in the preoperative holding area (table 1). Rescue therapy in the form of parental presence was necessary for three patients in the placebo group and one in the intervention group. Data from these patients were analyzed based on intention to treat.

Primary Outcome

A multivariable logistic regression model in which the dependent variable was the presence or absence of postoperative negative behavioral changes and the independent variables were group assignment (*i.e.*, midazolam/placebo) and the time point after surgery (*e.g.*, POD 1)

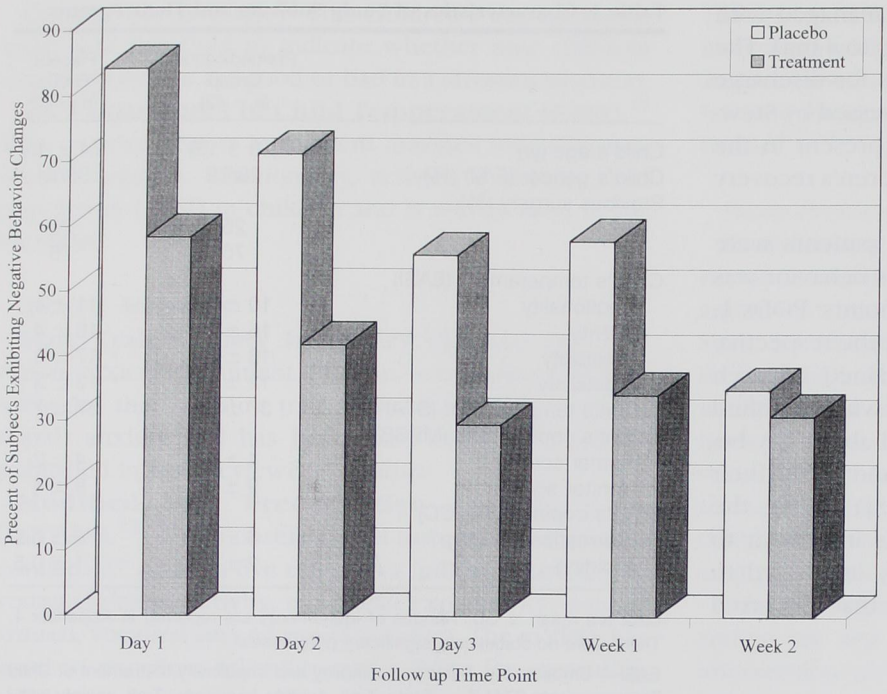

Fig. 2. Percent of negative changes found in the two groups across the follow up period. POD = postoperative day.

was constructed. Group assignment (R = 0.18, P = 0.0001) and time after surgery (R = −0.20, P = 0.0001) were identified as independent predictors for postoperative behavior. That is, the frequency of negative postoperative behavioral changes decreased with time after surgery and was dependent on whether the children were in the midazolam or placebo group. As can be seen from figure 2, on PODs 1–7, fewer children in the midazolam group presented with negative behavioral changes compared with the placebo group. At week 2 postoperatively, although an overall decrease in the incidence of negative behavioral changes was observed, there were no differences between the placebo and intervention groups. The specific PHBQ categories most affected by the intervention were eating disturbances and separation anxiety ($P < 0.05$, fig. 3).

It is noteworthy that, based on parental report, postoperative pain did not differ between the placebo and intervention groups on any of the postoperative days ($F[1,69] = 0.04$, $P = 0.85$).

Other Covariables

Anxiety level along four time points—holding area (T_1), separation to operating room (T_2), entrance to the operating room (T_3), and introduction of the anesthesia mask (T_4)—was assessed by the mYPAS. Observed anxiety differed significantly between the two groups ($F[1,77] = 3.95$, $P = 0.041$). In addition, there was a significant Time × Group interaction ($P = 0.0001$). *Post hoc* analysis demonstrated that the midazolam group was significantly less anxious compared with the control group at separation to the operating room, entrance to the operating room, and introduction of the anesthesia mask ($P < 0.05$). In the Postanesthesia Care Unit, there were no significant differences between the placebo and midazolam groups regarding pain scores, Postanesthesia Care Unit excitement scores, or incidence of nausea or vomiting.

Discussion

In this study, significantly fewer children who were premedicated before surgery presented with negative behavioral changes on PODs 1–7. Postoperative behaviors most affected included apathy and withdrawal, separation anxiety, and eating disturbances. At week 2 postoperatively, however, there were no significant differences between the placebo and intervention groups. We conclude, therefore, that in addition to its significant beneficial preoperative effects, sedative premedication improves postoperative behavioral outcomes in young children undergoing general anesthesia and outpatient surgery.

The perioperative period is frequently an extremely traumatic time for the child and the parents. Anxiety is

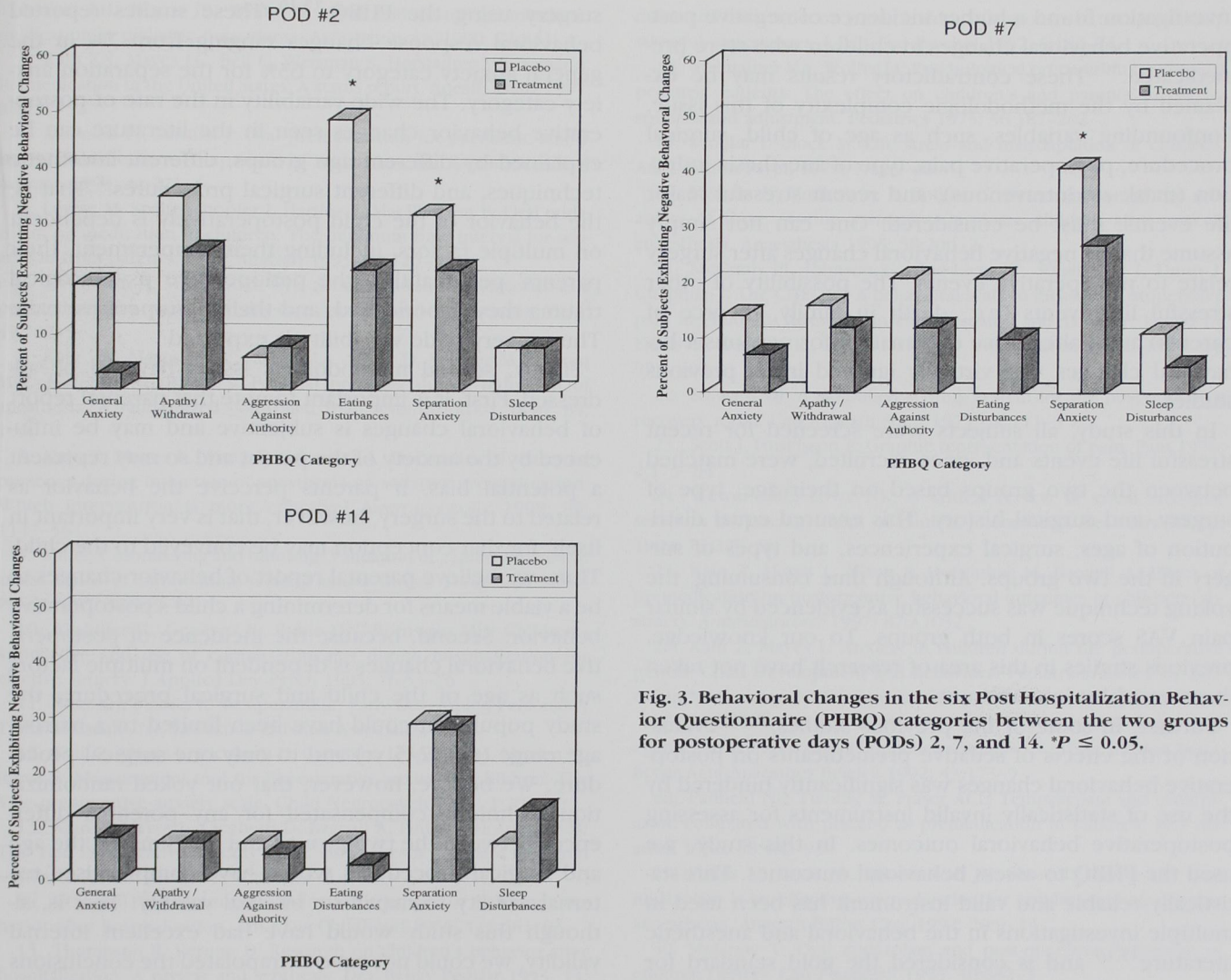

Fig. 3. Behavioral changes in the six Post Hospitalization Behavior Questionnaire (PHBQ) categories between the two groups for postoperative days (PODs) 2, 7, and 14. *$P \leq 0.05$.

attributed to separation from parents, loss of control, and uncertainty about the anesthesia, surgery, and the outcome of the surgical procedure.[26] Thus, it is not surprising that a significant number of children develop negative (maladaptive) behavioral changes such as separation anxiety, eating disturbances, and nightmares in the days, weeks, and months after surgery. In a previous investigation, we found that 54% of all children undergoing outpatient general anesthesia and surgery exhibit maladaptive behavioral responses 2 weeks postoperatively.[1] Increased anxiety of the child in the preoperative holding area predicted these later behavioral problems.[1] Multiple studies have reported that preoperative administration of sedative premedication can allay anxiety and facilitate separation of children from their parents as they enter the operating room.[2,4-6] Based on these observations, we hypothesized *a priori* that decreased preoperative anxiety may be associated with a decreased incidence of postoperative negative behavioral changes. We have demonstrated that this hypothesis is valid for the conditions used in this study. We further suggest that midazolam-related amnesia is the mediator for these postoperative behavioral outcomes. That is, the less the child remembers about the perioperative events, the less psychological trauma she or he experiences. Further studies are needed to prove this hypothesis.

Previous investigators who examined the association between preoperative sedative medication and postoperative behavioral changes report contradictory findings. Although two investigations report some beneficial effects of premedication on postoperative behavior,[27,28] others report no effect.[29] Further, a recent preliminary

investigation found a higher incidence of negative postoperative behavioral changes in children who were premedicated.[30] These contradictory results may be explained by the methodologic complexity of this issue. Confounding variables, such as age of child, surgical procedure, postoperative pain, type of anesthesia induction (mask *vs.* intravenous), and recent stressful major life events, must be considered. One can not simply assume that all negative behavioral changes after surgery relate to perioperative events. The possibility of other stressful life events (*e.g.,* death in family, divorce of parents) as an alternative explanation for new-onset behavioral changes was virtually ignored in all previous studies.

In this study, all subjects were screened for recent stressful life events and, once recruited, were matched between the two groups based on their age, type of surgery, and surgical history. This ensured equal distribution of ages, surgical experiences, and types of surgery in the two groups. Although time consuming, the yoking technique was successful as evidenced by similar pain VAS scores in both groups. To our knowledge, previous studies in this area of research have not taken these variables into account.

Further, in some of the previous studies,[29,30] evaluation of the effects of sedative premedicants on postoperative behavioral changes was significantly hindered by the use of statistically invalid instruments for assessing postoperative behavioral outcomes. In this study, we used the PHBQ to assess behavioral outcomes. This statistically reliable and valid instrument has been used in multiple investigations in the behavioral and anesthetic literature[15,16] and is considered the gold standard for assessing behavioral changes after surgery. In addition, there were no differences between the two groups regarding postoperative pain as reported by parents. Thus, the postoperative changes found in this study are not likely related to different levels of postoperative pain.

In the current study, we found that ≈30% of children undergoing general anesthesia and outpatient surgery have maladaptive behavioral patterns 2 weeks after surgery. This incidence is lower than previously reported (54%) by our study group.[1] This is not surprising given the wide variability in the incidence of behavior changes reported in the literature. Earlier studies involving children undergoing hospitalization and surgery reported that the rate of postoperative behavioral changes ranges from 28–88% of children.[28,31,32] In a recent meta-analysis series, Vernon and Thompson identified 29 studies examining children's behavior after hospitalization and surgery using the PHBQ.[15,16] These studies reported behavioral response changes ranging from 7% in the general anxiety category to 65% for the separation anxiety category. The wide variability in the rate of postoperative behavior changes seen in the literature can be explained by different age groups, different anesthetic techniques, and different surgical procedures.[1] That is, the behavior of the child postoperatively is dependent on multiple factors, including their temperament, their parents' personalities, the perioperative psychological trauma they experienced, and their postoperative pain. Thus, a very wide variability is expected.

Finally, several methodologic issues have to be addressed. First, it is important to note that parental report of behavioral changes is subjective and may be influenced by the anxiety of the parent and so may represent a potential bias. If parents perceive the behavior as related to the surgery, however, that is very important in itself, for that conception may be conveyed to the child. Thus, we believe parental report of behavior changes to be a viable means for determining a child's postoperative behavior. Second, because the incidence of postoperative behavioral changes is dependent on multiple factors such as age of the child and surgical procedure, the study population could have been limited to a narrow age range (*e.g.,* 2–5 yr) and to only one surgical procedure. We believe, however, that our yoked randomization technique compensated for any potential differences between the two groups and that limiting the age and surgical procedures would have compromised external validity to maximize internal validity. That is, although this study would have had excellent internal validity, we could not have extrapolated the conclusions from this study to the general population of children undergoing surgery.

We conclude that children who are premedicated before surgery with midazolam 0.5 mg/kg have a lower incidence of negative behavioral changes in the postoperative period. Thus, in addition to its significant beneficial preoperative effects, sedative premedication has beneficial postoperative effects.

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