Preoperative Melatonin and Its Effects on Induction and Emergence in Children Undergoing Anesthesia and Surgery

Zeev N. Kain, M.D., M.B.A.,* Jill E. MacLaren, Ph.D.,† Leslie Herrmann, B.S.,† Linda Mayes, M.D.,‡ Abraham Rosenbaum, M.D.,|| Justin Hata, M.D.,|| Jerold Lerman, M.D., F.R.C.P.C., F.A.N.Z.C.A.##

Background: Studies conducted in adults undergoing surgery reported a beneficial effect of oral melatonin administered before surgery. There is a paucity of such data in children undergoing anesthesia and surgery.

Methods: Children undergoing surgery were randomly assigned to receive preoperatively oral midazolam 0.5 mg/kg or oral melatonin 0.05 mg/kg, 0.2 mg/kg, or 0.4 mg/kg. The primary outcome of the study was preoperative anxiety (Yale Preoperative Anxiety Scale). The secondary outcomes were the children’s compliance with induction (Induction Compliance Checklist), emergence behavior (Keegan scale), and parental anxiety (State-Trait Anxiety Inventory).

Results: Repeated measures ANOVA showed that children who received melatonin at any of the three doses were more anxious compared with children who received midazolam (P < 0.001). Parental anxiety did not differ on the basis of the experimental condition (P = ns). The melatonin groups showed a dose-response effect on emergence behavior. Children who received melatonin developed less emergence delirium compared with those who received midazolam (P < 0.05), and the effect was dose related; the incidence after 0.05 mg/kg melatonin was 25.0%, incidence after 0.2 mg/kg melatonin was 8.3%, and incidence after 0.4 mg/kg melatonin was 5.4%.

Conclusions: Midazolam is more effective than melatonin in reducing children’s anxiety at induction of anesthesia. Melatonin showed a direct dose-dependent effect on emergence delirium.

UP to 65% of children experience intense anxiety throughout the perioperative period, especially in the preoperative holding area and during induction of anesthesia.1 Intensity of perioperative anxiety is a predictor of both emergence delirium in the postanesthesia care unit and new-onset maladaptive behavioral changes (e.g., nightmares, enuresis, separation anxiety).2–4 To reduce preoperative anxiety, midazolam is widely used for premedication in children. Midazolam, which was first introduced as an oral premedication for children in the 1980s, rapidly achieved widespread acceptance as the preferred premedication before induction of anesthesia. Currently, it is the preferred premedication more than 90% of the time.5,6 Midazolam acquired widespread acceptance because of its rapid absorption after oral ingestion; it can also be administered via multiple routes and confers a reduced incidence of nausea compared with other benzodiazepines.7 However, midazolam has several drawbacks, including paradoxical reactions, interactions with opioids, variable bioavailability and elimination half-life, and delayed discharge from the postanesthesia care unit after brief procedures.7 Moreover, the effects of midazolam have been shown to vary with the age and temperament of the child.8 In light of these drawbacks, an alternative to midazolam might have widespread appeal.

Consideration of these findings has generated a great deal of interest in the potential uses of melatonin in the perioperative setting. This nocturnal neurohormone is secreted by the pineal gland, retina, and gastrointestinal tract. It has several diverse functions, including antioxidative, oncostatic, antiinflammatory, and anticonvulsant activities, as well as regulation of circadian rhythms and the reproductive axis.9,10 Melatonin has numerous uses: treatment of sleep disorders and jet lag,9,10 reduction of oxidative stress in neonates in the perioperative period,11 protection of the skin from ultraviolet damage, and treatment of psychosis in the intensive care unit.12 Most importantly, its hypnotic effects13 may be exploited for its use as a preoperative sedative.

Several studies reported that melatonin is as effective as midazolam in reducing preoperative anxiety in adults.14 Although evidence does not support such a role in the elderly.15 Two recent trials involving children reported that melatonin was as effective in reducing preoperative anxiety as midazolam.16,17 Moreover, melatonin was associated with a more rapid recovery, a reduced incidence of emergence delirium, and reduced incidence of sleep disturbances 2 weeks after surgery when compared with midazolam. However, both trials suffered from methodological deficiencies such as small sample sizes (with resultant low power) and failure to control for the time of day (important, given variability in endogenous melatonin levels throughout the day).

Accordingly, the purpose of this randomized controlled trial was to investigate the purported effects of...
melatonin on reducing preoperative anxiety and the incidence of emergence delirium in children using a rigorous study design.

Methods and Materials

The institutional human investigation committee (Yale University and Yale-New Haven Children’s Hospital, New Haven, Connecticut) approved the study protocol, and appropriate consent and assent were obtained from all parents and their children. The institutional human investigation committee also made the determination that an Investigational New Drug approval or a letter of exemption from the Federal Drug Administration is not needed because melatonin is a nonmedicinal compound that is widely used. A total of 148 children were included in this randomized controlled trial. Children were 2–8 yr old, American Society of Anesthesiologists physical status I or II, and scheduled for general anesthesia and outpatient elective surgery. All children with a history of chronic illness, prematurity, or developmental delay were excluded from the study.

Pilot Study

The purpose of the pilot study was to establish the doses of melatonin to be used in the study. In the pilot study, the level of sedation was evaluated in 21 children (age, 3–7 yr) who received one of three doses of oral melatonin: 0.3 mg, 1 mg, or 7.5 mg (Sigma Chemical, St. Louis, MO). These doses were selected on the basis of published reports that did not normalize the dose according to the body weight. The level of sedation was assessed by observing the parents and their children, as well as by measuring anxiety using the modified Yale Preoperative Anxiety Scale (mYPAS) 45 min after the melatonin was administered. The psychometric properties of the mYPAS are described in the Baseline and Outcome Measures section.

Interventions

When the pilot study was completed, eligible children were assigned to one of four groups, with doses based on a computer-generated random-numbers table. Children in the three melatonin groups received doses of 0.05, 0.2, or 0.4 mg/kg (maximum 20 mg for all doses). These doses were determined by dividing the total doses used in the pilot study by the respective weight of the children. The minimum dose of 0.05 mg/kg, and the maximum dose of 20 mg were based on published literature. Melatonin was purchased from Sigma Chemical, which provided batch-by-batch certificates of analysis authenticating the purity of each batch. This ensured standardization of the intervention; commercial preparations of melatonin vary widely in their actual melatonin concentrations. Children in the midazolam group (Hoffman Laroche, Nutley, NJ) received 0.5 mg/kg oral midazolam syrup. The melatonin solution was prepared in our investigational pharmacy by using a vehicle similar to that for commercial oral midazolam such that the solutions were indistinguishable. The research assistants, health care providers, and observers involved in this study were blind to the study drug and dose. To control for diurnal variation in melatonin blood concentrations, only children whose surgery was scheduled between 9 AM and 1 PM were recruited. All premedications were administered approximately 45 min before induction of anesthesia.

Baseline and Outcome Measures

Emotionality, Activity, Sociability, and Impulsivity Scale. This standardized tool, which assesses temperament in children, includes 20 items in four behavioral categories: Emotionality, Activity, Sociability, and Impulsivity. A parent was presented with individual patterns of behaviors and responses to daily events and asked to rate the child on a five-point scale. The score ranges from 5 to 25 for each category, with larger scores indicating greater baseline emotionality, activity, sociability, or impulsivity. The instrument has good validity when compared with other measures of temperament for preschool-age children. Test-retest reliability of the Emotionality, Activity, Sociability, and Impulsivity scale was excellent when mothers rated their preschool children on adjacent months.

Yale Preoperative Anxiety Scale. This observational measure of preoperative anxiety was developed and validated in a previous investigation. The mYPAS consists of 27 items in five categories of behavior indicating anxiety in young children (activity, emotional expressivity, state of arousal and vocalization). Using Kappa statistics, all mYPAS categories have good to excellent interobserver and intraobserver reliability (0.73–0.91); when validated against other global behavioral measures of anxiety, the mYPAS had good validity (r = 0.64). The mYPAS score ranges from 22.5 to 100, with greater scores indicating greater anxiety. Since its development, this scale has been used in multiple investigations.

State-Trait Anxiety Inventory. This widely used self-report scale is an instrument used to assess anxiety in the parent. To date, over 1,000 studies involving research using the State-Trait Anxiety Inventory (STAI) have been published in peer-reviewed literature. The questionnaire contains two separate 20-item, self-report rating scales for measuring trait and state anxiety. Parents respond on a four-point scale for each item, with the total scores for situational and baseline questions separately ranging from 20 to 80. The score increases directly with the level of anxiety. Test-retest correlations for the STAI are excellent, ranging from 0.73 to 0.86. The validity of the instrument was examined in two studies in which the STAI was given under high- and low-stress conditions to
large samples of students. The r value ranged from 0.83 to 0.94, suggesting very good validity.

**Induction Compliance Checklist.** This observational scale was developed by our laboratory in a previous investigation. The Induction Compliance Checklist (ICC) includes a checklist containing 11 items indicating compliance during induction of anesthesia. The ICC score is the sum of the items checked. A perfect induction, during which the child does not exhibit negative behaviors, fear, or anxiety is scored as 0. Intraclass r values for this scale ranged from 0.995 to 0.998. The interclass r value between the two observers was excellent at 0.978.

**Emergence Behavior**

Emergence behavior was assessed continually by trained assessors when the child awakened in the recovery room. Emergence behavior was rated on a 3-point scale developed and validated by Keegan et al., with 1 indicating no signs of emergence delirium and 3 indicating moderate to severe signs of emergence delirium, including crying, thrashing, and need for restraint. This protocol was initiated before publication of the Pediatric Anesthesia Emergence Delirium Scale, and thus was not available to use in this trial.

**Study Protocol**

**Recruitment Phase and Holding.** After recruitment, written consent, demographic data, and baseline measurements were recorded. These included temperament and child (mYPAS) and parental trait anxiety (STAI). About 45 min before induction of anesthesia, children received their designated intervention.

**Separation.** Children were evaluated upon separation from parents (mYPAS). Parents were not present at induction of anesthesia. Parents completed a measure of anxiety (STAI) after their child separated.

**Induction of Anesthesia.** Upon arrival in the operating room, a pulse oximeter probe was placed on child’s finger. Seventy percent nitrous oxide in a balance of oxygen was delivered through a scented facemask at a fresh gas flow of 10 l/min. After 2 min, sevoflurane was introduced in a concentration of 0.5% and increased every three breaths to a maximum of 6%. The child was manually restrained if the child became noncompliant during induction, and the induction continued. A blinded observer evaluated the behavior of the child during induction using the mYPAS and ICC at two times: (1) upon entry into the operating room and (2) upon application of the facemask.

**Postanesthesia Care Unit.** The incidence of emergence delirium was assessed during the first 15 min after the child awoke. The score reported is the maximum value measured during that period. Children were discharged home one to 2 h after the conclusion of their surgery.

**Study Design**

The null hypothesis of this study was that there was no difference in anxiety among the four melatonin doses and midazolam. Sample size was based on previous investigations involving children’s anxiety and melatonin. The effect size for a clinically relevant difference among the treatment groups was a 15-point difference in mYPAS scores between the melatonin and midazolam groups (based on an assumption of a midazolam mYPAS score of 42 with a SD of 18). A sample size of 35 subjects in each group (yielding a total number of 140) provided 90% power to detect an effect size difference in anxiety of 0.4 among the four groups, with an alpha of 0.05. Group differences in normally distributed data were analyzed using one-way analysis of variance. Changes in anxiety over time and their relationships to group assignment and dose were analyzed using two-way repeated measures analysis of variance. Follow-up analyses included one-way ANOVAs at significant timepoints with post hoc independent samples t test with Bonferroni correction.

### Table 1. Baseline Characteristics of Parents and Children

<table>
<thead>
<tr>
<th></th>
<th>Melatonin 0.05 mg/kg, n = 36</th>
<th>Melatonin 0.2 mg/kg, n = 36</th>
<th>Melatonin 0.4 mg/kg, n = 37</th>
<th>Midazolam, n = 39</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>5.4 ± 2.3</td>
<td>4.7 ± 2.5</td>
<td>5.1 ± 2.2</td>
<td>5.2 ± 2.4</td>
<td>ns</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>44.4</td>
<td>42.8</td>
<td>51.4</td>
<td>40.0</td>
<td>ns</td>
</tr>
<tr>
<td>Ethnicity, % white</td>
<td>77.1</td>
<td>77.8</td>
<td>87.1</td>
<td>80.0</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Temperament</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotionaly</td>
<td>10.4 ± 3.4</td>
<td>10.1 ± 4.1</td>
<td>11.4 ± 3.4</td>
<td>11.6 ± 4.3</td>
<td>ns</td>
</tr>
<tr>
<td>Activity</td>
<td>16.9 ± 3.9</td>
<td>15.7 ± 4.2</td>
<td>15.2 ± 4.0</td>
<td>16.0 ± 3.3</td>
<td>ns</td>
</tr>
<tr>
<td>Sociability</td>
<td>18.8 ± 2.4</td>
<td>18.8 ± 2.3</td>
<td>18.1 ± 2.8</td>
<td>18.3 ± 12.3</td>
<td>ns</td>
</tr>
<tr>
<td>Impulsivity</td>
<td>12.6 ± 3.9</td>
<td>12.3 ± 3.6</td>
<td>11.6 ± 3.5</td>
<td>13.4 ± 3.0</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Parents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother age, years</td>
<td>35.6 ± 5.1</td>
<td>36.6 ± 4.9</td>
<td>36.0 ± 6.7</td>
<td>37.7 ± 6.6</td>
<td>ns</td>
</tr>
<tr>
<td>Father age, years</td>
<td>37.6 ± 6.1</td>
<td>38.6 ± 5.7</td>
<td>38.8 ± 7.5</td>
<td>38.6 ± 7.6</td>
<td>ns</td>
</tr>
<tr>
<td>Trait Anxiety, STAI</td>
<td>36.7 ± 5.0</td>
<td>35.2 ± 5.4</td>
<td>36.1 ± 4.4</td>
<td>37.3 ± 54.8</td>
<td>ns</td>
</tr>
<tr>
<td>Preadmissions visit, % attended</td>
<td>48.4</td>
<td>55.9</td>
<td>45.7</td>
<td>32.0</td>
<td>ns</td>
</tr>
</tbody>
</table>

Except where noted, data are mean ± standard deviation, Midazolam dose 0.5 mg/kg.

STAI = Spielberger State-Trait Anxiety Inventory.

Anesthesiology, V 111, No 1, Jul 2009
corrected $P$ values. Data are reported as mean ± SD. All analyses were performed using SPSS 14.0 (SPSS, Chicago, IL).

**Results**

**Pilot Data**

Pilot data indicated that the level of anxiety (mYPAS scores) after 7.5 mg of melatonin was similar to that after 0.3 mg and 1.0 mg (55 ± 23 vs. 61 ± 27 vs. 65 ± 26, respectively). Nearly all parents reported that their child became sleepy or sedated after melatonin. Two children reported a transient headache (lasting less than 15 min in each case), but such headaches are not uncommon because they are most likely due to mild dehydration rather than melatonin.

**Primary Outcome: Child Anxiety**

A total of 148 children were recruited for the main study. Baseline characteristics were similar among the four groups (table 1). Two-way repeated measures ANOVA results indicated a significant group-by-time interaction on children’s anxiety (fig. 1). Follow-up one-way ANOVAs on the mYPAS scores at each time indicated that the groups did not differ in their anxiety in the holding area or at separation from parents. However, the mYPAS scores differed significantly at induction of anesthesia, with children who received midazolam displaying significantly less anxiety than those who received any dose of melatonin. There were no significant differences among the melatonin doses at induction of anesthesia.

**Secondary Outcomes: Parent Anxiety, Induction Compliance, and Emergence Behavior**

Regarding parental anxiety, there was a significant main effect of time, with significant increases in parent anxiety between the holding area and separation in all groups, but no significant main effect of dose or interaction (table 2).

The proportion of high compliance rating (ICC score of 0) was significantly greater in the midazolam group when compared with the melatonin groups (73.3% vs. 49.5%, $P < 0.001$; fig. 2). However, pairwise comparisons of ICC = 0 scores of melatonin doses with midazolam were nonsignificant, likely due to the small sample size (type II error). The proportion of children with evidence of emergence delirium (Keegan score of 3) differed among the treatment groups ($P < 0.05$) (table 2). The incidence of emergence delirium was greatest in the midazolam group (25.6%). Melatonin treatment groups demonstrated a dose-response effect on emergence and the incidence of emergence delirium was greatest after 0.05 mg/kg melatonin (25.0%), followed by 0.2 mg/kg (8.3%) and 0.4 mg/kg melatonin (5.4%).

**Table 2. Group Effects on Secondary Outcomes**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parent state anxiety, STAI (mean ± SD)</th>
<th>Parent state anxiety, STAI (mean ± SD)</th>
<th>Parent state anxiety, STAI (mean ± SD)</th>
<th>Parent state anxiety, STAI (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin 0.05 mg/kg, n = 36</td>
<td>43.0 ± 9.5</td>
<td>42.4 ± 9.9</td>
<td>39.2 ± 9.4</td>
<td>41.2 ± 11.3</td>
</tr>
<tr>
<td>Melatonin 0.2 mg/kg, n = 36</td>
<td>46.1 ± 10.3</td>
<td>46.1 ± 13.2</td>
<td>42.8 ± 11.3</td>
<td>44.1 ± 12.0</td>
</tr>
<tr>
<td>Melatonin 0.4 mg/kg, n = 37</td>
<td>45.1 ± 10.3</td>
<td>46.1 ± 13.2</td>
<td>42.8 ± 11.3</td>
<td>44.1 ± 12.0</td>
</tr>
<tr>
<td>Midazolam, n = 39</td>
<td>46.1 ± 13.2</td>
<td>42.8 ± 11.3</td>
<td>44.1 ± 12.0</td>
<td>ns</td>
</tr>
</tbody>
</table>

Midazolam dosing was 0.5 mg/kg.

STAI = Spielberger State-Trait Anxiety Inventory.
Discussion

The primary purpose of this study was to determine whether the anxiolysis associated with 0.05, 0.2, or 0.4 mg/kg (maximum dose of 20 mg) oral melatonin differed from that of midazolam in children scheduled for surgery. In the doses studied, we found that oral midazolam is a more effective anxiolytic than oral melatonin. Regarding the secondary hypothesis of this study, we demonstrated that the parents’ anxiety increased during the preoperative period after all premedications. The compliance of children at induction of anesthesia after premedication with oral midazolam was significantly greater than with all of the melatonin doses. Finally, we noted that oral melatonin reduces the incidence of postoperative emergence delirium to a greater extent than oral midazolam.

Two recent studies compared preoperative midazolam with melatonin in children.16,17 As in the current study, they noted that melatonin was more effective than midazolam in attenuating emergence delirium. However, they also reported that melatonin was as effective as an anxiolytic as oral midazolam. This latter finding deserves a thoughtful discussion. As indicated in the introduction, methodological concerns may have limited the validity of these previous studies.16,17 The failure to control for the time of day in which the study was performed and issues related to lack of valid assessment tools could explain the anxiolytic effects of melatonin in the previous studies. The current study was a double-blind randomized controlled trial that included a certified dose of melatonin and validated outcome tools.

Outcome measures are particularly relevant, given that one of the previous trials reported the use of mYPAS but did not provide any details regarding the reliability of the tool in the hands of those investigators.16 The use of mYPAS necessitates significant ongoing training of the research assistants to assure high interreliability and intrareliability. In our laboratory, these reliabilities have to exceed 0.9 before a research assistant can evaluate anxiety using the mYPAS tool. Furthermore, the other study used an outcome measure that has not been validated.17 Consistent with our result, Sury and Fairweather found that oral melatonin was not effective as a sedative for children undergoing magnetic resonance imaging.35 These investigators randomized children to receive either 3 or 6 mg of melatonin or placebo followed by chloral hydrate and found no additive benefit of melatonin on time taken to reach deep sedation.

Currently there is no consensus on the appropriate dose of melatonin for sedation in children. Melatonin dosing for children is reported to be between 0.3 mg and 20 mg.18,19 Doses as great as 20 mg have been administered to children without adverse side effects apart from sedation.20 Nonetheless, what remains unclear is the most appropriate dose to induce sedation. On the basis of these results, we cannot exclude the possibility that doses of melatonin in excess of 20 mg may be necessary to reduce anxiety. For reasons of patient care and safety, we were hesitant to exceed the doses indicated in previously published literature.

Several methodological limitations related to this study should be noted. First, we cannot exclude the possibility that larger doses of melatonin would have reduced preoperative anxiety to a greater extent than that observed here. Nonetheless, previous studies used similar or smaller doses compared with those used in this study and reported salutary effects of melatonin on anxiety. Second, to maintain similar endogenous levels of melatonin, we did not recruit children who were scheduled for surgery before 9:00 AM. Theoretically, the doses used in this study could be effective for children who received melatonin very early in the morning. Despite these limitations, the conclusions of this study are strengthened by our effort to control all confounding variables. An additional concern is the issue of bioavailability of the melatonin that was used in our study. That is, purchasing a chemical from Sigma Chemical Company and compounding it locally raises questions about bioavailability and reproducibility of the resultant product. Indeed, the reader should note that the bioavailability of melatonin in this study was not known and could have been quite variable among individuals. Also, the formulations our pharmacy prepared were not tested; therefore, we do not know how the variability of the resultant product that was used in the study.

Although we compared melatonin to the standard of care for preoperative anxiolysis in children (i.e., midazolam), one might legitimately question whether melatonin is superior to placebo. To address this question, we compared the mYPAS scores at induction of anesthesia in children who were historical controls (52 ± 26)34 with those who received melatonin in this study (fig. 1). We found no differences between the two groups. We can conclude that melatonin is not only inferior to midazolam, but it also does not differ from a placebo control group. Finally, we administered the premedications 45 min before separation from the parents based on two previous pediatric studies that demonstrated salutary effects of melatonin.1–3

In conclusion, we found that oral melatonin in doses up to 0.4 mg/kg (maximum 20 mg) administered to children before surgery is not as effective as oral midazolam in reducing preoperative anxiety. We did find, however, that melatonin is effective in reducing the incidence of emergence delirium in children undergoing general anesthesia. Therefore, we recommend oral midazolam for preoperative anxiolysis in children scheduled for surgery.

References


