Obstetrical and Pediatric Anesthesia

High levels of impulsivity may contraindicate midazolam premedication in children

[De hauts niveaux d'impulsivité peuvent être une contre-indication à une pré-médication de midazolam chez des enfants]

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Purpose: To investigate the effects of midazolam on emotional reactivity during induction of anesthesia in a pediatric day surgery setting. A secondary purpose was to determine if these effects were influenced by child temperament factors.

Methods: Forty children (age four to six years) scheduled for myringotomy were randomly assigned, in a double blind fashion, to receive either oral midazolam 0.5 mg·kg⁻¹ mixed with acetaminophen suspension or acetaminophen alone. The Emotionality, Activity, Sociability, and Impulsivity (EASI) scale was used as a measure of child temperament. The modified Yale Preoperative Anxiety Scale (m-YPAS), an observer-rated measure of state anxiety, was employed to assess anxiety pre- and post-drug, and also at induction of anesthesia.

Results: Children who received midazolam reacted significantly less to induction of anesthesia than did children in the placebo control group, $F(1, 38) = 7.46, P = 0.01$. A significant positive association was observed between baseline levels of anxiety and observer-rated anxiety at anesthetic induction, but only in the placebo group, $r = 0.58, P < 0.01$. A significant positive association was observed between levels of impulsivity at baseline and observer-rated anxiety at anesthetic induction, but only in the midazolam group, $r = 0.42, P < 0.05$.

Conclusions: Midazolam dampened adverse reactivity during anesthetic induction, particularly among children with high baseline levels of anxiety. Baseline level of impulsivity was positively associated with adverse reactions to anesthesia induction in the drug group, but not in the placebo group, suggesting that high levels of trait impulsivity may contraindicate the use of midazolam as a preoperative medication.

Objectif : Rechercher les effets du midazolam sur la réactivité émotionnelle pendant l'induction de l'anesthésie dans le contexte de la chirurgie pédiatrique d'un jour. Aussi, déterminer si ces effets sont soumis à des facteurs de tempérament de l'enfant.

Méthode : Quarante enfants, de quatre à six ans, devant subir une myringotomie, ont été répartis au hasard et à double insu. Ils ont reçu 0,5 mg·kg⁻¹ de midazolam oral mêlé à une suspension d'acétaminophène ou seulement de l'acétaminophène. L'échelle EASI (Émotivité, Activité, Sociabilité et Impulsivité) a permis de mesurer le tempérament des enfants. L'échelle modifiée d'anxiété préopératoire de Yale, une mesure de l'état d'anxiété cotée par un observateur, a servi à évaluer l'anxiété avant et après la médication et à l'induction anesthésique.

Résultats : Les réactions ont été significativement moindres à l'induction de l'anesthésie avec le midazolam qu'avec le placebo, $F(1, 38) = 7,46, P = 0,01$. Une association positive significative a été notée entre les niveaux d'anxiété de base et l'anxiété cotée par l'observateur à l'induction dans le groupe témoin seulement, $r = 0,58, P < 0,01$. Une association positive significative a été notée entre les niveaux d'impulsivité de base et l'anxiété cotée par l'observateur à l'induction chez les enfants sous médication seulement, $r = 0,42, P < 0,05$.

Conclusion : Le midazolam a diminué la réactivité indésirable pendant l'induction anesthésique, surtout chez les enfants qui avaient des niveaux de base élevés d'anxiété. La présence d'une impulsivité de base a été positivement associée aux réactions indésirables à l'induction seulement chez les enfants qui ont reçu le médicament, ce qui indique que de hauts niveaux d'impulsivité peuvent être contre-indiqués à l'usage de midazolam comme médication préopératoire.

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PREOPERATIVE anxiety is a common problem in children, which can make the procedure more difficult for the patient and medical personnel.¹ One of the most stressful events in the perioperative period is induction of anesthesia. Worry about such pre-surgery events can increase the child's anxiety level and also prolong the preparation for, and recovery from surgery.¹ Excessive anxiety during the induction of anesthesia may be associated with decreased oxygen saturation.² In children, excessive anxiety concerning the operation, including fear of anesthesia induction, can lead to postoperative maladaptive behavioural responses, and as such most children undergoing minor surgery and short hospitalization (72%–78%) demonstrate some behavioural changes during the first two weeks at home.^{3,4} In children, preoperative anxiety has been related to negative physiological and psychological reactions following surgery, including nightmares, separation anxiety, eating problems, and increased fear of doctors.^{5,6}

Childhood temperament, the hereditary characteristics of an individual's nature,⁷ has been found a useful predictor of how a child will react to a variety of potentially stressful situations.⁸ For example, temperament, age, and the quality of previous medical encounters have been shown to predict children's preoperative anxiety levels.⁵ Temperament characteristics might also be good predictors of how children react to anesthetic induction and to preoperative benzodiazepine administration. To evaluate this notion, it is necessary to assess children's temperament, as well as their preoperative anxiety levels at baseline and at mask induction.

Oral administration of midazolam has been described as an effective preanesthetic medication in healthy children.⁹ Relative to placebo, midazolam improves children's reactions to parental separation and their cooperation with mask induction, while not leading to prolonged recovery.¹⁰ Kain *et al.* found that oral midazolam was more effective than parental presence in managing a child's anxiety behaviour at anesthesia induction.¹¹

Our primary hypothesis was that children treated preoperatively with midazolam would have lower observer-rated anxiety in response to anesthetic mask placement, as rated on the modified Yale Preoperative Anxiety Scale (m-YPAS), an observer-rated measure of state anxiety, than children who were treated with placebo. We also predicted that children with higher pre-drug baseline levels of observer-rated anxiety would benefit more from midazolam's anxiolytic effects than would children with lower pre-drug baseline levels of

observer-rated anxiety.¹² Since state anxiety and trait emotionality scores tend to be highly correlated,¹³ we also hypothesized that children with higher trait emotionality, as measured by the Emotionality, Activity, Sociability, and Impulsivity (EASI), would benefit more from midazolam's anxiolytic effects than would children with lower trait emotionality, and that lower levels of both Activity and Impulsivity would be related to higher m-YPAS scores at mask induction in the placebo group.¹⁴

Methods

Participants

Participants were children scheduled for myringotomy with tympanostomy tube insertion (not in conjunction with any other surgery) at a tertiary care pediatric hospital. Aside from their need for myringotomy, participants were otherwise healthy. Children were excluded if they had a history of neurological or cognitive impairment or disease, previous adverse reaction to a benzodiazepine, or were taking medication other than antibiotics. Both written informed consent from the child's parent and verbal assent from the child were obtained prior to participation. The study was approved by the IWK Health Centre Research Ethics Board.

Experimental design

Participants were randomly assigned to one of two groups (drug or placebo) with 20 participants per group prior to day of surgery. The midazolam group received a mixture of acetaminophen suspension 15 mg·kg⁻¹ (Children's Tylenol™, grape-flavoured, McNeil Consumer Products, Guelph, ON, Canada) and midazolam 0.5 mg·kg⁻¹ (Versed™ [Roche] for *iv* administration, 5 mg·mL⁻¹); the placebo group received only acetaminophen. Acetaminophen is given routinely to children at the IWK Health Centre before myringotomy. Drug administration was double-blind in that the child, his/her parents, the anesthesiologist, and the researcher who was testing the child were not aware of the child's drug group assignment. One investigator (G.A.F.) and the day surgery nurse were aware of the grouping, but did not participate in assessment. In case of complications, nurses or doctors could discover the child's drug group status by opening the randomization envelope in the child's chart. A second observer simultaneously scored the m-YPAS for a random ten of the 40 study participants for reliability.

Tasks and procedure

When an eligible child was scheduled for myringotomy, an information package about the study was

sent to the child's parents. One week later, they were contacted by telephone and informed of the study purposes and procedures. If parents provided verbal consent for their child to participate in the study they were asked to complete the EASI questionnaire one week before surgery.

Approximately 90 min before surgery, a researcher obtained parent's written informed consent and the child's verbal assent for participation in the study. Children's baseline anxiety levels were rated by the researcher using the m-YPAS,¹ without the "use of parent" rating. The parent was separated from the child when the child was admitted to the operating room, and therefore was not available to the child in all situations, so the score on this variable was dropped. The m-YPAS was used at three different times: before drug administration, after drug administration, and when the anesthetic mask was applied to the face.

Approximately 60 min before surgery, the participants received either the midazolam/acetaminophen mixture or the acetaminophen alone. Approximately 20 min post-drug administration anxiety levels were rated once again using the m-YPAS and the child was taken to the operating room. All of the children were separated from their parents when leaving the day surgery area, which is usual IWK Health Centre procedure. For all study participants, anesthesia was induced using only halothane/nitrous oxide/oxygen by inhalation. The researcher again rated the child's anxiety during induction using the m-YPAS.

Statistics

Four separate sets of analyses were completed: 1) series of independent sample t tests and Chi-square analyses were completed to examine between-group comparisons on age, gender distribution, time between drug administration and surgery onset, any previous surgery, previous myringotomy, prior experience with midazolam, current use of antibiotics, or scores on the relevant subscales of the temperament measure; 2) reliability analyses were completed to examine the internal consistency for EASI subscales; 3) between-and within-group comparisons using a 2 (drug group: midazolam *vs* placebo) $\times$ 3 (testing time: pre-drug baseline *vs* post-drug baseline *vs* mask induction) repeated measures ANOVA was performed on m-YPAS total scores; and 4) bivariate correlations were computed (separately within each drug group) between m-YPAS anxiety scores at baseline and at anesthetic induction, and scores on the two relevant EASI subscales (i.e., emotionality and impulsivity) and m-YPAS scores at anesthetic induction.

TABLE Comparisons of demographic and temperamental variables between drug groups

		Drug group			
		Placebo (<i>n</i> = 20)		Midazolam (<i>n</i> = 20)	
		Mean	SD	Mean	SD
Age (in months)		65.3	11.9	65.8	8.8
Time from medication to surgery (in minutes)		60.3	15.8	60.8	16.7
EASI-emotionality		13.2	3.0	11.2	3.3
EASI-activity		16.7	3.6	17.3	2.8
EASI-sociability		18.4	2.0	17.6	3.2
EASI-impulsivity		14.7	4.0	14.4	2.9
Gender	<i>n</i> males	11		13	
	<i>n</i> females	9		7	
Other Medications	<i>n</i> yes	5		3	
	<i>n</i> no	15		17	
Previous Surgery	<i>n</i> yes	10		15	
	<i>n</i> no	10		5	
Previous Myringotomy	<i>n</i> yes	10		15	
	<i>n</i> no	10		5	
Previous Midazolam	<i>n</i> yes	0		1	
	<i>n</i> no	20		19	

SD = standard deviation; EASI = Emotionality, Activity, Sociability, and Impulsivity scale.

Sample size

The one previous study in this area that has made a link between EASI scores and children's preoperative anxiety was conducted by Kain and colleagues.⁵ They found a significant negative correlation between EASI activity scores and preoperative anxiety scores in unmedicated children undergoing surgery ($r = -0.37$). The minimum *n* for this size correlation coefficient to be significant is $n = 20$.¹⁵ Thus, in the current study we chose a sample size of 20 per cell of our design.

Results

Forty children (24 boys, 16 girls), four to six years of age (mean age = five years, 5 months; standard deviation = ten months) participated. One child with Down's syndrome and another with severe mental retardation were excluded. There were no significant differences in demographic variables between the midazolam and placebo groups (Table).

Overall effect of midazolam on anxiety

The results of the 2×3 ANOVA indicated that observer-rated anxiety as measured by m-YPAS scores differed significantly between the two groups, $F(1, 38) = 6.01$, $P < 0.05$. The m-YPAS scores also differed significantly as a function of testing time, $F(2, 76) = 5.32$, $P < 0.05$. These main effects were qualified by a significant drug group $\times$ testing time interaction, $F(2, 76) = 4.77$, $P < 0.05$ (Figure). To further clarify the nature of this interaction, simple effects of drug group were examined at each testing time. There was no significant simple effect of drug group at either the pre-drug, $F(1, 38) = 1.48$, n.s., or the post-drug, $F(1, 38) = 0.82$, n.s., baselines. However, consistent with our prediction a significant effect of drug group was observed at mask induction, $F(1, 38) = 7.46$, $P = 0.01$, with midazolam-treated children being rated as less anxious than placebo-treated children (Figure). We also examined the simple effects of test time in each drug group. There was a simple effect of test time in the placebo group, $F(2, 38) = 5.73$, $P < 0.01$, with scores at mask induction being higher than scores at either the pre-drug, $t(19) = 2.61$, $P < 0.05$, or post-drug, $t(19) = 2.74$, $P = 0.01$, baselines, and scores failing to differ from the pre-drug to the post-drug baselines, $t(19) = 0.39$, n.s. In contrast, there was no significant simple effect of test time in the midazolam group, $F(2, 38) = 0.23$, n.s., indicating that observer-rated anxiety scores did not change significantly across the three testing times in the children treated with midazolam. The Emotionality and Impulsivity subscales of the EASI showed marginally acceptable internal consistencies of 0.55 and 0.61, respectively. However, the activity subscale showed an unacceptably low internal consistency of 0.47. Thus, only the Emotionality (EASI-E; intensity of emotional reactions) and Impulsivity (EASI-I; quickness of response) subscales were used in this analysis. Internal consistencies across the four categories of anxious behaviours on the m-YPAS were acceptable to excellent ranging from 0.67 (at pre-drug baseline) to 0.90 (at mask placement). Inter-rater reliability coefficients for the m-YPAS were excellent, ranging from 0.96 (at pre-drug baseline and mask placement) to 1.00 (at post-drug baseline).

Influence of temperament characteristics

In the placebo group, correlational analyses revealed that m-YPAS observer-rated anxiety rating at pre-drug baseline was related to the rating at the induction of anesthesia ($r = 0.58$, $P < 0.01$). This relationship between pre-drug baseline and mask-induction anxiety ratings did not exist in the midazolam group ($r = 0.18$, n.s.). By virtue of their higher baseline levels

FIGURE Mean m-YPAS scores as a function of drug groups (midazolam and placebo) and testing time (pre-drug, post-drug, and mask induction).

of anxiety, highly anxious children appear to benefit more than less anxious children from the anxiolytic effects of midazolam at mask placement.

Contrary to hypothesis that children with higher trait emotionality would benefit more from midazolam's anxiolytic effects than children with low emotionality, the EASI-E was not correlated with the m-YPAS observer-rated state anxiety scores at anesthetic mask placement in either the placebo ($r = 0.22$, n.s.) or the midazolam ($r = 0.10$, n.s.) groups.

Correlation of the EASI-I score with the overall m-YPAS score at the induction of anesthesia in the placebo participants did not prove statistically significant ($r = -0.25$, n.s.). However, a significant positive relationship existed between EASI-I scores and m-YPAS scores in the midazolam-treated children ($r = 0.42$, $P < 0.05$). Examination of particular components of the anxiety response at mask induction revealed that the positive relationship of EASI-I scores with "anxiety" at mask induction in midazolam-treated children was only evident for the 'activity' ($r = 0.54$, $P < 0.01$) and 'vocalization' ($r = 0.41$, $P < 0.05$) ratings on the m-YPAS. Correlations with 'activity' and 'vocalization' in the placebo group were not significant ($r = -0.33$, $P < 0.08$ and $r = -0.26$, n.s., respectively).

Discussion

As hypothesized, children treated preoperatively with midazolam were observer-rated as having lower anxiety in response to anesthetic mask placement than children who were treated with placebo. Given the nature of the anxiety ratings on the m-YPAS, which include not only arousal and displays of emotion, but

also vocalizations and activity, this calming effect in the midazolam group at mask placement could be due to a combination of the sedative and the anxiolytic effects of the drug.¹⁶ This finding is in agreement with previous studies which also found that midazolam has an anxiolytic effect if given to children as a pre-medication.^{9,10} The significant decrease in observer-rated anxiety levels for midazolam, compared to placebo, was not evident at post-drug baseline. This pattern suggests that midazolam's anxiolytic effects are only observable at times of normally heightened anxiety, such as during mask induction of anesthetic.

This midazolam-induced decrease in anxiety levels was even more pronounced for children with higher baseline levels of anxiety. It was shown that children with high baseline levels of observer-rated anxiety benefited more from the anxiolytic effects of midazolam when compared to children with lower baseline observer-rated anxiety levels. The drug did not have as much anxiolytic benefit at mask placement in the low baseline state anxious children mainly because low baseline state anxious children were not particularly anxious during mask induction, even when administered placebo. These results are consistent with previous findings that responses to benzodiazepines are highly dependent on participants' trait anxiety levels.¹²

One of the particular aims of this study was to find out what type of children would benefit most from the use of midazolam in terms of parent-rated child temperament variables. It was hypothesized that trait emotionality, as measured on the EASI, might be a good predictor of how children would react in a stressful, preoperative situation when administered a placebo, and that trait emotionality might predict which children would benefit most from midazolam administration. Although no support was obtained for either of these hypotheses when total m-YPAS scores at mask placement served as the dependent measure, results more consistent with hypotheses were obtained when particular aspects of the anxiety response at mask placement were observed independently. Specifically, EASI-E scores were related to the "state of apparent arousal" aspect of the anxiety response at mask induction among placebo-treated, but not midazolam-treated children. Thus, it is possible that children whose parents identify them as being more emotional are more susceptible to the effects of midazolam on observable arousal during stress. This speculation requires replication in an independent sample, particularly given the marginal significance of the finding. Future research might consider using a more specific measure of trait anxiety [such as the Children's State-Trait Anxiety Inventory—Trait subscale]¹³ rather than

the more global measure of trait emotionality (which encompasses trait anxiety, alienation, and aggression)¹⁷ as a predictor of state anxiety during mask induction and susceptibility to midazolam anxiolysis.

We also found a positive relation between trait impulsivity and state anxiety at mask placement, but only in the midazolam group. This relationship also stands to reason, because if a child has a more reactive temper he/she would probably be more likely to act out in a situation that upsets them. There has to be something more than just a quick temper involved, however, since this relationship was only seen in the midazolam group.

It was also found that a high baseline level of impulsivity on the EASI-I was specifically related to high levels of vocalizations and activity on the m-YPAS at mask placement, but only in the midazolam group. Children with high levels of impulsivity in the midazolam group acted out more at mask induction when compared to children with low levels of impulsivity in the midazolam group. In fact, levels of "anxiety" in the midazolam-treated children with high levels of impulsivity were similar to the levels of "anxiety" seen in highly impulsive children treated with placebo, showing that highly impulsive children failed to benefit from the anxiolytic/sedative effects of midazolam. This suggests that midazolam may have led to a disinhibiting effect on the more "acting out" aspects of the anxiety response in highly impulsive children that eliminated any anxiolytic/sedative benefit of the drug.

There is limited literature on the phenomenon of benzodiazepine-induced disinhibition, and what literature does exist is usually in the form of case studies.¹⁸ These cases usually describe people who have had adverse emotional and behavioural reactions to benzodiazepines. For example, one case study describes Ms. A., who attributed her uncharacteristic outbursts of anger to her use of the benzodiazepine alprazolam.¹⁹ However, most of the benzodiazepines reported in these studies were prescribed for longer periods of time, whereas midazolam is almost exclusively used acutely in the hospital setting.²⁰ One previous study does support a relationship between high baseline impulsivity and benzodiazepine induced hostility.²¹ Participants treated with the benzodiazepine chlordiazepoxide, but not those treated with placebo, showed significantly more hostility during a frustration-evoking challenge when compared to their baseline scores, as measured by the Buss-Durkee Hostility Inventory.²² The present findings suggest that highly impulsive children, as parent-rated on the EASI, do not benefit from preoperative administration of midazolam.

Previous research has shown that low levels of activity on the EASI were related to increased anxiety in children undergoing surgery, at the time of separation from the parent.³ Although we had made similar predictions for children in the placebo group undergoing mask induction in the present study, we were unable to test this hypothesis due to unacceptably low internal consistency values for this scale. In fact, internal consistency values were only marginal even for the emotionality and impulsivity scales on the EASI. We therefore recommend that future studies use alternative measures of child temperament with superior psychometric properties.

It appears that for premedication, midazolam may be unnecessary if the child has low state anxiety, and contraindicated if the trait impulsivity score is high. Midazolam is most clearly of benefit only if the child has a high state anxiety level at baseline (first assessment in Day Surgery). Replication of this study using other measures of temperament and anxiety is in progress. Confirmation of these results could substantially impact perioperative care, and quantitative assessment of temperament and anxiety preoperatively could become essential in pediatric anesthesia practice.

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