The effect of orally administered midazolam on children of three age groups during restorative dental care

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Abstract

Purpose: *The effects of orally administered midazolam on three groups of preschool children who differed by age only and required dental treatment were studied. Sixty-one children age 24-58 months participated in this institutionally-approved study.*

Methods: Selection criteria for the children included: demonstrated disruptive behaviors; healthy (ASA I); required at least one restorative appointment involving a posterior quadrant; no known drug allergies; were between two and five years of age; and had no prior experience with sedative trials. The children were divided into three groups according to age: Group I (24-35 months), Group II (36-47 months), and Group III (47-59 months). Each child received midazolam 0.5 mg/kg orally 15 minutes before treatment. Behavior was evaluated using the Ohio State Behavior Rating Scale (OS). Physiological parameters including heart rate, oxygen saturation, systolic and diastolic blood pressure were also evaluated. Data were analyzed using chi-square, cross tabulation, descriptive statistics, ANOVA, t-tests, and regression and correlation analysis.

Results: Results indicated no statistically significant difference in behavior across all age groups as evaluated by the OS.

Conclusion: No significant differences of clinical significance were noted.(Pediatr Dent 21:236-242, 1999)

Pediatric dentists use a number of pharmacologic agents to aid in the behavior management of young children. Chloral hydrate and meperidine are some of the most frequently used agents, and although safe if used properly, the effectiveness of these drugs in promoting desired behavior is highly variable. These agents require a significant time of onset as well as lengthy postoperative recovery time, and offer very little if any anterograde amnestic effect.[1-4] With these disadvantages, it should not be a surprise that practitioners have sought other agents to achieve a more ideal sedative effect. One agent that recently has gained some popularity within the dental profession is midazolam (Versed®, Roche Laboratories, Nutley, NJ), a relatively new benzodiazepine.

The studies involving children that have used midazolam administered orally prior to dental treatment are few in number.[6-9] The studies are often complicated by the introduction of other agents including nitrous oxide and confound the interpretation of the results. Furthermore, the range in age varies from study to study from a minimum of 1.5-6 years[6] to a maximum of 3-16 years.[6] Cognitive development is associated with age[10] and pediatric dentistry literature often recognizes and categorizes young children into "pre-cooperative" and "cooperative" with the pivotal age being three years (children younger than three years are considered "pre-cooperative").[11] No studies in the literature have looked at the relationship of the child's age and the effectiveness of the drug including midazolam during sedation for dental treatment.

The primary purpose of this study was to assess the effectiveness of oral midazolam when used alone on sedated children's behavior for dental treatment as a function of three age groups, namely two-, three-, and four-year olds. The clinical hypothesis for this study was that there would be a difference in behavior as a function of these age groups; children less than three years of age were expected to exhibit less cooperative behaviors, even with midazolam. As stated, this hypothesis was based on the general body of knowledge about cognitive development and cooperative ability of children in this age range. It was also based, in part, on studies that suggested an age-related response.[12-14]

Materials and Methods

Sample and Design

In this institutionally approved study, 61 subjects between the ages of 24-58 months were recruited. The study design involved a convenience sample of the first 61 children who met the inclusion criteria during their initial screening appointment at the Columbus Children's Hospital Dental Clinic. Inclusion criteria included all patients who were healthy (ASA I); required one restorative treatment appointment involving a posterior quadrant; demonstrated disruptive behaviors (i.e. definitely negative scores on the Frankl scale[15]); had no known drug allergies; were between 24-60 months of age; and had no prior experience with sedative trials. Children were excluded from the study if they had any conditions that were considered contraindicated to the use of midazolam; had a cold or influenza within the past two weeks; had head trauma or seizures at least

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Table 1. Pre-operative Sub-scales and Their Corresponding Response Categories Used to Rate the Children Prior to Sedation

Clinical sub-scale	Response categories
Patient interaction	1. Talks freely without prompting 2. Talks most of the time after initial prompting 3. Talks only when prompted 4. Refuses to talk 5. Unable to talk (age or foreign language)
Behavioral interaction	1. Smiles when addressed and is easily approached 2. Shows no expression initially, but is approachable 3. Frowns most of the time; intermittently makes eye contact or averts head 4. Frowns initially then cries; no eye contact or averts head 5. Cries when initially seen and actively seeks parent to hold/protect patient
Level of cooperation	1. Follows all requests without hesitation 2. Follows most requests, but with hesitation following prompting 3. Rarely follows any request; appears angry but doesn't cry 4. Never follows any request; cries and is combative

two weeks prior to receiving midazolam; or were not in compliance with the clinic protocol (e.g., violated pre-operative instructions). The sedation protocol was consistent with the American Academy of Pediatric Dentistry (AAPD) Guidelines for Conscious and Deep Sedation.[16]

The parents of children who met the inclusion and exclusion criteria were approached by the principal investigator regarding the child's participation in the study. Subjects were assigned to one of three groups based on their age: Group I (24-35 months), Group II (36-47 months), or Group III (48-59 months) resulting in a distribution of 19, 23, and 19 patients per group, respectively.

The dependent variables measured were:

- the pre-operative assessment of the child's behavior during the initial phases of the visit including physical examination and airway assessment,
- the behavior of the children using the Ohio State University Behavior Rating Scale[17] (OS),
- physiologic variables including heart rate, oxygen saturation and systolic and diastolic blood pressure.

Procedure

On the day of sedation, each patient's medical history was reviewed with the parent and a physical examination was performed including assessment of the airway for tonsil size per AAPD guidelines using the methodology described by Fishbaugh et al. [18] The child's weight was obtained by a dental assistant and informed consent was obtained from the parent. Pre-operative - vital signs were performed by the dental assistant using a blood pressure cuff (Dinamap) and an oxygen (O_2) probe (Nellcor Pulse Oximeter).

Each patient received midazolam (0.5 mg/kg) by the oral route, initially administered in a cup. If the patient was non-compliant, the drug was squirted slowly into the buccal vestibule with a needleless 3-cc irrigating syringe. The drug was flavored with Nuflavor®(Lancer Orthodontics, San Marco, CA.), an alginate flavoring agent. Following drug administration, the child remained in a quiet darkened room with the parent for 15 minutes.

At the end of the 15-minute period, the child was separated from the parent and carried by the assistant to the treatment room where monitors were affixed. The blood pressure cuff was placed on the right arm and the O_2 probe was placed on the left second toe. A nasal hood was placed over the child's nose and O_2 was set at 100% concentration at 5 L/min flow as recommended by Rohlfing et al.[19] Although the child was not initially wrapped in a Papoose Board, disruptive behaviors considered potentially harmful to the child or personnel that could not be modified by talking, coaxing, or encouraging the child resulted in the use of the papoose board for the remainder of treatment. The papoose board was used at any time during the procedure when this type of behavior occurred and was at the discretion of the operator. Physiological parameters were recorded continuously (e.g., oxygen saturation) or continually (e.g., blood pressure) and the values of each parameter recorded by an assistant every five minutes throughout the procedure.

Behavior

The child's behavior during the operative visit was assessed using the following:

- *Pre-operative assessment*: a battery of sub-scales indicating the child's behavior during the initial phases of the visit including the physical examination and airway assessment.
- *Intra-operative videotaping*: the sedation was videotaped and analyzed for continuously occurring, operationally-defined behaviors.
- *Parental assessment of child temperament:* a parental assessment of the child's behaviors in general was done to determine if any behaviors may predict intra-operative behaviors.

Pre-operative Assessment scales

The battery of sub-scales included three different scales identified on our standardized clinical sedation form as: patient interaction, behavioral interaction, and level of cooperation. The patient interaction scale addressed the child's dominant means of responding verbally to the principal investigator during the physical examination. The behavioral interaction scale addressed the child's expressions of emotions during the physical examination. The level of cooperation scale addressed the actions of the child when requested to do certain activities (e.g., open their mouth voluntarily). The categories of each sub-scale can be seen in Table 1. The principal investigator was responsible for rating the child's behaviors with these scales.

Table 2. Temperament Questionnaire Abridged and Modified from the Behavioral Style Questionnaire

1. My child enjoys new environments and change.						
	Never	Rarely	Sometimes	Often	Very Often	Always
2. My child enjoys a visit to the doctor.						
	Never	Rarely	Sometimes	Often	Very Often	Always
3. If an adult who is unknown to my child would visit my house, my child would tend to cling or come to me when the adult comes into the house.						
	Never	Rarely	Sometimes	Often	Very Often	Always
4. When exposed to a new situation, my child tends to be shy and timid.						
	Never	Rarely	Sometimes	Often	Very Often	Always
5. My child tends to play well with other children.						
	Never	Rarely	Sometimes	Often	Very Often	Always
6. My child tends to cry or "pitch a fit" when I take away a bottle or a favorite toy.						
	Never	Rarely	Sometimes	Often	Very Often	Always
7. For today, I predict my child's sedation will be:						
- Completely successful (my child will sleep or cooperate for the dentist).						
- Fairly successful (my child may cry at times, but generally be cooperative with the dentist).						
- Totally unsuccessful (my child will cry most of the time and definitely not cooperate with the dentist).						

Intra-operative videotaping

The entire sedation, from the initial application of sedation monitors to the completion of the restorative procedures, was videotaped and the OS was used to analyze the behavior.[17] The OS was used to rate the child's behavior, which was divided into two phases—pre-treatment phase and treatment phase. The pre-treatment phase involved the rating of continuous behavior from the time monitors were placed to the initiation of the restorative procedure. The procedures accomplished during the pre-treatment phase included topical anesthetic application, local anesthetic injection, and rubber dam placement. The treatment phase involved rating of continuous behavior from the beginning of tooth preparation or extraction to the end of treatment.

The OS involves four mutually exclusive behavioral categories based on head and bodily movements, crying, and oral/physical resistance. The categorical codes were:

- Q—for quiet behavior with no movement
- C—for crying behaviors with no struggling
- M—for movement behaviors with struggling only, no crying
- S—for crying and struggling disruptive behaviors.

The Automated Counting System (ACS)™ (JAGTECH, Rockville, MD) computer software program, was used to quantify the behavioral categories. A trained unbiased rater viewed the videotapes of the sedation visits and recorded the patient's behavior according to the behavioral code. The rater would press the respective keyboard key (i.e., Q, C, M, or S) and the software program would record the frequency, total duration, and mean duration of each categorical code. The data derived from this program were used to calculate the percentage duration of each behavioral category. It was important to use percentages of behaviors for purposes of standardizing each patient visit on a 100% scale.

Parental assessment of temperament

Finally, the parents were given a seven-item questionnaire that was drafted and modified from the Behavioral Style Questionaire,[20,21] a measurement of child temperament (Table 2). Temperament has been shown to be a predictor of behaviors during sedation and initial examination procedures.[17,21] The parents completed the questionnaire following their separation from the child on the day of the sedation.

Data Analysis

The data were analyzed with a Chi-square, cross-tabulation, descriptive statistics, ANOVA, *t*-tests, regression and correlational analyses. The analysis was done with SPSS+ PC software program (SPSS, Chicago, IL).

Results

Physiologic and behavioral data were collected from 61 sedation visits involving 30 males and 31 females, whose age ranged from 24 to 58 months (mean=41±9.38 months). The patients' weight ranged from 10.5 kg to 20 kg (mean=14.4±2.5 kg).

A Chi-square analysis indicated no significant difference in the distribution of patients' sex by age group. The distribution of males/females for each group was 11/8, 8/13, 11/8 for groups I, II, and III, respectively. As expected, an ANOVA revealed a significant difference in the patients' age, weight, and dose of midazolam received as a function of age group ($F=170.9$, $P<0.001$; $F=10.08$, $P<0.001$; and $F=10.08$, $P<0.001$, respectively).

Physiological Parameters

A one-way ANOVA for physiological parameters as a function of age group was done. No statistical difference was found as a function of age group for any physiological parameters.

Behavior

Pre-operative assessment scales. A cross-tabulation involving a Chi-square analysis of patient interaction, level of cooperation, and patient behavior sub-scales by age groups indicated that only the distribution of response categories in the level of

Table 3. Mean Percent Behavior as a Function of Age Group

Behavioral Category	Age Group 1 Mean% (SD)	Age Group 2 Mean% (SD)	Age Group 3 Mean% (SD)	F	*P*
Crying	29.2 (18.0)	26.7 (22.1)	37.6 (27.5)	1.27	0.29
Movement	14.4 (7.50)	12.5 (7.02)	11.0 (10.1)	0.85	0.43
Quiet	43.6 (21.8)	49.1 (26.7)	41.6 (28.3)	0.47	0.63
Struggle	12.7 (16.1)	11.6 (14.9)	9.7 (15.7)	0.19	0.83

cooperation sub-scale was statistically significant (χ^2=13.4, *P*<0.03).

Intra-operative videotaped scale. An analysis of the OS scale indicated that the distribution of behaviors across age groups was quite similar and no significant differences were found when the percentages of the four behaviors were summated for the entire visit. Likewise, no significant difference was noted for the four behaviors in either phase of treatment or for frequency of occurrence of the four behaviors summated across the entire visit or for either phase of treatment. The behavior accounting for the greatest distribution of time for each group was the category of quiet; however this behavior represented less than 50% of the entire sedation visit time. The mean (± SD) for crying, movement, quiet, and struggle behaviors as a function of age group is summarized in Table 3.

Significant differences between pre-treatment phases and treatment phases were found for all videotaped behaviors. A significant increase occurred in both crying and struggling behaviors during treatment compared to pre-treatment procedures. A significant decrease in moving and quiet behaviors was observed during treatment when compared to pre-treatment.

An analysis using *t*-tests indicated a significant difference between genders for percent crying, quiet, and struggling behaviors during the pre-treatment phase and for percent movement, quiet, and struggling behaviors during the treatment phase. Also, there was a significant difference between genders for both quiet and struggling behaviors summated across both phases. In general, the female patient tended to be quieter, exhibit less struggling than the male.

Intra-rater reliability was evaluated using five different videotaped segments. Each segment was rated three times by the same rater. The first reliability rating was conducted after 20 tapes were rated, the second after 40 tapes were rated, and the third after 61 tapes were rated. A Pearson correlation coefficient (r>0.83) for all behavioral categories was determined comparing the first, second, and third rating. The most common behaviors of crying and quiet had correlation coefficients exceeding 0.99 (*P*<0.01) suggesting very high intra-rater reliability. Standard ANOVA was also conducted and revealed no statistically significant difference among behavioral categories.

Parental assessment of temperament. A stepwise regressional analysis indicated that certain questions relating to child temperament were moderately predictive of the child's behavior during the initial work-up of the child and in the pre-treatment phase. Question 2, which inquired about the child's response to a visit to a doctor was predictive of the level of cooperation and behavioral interaction of the child (r=.42, *P*<0.002 and r=.47, *P*<0.001, respectively). Additionally, question 3, relating the child's degree of attachment to the parent when an unknown adult visits their home, when added to question 2 in the stepwise regression, increased the prediction of behaviors in the behavioral interaction sub-scale (r=.54, *P*<0.001). Questions 1 (relating the child's acceptance to change and new environments) and 4 (relating shyness of the child in a new environment) were significant predictors to the patient interaction sub-scale (r =.45, *P*<0.001 for question 1 in the first step and r=.55, *P*<0.001 when question 4 was added to question 1). Question 3 was predictive of the percent crying and quiet in the pre-treatment phase (r=.32, *P*<0.02 and r=.27, *P*<0.04, respectively).

Discussion

The overwhelming and somewhat surprising results of the study showed no significant difference in behavior among age groups for the behaviors rated. A secondary purpose to the study was to evaluate the effect of oral midazolam on the physiological parameters that are typically monitored during light sedative procedures (i.e., heart rate, systolic and diastolic blood pressure, and oxygen saturation) as a function of age groups. There was no significant difference in physiological parameters.

The results indicated that the children in the three age groups differed significantly in age, weight, and dose of midazolam; however, the distribution of male and female was not significantly different among groups. These findings are expected and suggest that these variables and the sex of the sample were evenly distributed among groups. Further, the age, weight, and dose would be expected to differ because of the study's design of assigning patients to the corresponding three age groups.

Behavior

The analysis of the level of cooperation sub-scale that is designed to measure patient responsiveness to directions indicated that there was a significant difference in the distribution of response categories as a function of age groups. The two-year-olds were less likely to follow directions. This finding is not unexpected and is consistent with the clinical hypothesis that younger children are more immature cognitively.

ANOVA of the videotaped behavior using the OS did not show any significant difference among age groups for either the pre-treatment or treatment phase when analyzed separately. However, *t*-test analysis for pre-treatment versus the treatment phase did show a significant difference for all behaviors.

These findings suggest that oral midazolam in the dose used in this study is not effective in overcoming strong emotional outbursts associated with dental treatment of young children whose age range encompasses 24-60 months. The fact that the children in this study may be different cognitively and emotionally from cohorts of their age group may account for the lack of pharmacological effect. Saarnivaara et al.[22] reported a difference between children whose age was greater than five years of age compared to those less than five years old during venipuncture in the operating room. Children older than five years were more cooperative. Rita et al.[23] reported similar results. It is possible that an age-related effect does exist for orally administered midazolam , but the effect is only seen with children older than five years.

Another possibility is that orally administered midazolam may have a disinhibitory effect in young children. The anxiolytic effect of the drug may eliminate or reduce what little coping or cooperative ability preschoolers have learned, and thus cause the marginally cooperative child to act like a precooperative child. The weak inverse association between increasing age and disruptive behavior seen in this sample prior to the administration of the drug seems consistent with this explanation.

One of the most puzzling phenomena associated with the oral use of midazolam is the post-treatment "angry" response or paradoxical agitation that certain children seem to exhibit. This type of behavior was noted by the primary investigator and other dental personnel familiar with midazolam and this angry response has been noted in the medical literature. [24-26] The angry response can be characterized as the child displaying bouts of uncontrollable loud crying and directed verbal screams with or without thrashing when an attempt is made to console the child. Many times the child continues to play with toys, yet is displaying uncontrolled loud crying and screaming. The angry response typically becomes manifested approximately 20-40 minutes after midazolam has been administered and may last up to several hours. This phenomenon needs further study.

Behavior and Gender

The data from this study seemed to suggest that gender may play a role in the level of cooperation of the child during treatment. Regardless of age, females demonstrated more positive behavior during treatment. Girls tended to be more quiet and struggled less than boys and this finding was statistically significant. No statistically significant difference was found for an age related difference by age group and gender. This finding seems to contradict much of what has been reported in the literature with respect to gender and behavior in stressful situations.

Feine et al.[27] reported that young females rated noxious heat stimuli more intensely then males. They suggested that there may be a physiologic difference in nociceptive discrimination in males and females rather than a difference in emotional response. Aho et al.[28] reported gender difference in the frequency and intensity of fears related to the medical setting. Girls were more likely to have fears and they were more intense than those of boys. Needleman et al.[3] reported that sedations of male children had 15.5% greater success ($P<0.01$) than sedations of female children. Tsinidou et al.[29] reported similar results.

A possible explanation for the results of the present study may be related to the gender of the operator. The operator in this study was a male. Previous studies, however, do not support this possibility. [3, 27] They report no difference in gender related behavior with respect to the gender of the operator. It is possible that midazolam has properties that may have gender-related effects in young children, favoring cooperative behavior in females. Future studies may be required to test this hypothesis.

Other Behavioral Effects

Overall percent quiet time as measured by the OS in this study was between 42% and 49% depending on age group. This is considerably less than percent quiet time reported by McCann et al.[30] in a study where the OS was used to evaluate a similar population of patients sedated with chloral hydrate and hydroxyzine with or without nitrous oxide. The group without nitrous oxide supplementation exhibited 70% percent quiet time. Percent crying was also lower in the chloral hydrate group; 20% compared to a range of 26%-38% in the current study.

Similar results were reported in a study by Matusak et al.[31] These findings suggest that in the age range of patients studied, chloral hydrate/hydroxyzine regimen is more likely to promote quiet behavior. On the other hand, Reeves et al.[7] reported no difference between the two regimens when evaluated by a different scale. Future studies comparing midazolam and chloral hydrate (both administered with hydroxyzine) and utilizing the OS in a blinded crossover design could test this hypothesis directly. The effect of nitrous oxide and midazolam should also be evaluated for potential synergistic effects.

The results of the questionnaire relating to child temperament completed by the parent were interesting. In essence, the regression analysis showed a weak to moderate prediction of the temperament questions to the children's behaviors in the initial work-up and pre-treatment phases of the study. The factors of the child's response to change and new environments, being approached by an unknown adult, shyness, and degree of attachment to the parent in the presence of another adult appear to be pivotal in predicting a child's behavior during the early phases of a sedation visit.

This finding is not unlike that of Lochary et al.[17] who also showed that child temperament sub-scales of approachability and adaptability are important predictive variables for children's behaviors when sedated with meperidine. Radis et al.[21] also found approachability and adaptability to be significant predictors of child behaviors during an initial examination visit to the dentist. Consistency among these studies suggest a limited set of child behaviors that the dentist can observe and anticipate a generalized outcome during the provision of treatment. For instance, if the child exhibits strong shyness and attachment behaviors during the collection of vital signs, then the likelihood of more disruptive behaviors would seem to increase during the operative phase of a dental visit.

The rater of the OS was most reliable according to the analysis of the data. When the rater reviewed the same videotapes repeatedly, the correlation between the repeated ratings for each behavior were extremely strong ($r>.9$). Several studies have shown that a trained rater is very consistent in the use of the computerized analysis of children's behaviors when the OS is used. [17,21,30,31]

Physiology and Adverse Effects

No statistical differences were found for heart rate, systolic and diastolic blood pressure, and oxygen saturation across age

groups. No significant adverse reactions occur in any of the sedations that were conducted. No significant (<95%) oxygen desaturations (excluding false readings due to movement) were recorded. All children who were sedated remained awake and no clinically evident respiratory depression was noted. None of the children experienced nausea or vomiting during treatment or in recovery.

The most common side effect included hiccups and loss of balance. As previously discussed, postoperatively paradoxical agitation was seen on a number of occasions, but it was not formally recorded as part of the study protocol. Most often it presented as children having a tantrum; not wanting to leave the toys in the recovery room when they were ready for discharge. On a few occasions, the level of agitation was heightened to the point of loud screaming and attempts at harming the accompanying parent. All the cases were self limiting within 45-60 minutes.

Conclusions

1. No significant difference in behaviors as a result of oral midazolam sedation were noted in comparing children ranging in age from 2 to 4 years.
2. Used orally Midazolam promotes quiet behavior 42%-49% of the time in uncooperative 24-60 month old children.
3. Midazolam may be more effective in promoting adesired behavior in girls than in boys in these age groups.
4. When given orally in a dose of 0.5 mg/kg, Midazolam does not appear to significantly affect the physiology of these young children.

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