Comparison of Oral Midazolam With and Without Hydroxyzine in the Sedation of Pediatric Dental Patients

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Abstract

Purpose: The purpose of this study was to compare the effectiveness of midazolam (MDZ) alone to a combination of MDZ and hydroxyzine (MDZH) when sedating young children for dental treatment.

Methods: This was a prospective, double-blinded, crossover clinical study of young uncooperative children in need of at least 2 restorative visits. Twenty-eight children, ages 21 to 56 months, with a mean age of 36.6 months, participated in this study. The subjects were assigned randomly to receive either 0.5 mg/kg of oral MDZ 20 minutes prior to the beginning of dental treatment or the combination of 0.3 mg/kg oral MDZ with 3.7 mg/kg of hydroxyzine 30 minutes before treatment. The alternative drug regimen was administered at the second appointment. All subjects also received 50% nitrous oxide and were restrained with a papoose board. The child's behavior (quiet or crying, relaxed or moving) was evaluated every 5 minutes by an experienced pediatric dentist who was unaware of the drug given to the child. At the conclusion of treatment, each session was evaluated for overall effectiveness.

Results: Regardless of the type of premedication, more patients exhibited quiet behavior at the beginning of treatment, with an increase in crying and movement toward the end of treatment. Regarding movement, a significant difference was observed during the first 20 minutes between the 2 regimens. MDZ showed more children exhibiting movement. During the first 30 minutes of treatment, more children cried in the MDZ group, while MDZH presented more children asleep or quiet. No significant differences were found in behavior as a function of the order the sedative regimens were given. No significant differences between the 2 regimens regarding overall behavior and success (t=0.655 at 27 degrees of freedom; P=.518) were found.

Conclusions: The combination of hydroxyzine (3.7 mg/kg) with MDZ (0.3 mg/kg) administered 30 minutes before treatment resulted in safe and effective sedation for the dental treatment of young children. This combination's use might be more advantageous when compared to MDZ alone, resulting in less crying and movement during the first 30 and 20 minutes, respectively. (*Pediatr Dent.* 2004;26:492-496)

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Conscious sedation is frequently employed for the management of precooperative or extremely anxious preschool dental patients. Many medications have been used to sedate children in the dental office safely and successfully. Narcotics, antihistamines, hypnotics, and benzodiazepines have all been used separately and in combination in an attempt to find an ideal sedation regimen, which may be used for most clinical situations. Among these are 2 time-tested premedications that have each been successfully used on their own, midazolam (MDZ) and hydroxyzine. Both are remarkably safe and have no serious side effects. The ideal combination will provide: (1) safety; (2) minimum respiratory depression; (3) adequate sedation; (4) minimal patient movement; (5) early onset of drug action; and (6) adequate working time (adequate duration of action).

Table 1. Behavior Criteria (Modified The Ohio State University Behavior Rating Scale)

Crying: patient crying, noticeably annoyed, treatment difficult but possible.
Quiet: patient quiet, not asleep, with only slight, inconsequential movements.
Sleeping: patient asleep, easily aroused, no movement.
Movement: patient extremely defiant, strong movement, treatment extremely difficult.

MDZ is a potent, short-acting benzodiazepine sedative hypnotic, which has been regularly used by anesthesiologists as a premedication for general anesthesia and routinely used in pediatric dentistry for short dental procedures.[1-3] In addition to its sedative properties, MDZ has anticonvulsant,[1] muscle-relaxant, and amnesic effects.[4] It is well absorbed orally, with an absorption half-life of 13 minutes. Because of MDZ's high-lipid solubility, it is readily absorbed by the gastrointestinal tract and central nervous system. MDZ reaches a peak plasma concentration at 1.25 hours and has an elimination half-life of 2.3 hours.[1]

Pediatric dentists have used hydroxyzine safely as a sedative agent for many years for the sedation of young dental patients.[5,6] It is an antihistamine with sedative and antiemetic properties. It has been used routinely, and, when limited to the recommended doses, there is no respiratory depression or known side effects. Adverse reactions are uncommon.

Few pediatric studies have investigated the use of MDZ in combination with other sedative medications.[7] One of the favorable characteristics of MDZ is its rapid onset, making it ideal for use in the dental office. Its relatively short duration of action, however, may rule out its use in dental procedures of more than 20 minutes.[5] Hydroxyzine has a slower onset of action with a longer duration of action. It would seem appropriate to use these 2 drugs together, one complementing the other, resulting in an ideal sedative combination appropriate for use in the dental office. A study comparing intranasal MDZ with oral MDZ utilized a flavored hydroxyzine suspension as an oral vehicle to administer parenteral MDZ, since, at the time, MDZ was marketed only for parenteral use.[2] The study, however, did not investigate its use as a supplementary drug to MDZ.

The purpose of this prospective, double-blinded, crossover clinical study was to compare the sedative effectiveness of MDZ alone with a combination of MDZ and hydroxyzine when sedating young children for dental treatment.

Methods

This study's experimental protocol was approved by the Institutional Human Subjects Ethics Committee of the Hadassah University Hospital in Jerusalem, Israel. Informed consent was obtained from all parents or legal guardians of participating subjects.

Table 2. Rating Scale to Evaluate General Behavior

Rating	Definition
1	Quiet>90% of treatment time, 1 undesirable behavior exhibited.
2	Quiet>50% of treatment time, no violent interrupting movements.
3	Crying>50% of treatment time, interrupting movements toward end of treatment.
4	Crying throughout treatment, interrupting movements from onset of treatment.
5	Crying and extremely defiant behavior throughout session, treatment extremely difficult.

Subjects

Twenty-eight subjects between the ages of 21 and 56 months, with a mean age of 36.6 months, participated in this study. They weighed between 10 and 18 kg, with a mean weight of 13.8 kg. All participants were in good health (ASA I) and required at least 2 restorative treatment sessions. The patients required sedation for treatment because of a "definitely negative" rating, according to the Frankl rating scale.[8]

Procedure

All subjects were without solid food for at least 4 hours prior to medication administration and without clear liquids 2 hours before treatment. The subjects were assigned randomly to receive either 0.5 mg/kg of oral MDZ 20 minutes prior to the beginning of dental treatment or the combination of 0.3 mg/kg oral midazolam with 3.7 mg/kg of hydroxyzine (MDZH) 30 minutes before treatment. The alternative drug regimen was administered at the second appointment. The medication was offered in a plastic cup or syringe to the patient by a member of the research team other than the operator or the independent evaluator to ensure that both were blind to the treatment regimen. If the child refused to drink, the medication was administered via a needleless syringe to the back of the mouth.

At the appropriate time, the child was transferred to the operatory and placed in a papoose board, and a pulse oximeter was attached to the subject's great toe (Nellcor Inc, Hayward, Calif). Fifty percent nitrous oxide/oxygen was administered, and treatment was rendered by 1 of 2 operators. Vital signs were monitored continuously.

Evaluation

Each patient was evaluated continuously by 1 of 2 independent observers for sleep/quiet/crying and body movement, with assessments recorded at 5-minute intervals. The observers were standardized by evaluating 20 assessments of behavior of children undergoing conscious sedation in a similar manner prior to the study. Nineteen of the 20 assessments were identical for an inter-rater

Table 3. Distribution of Ratings for General Behavior*

Rating	Midazolam alone		Midazolam and hydroxyzine	
	No.	%	No.	%
1	14	50	14	50
2	7	25	7	25
3	3	11	6	21
4	4	14	1	4
5	0	0	0	0

*Overall success rate (ratings 1 and 2) for both regimens=75%.

reliability of 95%. A modified version of The Ohio State University behavior rating scale[9] was used (Table 1). In addition, an overall evaluation was made of the child's behavior at the completion of the operative procedures (Table 2) similar to Houpt's scale of overall behavior.[10]

Data analysis

This study was designed so that each patient served as his/her own control, with time of day, operator, and type of procedure being relatively constant between the 2 treatment sessions.

Findings for movement, crying, quiet and sleep, and overall behavior were analyzed for statistically significant differences between the 2 drug regimens using the McNemar test. The means for treatment time and overall behavior of both regimens were analyzed using a paired *t* test.

Results

Crying/quiet/sleep

The percentages of crying behavior as a function of 8 time periods for both drug regimens are presented in Figure 1. Regardless of the type of premedication, more patients exhibited quiet behavior at the beginning of treatment, with an increase in crying towards the end of treatment. A significant difference was observed during the 30-minute time-period between the 2 regimens: MDZ showed more children crying, while MDZH presented more children asleep or quiet. During the first 7 points of measurement (0-30 minutes), the percentage of crying children was always lower in MDZH in comparison to MDZ. This finding was statistically significant ($P<.008$). No significant differences were found in behavior as a function of the order the sedative regimens were given.

Movement

The presence of movement pattern was similar in both MDZ and MDZH, with the incidences of movement increasing with treatment time (Figure 2). The percentage of children exhibiting movement during the first 5 points of measurement (0-20 minutes), however, was always lower in MDZH in comparison with MDZ. This difference was statistically significant ($P=0.031$).

General behavior rating

At the conclusion of treatment, each session was evaluated for overall effectiveness. The results are presented in Table 3. The success of sedation, including ratings of 1 and 2, was 75% for both regimens. Analysis using a paired *t* test showed no significant differences between the 2 regimens regarding overall behavior and success ($P=.518$). Analysis using a paired *t* test showed no significant differences between the 2 regimens regarding length of treatment visit: MDZ=37 minutes; MDZH=39.5 minutes ($P=.275$).

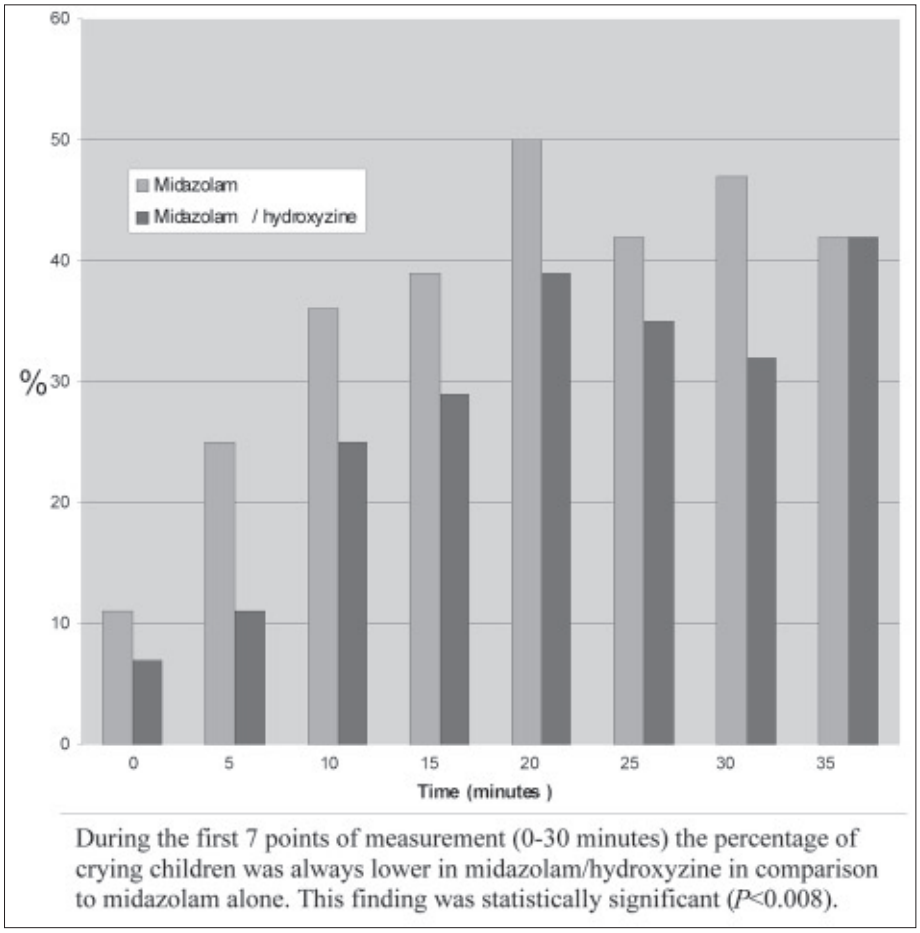

Figure 1. Percentage of children exhibiting crying behavior at 5-minute intervals.

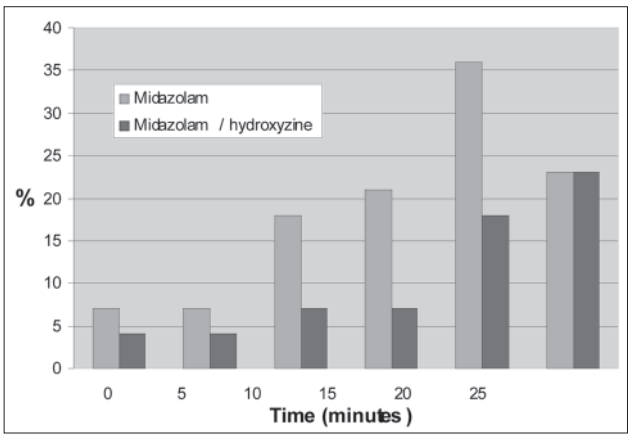

Figure 2. Percentage of children exhibiting movement at 5-minute intervals.

Vital signs and adverse reactions

Pulse and blood oxygen saturation level were continuously monitored with a Nellcor pulse oximeter. In general, vital signs remained stable throughout treatment procedures. No adverse reactions were observed in any of the sedation visits.

Discussion

This study's results demonstrate that the combination of oral MDZ with hydroxyzine supplemented by 50% nitrous oxide/oxygen inhalation is a safe and effective method to sedate young children for dental treatment. The combination of these drugs has advantages over their use as single agents. Hydroxyzine's onset of action is slow compared to MDZ. Yet, MDZ's duration of action is short, limiting its use to short dental procedures. As a combination, the 2 drugs facilitate early treatment time following administration and an adequate working time allowing most dental procedures. Indeed, this study's results showed that children sedated with MDZH were more likely to exhibit quiet and/or sleep behavior than with MDZ alone up to 30 minutes into treatment. This may be attributed to the combined actions of MDZ and hydroxyzine. Further into treatment, however, crying behavior was the same for both groups, due to the shorter duration of action of MDZ, the sedative effect of which dissipates after 20 minutes.

Recently, a study has been published investigating the combination of MDZ with meperidine (MPD).[7] Oral MDZ alone was found to be just as effective as MDZ with MPD at a dose of 0.5 mg/kg and 1 mg/kg, respectively. Higher doses of this combination, however, resulted in fewer disruptive behaviors in a current retrospective study.[11] MPD, a narcotic, potentiates the action of sedatives when taken in combination. Its side effects, which include nausea, vomiting, and respiratory depressions, however, make it less than desirable for sedation in a dental setting. In addition, sedation with opioids may increase the risk of local anesthesia toxicity, particularly with young children.[12]

On the other hand, hydroxyzine may be the more favorable drug when used in combination with MDZ, since its only frequent adverse reaction is drowsiness, which is favorable in sedation. One of the drawbacks of hydroxyzine is the relatively long waiting period between its administration and the start of treatment. This study's results show that addition of MDZ allows a significant reduction in the waiting time without compromising the effectiveness of the sedation. Indeed, 75% of the sedations were rated as being successful and none were aborted.

The choice of hydroxyzine dose was based on a previous study in which a dose of 3.7 mg/kg supplemented by 50% nitrous oxide/oxygen inhalation was found to be more effective than a standard dose of 50 mg, regardless of weight[13] and which had been subsequently used in other studies.[4,5] It is recommended to use MDZ alone for short dental procedures (eg, extractions or preventive resin restorations to be administered 20 minutes before). Longer procedures should use MDZH administered 30 minutes before.

A few of this study's limitations should be noted. Although significant differences were detected between the 2 groups during the first 20 to 30 minutes of treatment, other differences might exist but may not have been detected, due to the small number of subjects. Although movement was found in many subjects, the use of a papoose board only allowed observation of extreme movement. It is precisely these types of movements, however, that are of concern to the operator, and that may determine the success of the sedation. Another point is that the routine use of the papoose board may have contributed to the relatively high success rates of both regimens.

More research is needed to determine the role of medical immobilization in the success of conscious sedation. Future studies should also include the comparison of MDZH to hydroxyzine alone to elucidate the role of MDZ in shortening the waiting period before commencement of dental treatment.

Conclusions

1. The combination of hydroxyzine (3.7 mg/kg) with MDZ (0.3 mg/kg) administered 30 minutes before treatment resulted in safe and effective sedation for the dental treatment of young children.
2. The use of this combination might be more advantageous when compared to MDZ alone, resulting in less crying and movement during the first 30 and 20 minutes, respectively.

References

1. Kupietzky A, Houpt MI. Midazolam: A review of its use for conscious sedation of children. *Pediatr Dent.* 1993;15:237-241.
2. Hartgraves PM, Primosch RE. An evaluation of oral and nasal midazolam for pediatric dental sedation. *J Dent Child*. 1994;61175-181.
3. Primosch RE, Bender F. Factors associated with administration route when using midazolam for pediatric conscious sedation *J Dent Child*. 2001;68:233-238.

4. Kupietzky A, Holan, G, Shapiro J. Intranasal midazolam better at effecting amnesia after sedation than oral hydroxyzine: A pilot study. *Pediatr Dent*. 1996;18:32-34.
5. Shapira J, Holan G, Botzer A, Kupietzky A, Tal E, Fuks AB. The effectiveness of midazolam and hydroxyzine as sedative agents for young pediatric dental patients. *J Dent Child*. 1996;63:421-425.
6. Hasty MF, et al. Conscious sedation of pediatric dental patients: An investigation of choral hydrate, hydroxyzine pamoate, and meperidine versus chloral hydrate and hydroxyzine pamoate. *Pediatr Dent*. 1991;13:10-19.
7. Musial KM, Wilson S, Preisch, Weaver J. Comparison of the efficacy of oral midazolam alone versus midazolam and meperidine in the pediatric dental patient. *Pediatr Dent.* 2003;25:468-474.
8. Frankl S, Shiere F, Fogels H. Should the parent remain with the child in the dental operatory? *J Dent Child.* 1962;29:150-163.
9. Chambers WL, Fields HW, Machen JB. Measuring selected disruptive behaviors of the 36- to 60-month-old patient. Part 1: Development and assessment of a rating scale. *Pediatr Dent.* 1981;3:251-256.
10. Houpt M, Kupietzky A, Tofsky N, Koenigsberg SR. Effects of nitrous oxide on diazepam sedation of young children. *Pediatr Dent.* 1996;18:236-241.
11. Nathan JE, Vargas KG. Oral midazolam with and without meperidine for management of the difficult young pediatric dental patient: A retrospective study. *Pediatr Dent*. 2002;24:129-138.
12. Moore PA. Adverse drug interactions in dental practice: Interactions associated with local anesthetics, sedatives and anxiolytics, Part IV of a series. *J Am Dent Assoc.* 1999;130:541-554.
13. Shapira J, Holan G, Guelman M, et al. Evaluation of the effect of nitrous oxide and hydroxyzine in controlling the behavior of the pediatric patient. *Pediatr Dent.* 1992;14:167-170.

Abstract of the Scientific Literature

Prevalence of Overweight Texas Schoolchildren

The prevalence of children being overweight has more than doubled in the past 20 years. This study describes results from year 1 of a surveillance system to monitor body mass index in children at the state level. A sample of 6,630 children attending Texas public schools, representing fourth-, eighth-, and 11th-grade students within race/ethnic subpopulations, was assessed. Body mass index was calculated, and demographic information was obtained from a questionnaire. The prevalence of being overweight was 23%, 19%, and 16% for fourth-, eighth-, and 11th-grade students, respectively. Overweight prevalence was highest among Hispanic boys (30% to 33%), fourth-grade Hispanic girls (27%), and fourth- and eighth-grade African American girls (31% and 23%, respectively). Eleventh-grade white/other girls had the lowest prevalence of being overweight (6%). These data confirm the increasing prevalence of being overweight among US children, especially among Hispanic and African American students, compared to white/other students and fourth-grade students relative to eighth- and 11th-grade students.

Comments: The trend of children being overweight, which was highest among minority populations, is alarming because childhood obesity often persists into adolescence and adulthood. This is disturbing, in view of the fact that obesity is considered a risk factor for many chronic diseases as well as increased mortality. **FSS**

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Hoelscher DM, Day RS, Lee ES, Frankowski RF, Kelder SH, Ward JL, Scheurer ME. Measuring the prevalence of overweight in Texas schoolchildren. *Am J Public Health.* 2004;94:1002-1008.

49 references