Efficacy and Safety of Midazolam for Sedation in Pediatric Dentistry: A Controlled Clinical Trial

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ABSTRACT

Purpose: Pharmacological management of uncooperative children is becoming increasingly common in the dental setting. The purpose of this study was to determine the efficacy and safety of 3 different doses of midazolam for sedation in 2- to 4- year-old children with multiple dental needs and negative behavior.
Methods: Ten children participated in this crossover, controlled, double-blinded clinical trial, which evaluated their behavior, appointment length and patient response after administration of 3 different doses of midazolam or placebo. Oxygen saturation, heart rate, respiratory rate, and blood pressure were monitored in all sessions.
Results: Sedated children exhibited a more positive behavior compared to the placebo group, both at the beginning of the appointment (sitting in the chair) and during administration of local anesthesia (P=.008 and P<.03, respectively). The use of midazolam allowed for longer appointments, and doses of at least 0.3 mg/kg produced a higher rate of positive behavior overall. No changes in oxygen saturation, heart rate, respiratory rate, and blood pressure were observed.
Conclusion: Midazolam was effective and safe for pediatric sedation in the dosages studied. (J Dent Child 2013;80(3):133-8)

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The role of sedation in managing noncompliant pediatric patients has gained increased attention in recent decades because it allows a high quality of treatment, increased patient comfort, and parental reassurance. In spite of preventive measures in dentistry, there are still many young children with severe dental caries.

Fear of the dentist is still a problem for many people, despite a decrease in caries incidence.[1] In pediatric dentistry, fear, immaturity, and behavioral problems can affect children's compliance and increase the complexity of behavior management. In such cases, a few alternatives such as nitrous oxide, preoperative sedation, and general anesthesia have been suggested to make the dental treatment possible.[2,3]

The use of sedative drugs is an alternative to enable treatment when psychological techniques fail to improve a child's behavior. Sedative drugs allow the completion of invasive dental procedures whenever patient compliance is an issue and when general anesthesia is contraindicated. An important issue to consider when performing oral sedation in the dental setting is the uncertainty of its outcome, given that it is not possible to titrate the drugs to achieve the desired level of patient cooperation. The ideal oral sedative should be safe, easy to deliver, effective, capable of providing complete immobilization, titratable, reversible, have a fast onset, and produce no cardiorespiratory side effects.[4] At the moment, such agent does not exist.

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Drugs that have been historically prescribed as oral premedication in dentistry are barbiturates, chloral hydrate, opioids (narcotics), antihistamines, and phenothiazines, used either alone or in combination. The lack of specificity of some of these drugs for the control of anxiety and, consequently, the decrease in safety margins has led to their replacement by new drugs. One such group includes the benzodiazepines, which have superior selectivity in terms of anxiety control and high safety margin.[1]

Within that group, midazolam has become well known as a hypnotic, anticonvulsive, muscle relaxant, anterograde amnesia inducer, and effective anxiolytic drug. It has been widely used both in medicine and dentistry.[5-8] Midazolam has twice the strength and a half-life 10 times shorter than diazepam, another extensively used benzodiazepine.[9] The imidazole ring renders midazolam with 2 fundamental characteristics (water-solubility and a short half-life), making it different from the other benzodiazepines.[10]

An in-depth knowledge of the pharmacokinetics and pharmacodynamics of the drug selected is relevant for a successful outcome of the sedation appointment. In a survey evaluating 118 adverse events following sedation, 63% of them resulted in death or permanent neurological injuries. These events were related either to a combination of drugs or overdose, not to the type of drug that had been prescribed.[11]

There are several reports in the literature on the efficacy and safety of midazolam for dental treatment of children, adolescents, and adults.[4,6,12-23] However, the ideal dosage to provide the desired outcome in children has not yet been agreed upon. Most studies have examined other sedative agents administered prior to midazolam or its combination with other medications.[2] Consequently, further studies are necessary to clarify these important issues. Furthermore, differences in evaluation criteria and patients' age range have led to conflicting and inconclusive results.

In addition to efficacy, the safety of midazolam has been discussed in several studies using different methods, dosages, routes for administration, and evaluation criteria. It was found to be a safe drug since no cardiorespiratory depression has been encountered.[4,12,14,18-20,23]

The purpose of this study was to evaluate the efficacy and safety of 3 different doses of midazolam for the dental treatment of 2- to 4-year-old children.

METHODS

This was a double-blind, crossover, controlled, clinical trial, approved by the Committee on Ethics in Research Involving Human Subjects of the Federal University of Santa Catarina, Florianopolis, Santa Catarina, Brazil.

Two- to 4-year-old patients who attended the intramural pediatric dental practice at the Polydoro Ernani de São Tiago University Hospital in Florianopolis were considered for the trial. To participate in the study, children had to be healthy, uncooperative for dental treatment (according to the Frankl scale) and need at least 5 invasive procedures (restorative, endodontic, or surgical). The children were examined by a pediatrician at the University Hospital and were excluded from the study if they were not in good health and/or had a contraindication for sedation. After the parents agreed to participate an informed consent was obtained. Patients were instructed to fast for 6 hours prior to the appointment but drinking water was permissible up to 3 hours. The legal guardian was told to bring another adult to help take the child home safely and to report any changes to their child's health status, especially those involving the respiratory tract.

Patient allocation to a treatment group was carried out by an external collaborator through a lottery in all treatment sessions. The drug and the placebo were stored in similar containers to guarantee total concealment and were administered by the same examiner 30 minutes before the initiation of dental treatment. A dose of 0.2 mg/kg of oral midazolam was used in the first appointment. It was then increased to up to 0.4 mg/kg in the following sessions, according to individual needs and its efficacy in sedating the patient in the previous session. Midazolam was mixed in 3 ml of strawberry or grape yogurt, whichever the patient preferred.

In all the appointments, a calibrated examiner recorded blood pressure, oxygen saturation, heart rate, and respiratory rate, both at baseline and every 15 minutes thereafter, except for blood pressure which was measured every 30 minutes. A pulse oxymeter, precordial sthetoscope, and a blood pressure cuff were used for monitoring.

A data collection form, based on the examination record used in the pediatric dentistry clinic, was customized for the trial. The child's behavior was assessed using the Frankl scale at 4 different time points: (1) sitting in the dental chair; (2) during local anesthesia; (3) during the operative procedure; and (4) at the end of the appointment. A calibrated pediatric dentist, blinded to which treatment group the child was in, recorded the behavior. The calibration was done by an experienced psychologist who used videotapes to illustrate specific behaviors to be identified. Five days later, the training was repeated and an agreement of approximately 87% was observed, according to the kappa coefficient test.

The efficacy and safety of midazolam were assessed based on the depth of sedation using the Ramsay scale,[24] which consists of 6 points: (1) anxious and agitated, or restless, or both; (2) cooperative, orientated, and tranquil; (3) responding to commands only; (4) brisk response to light glabellar tap; (5) sluggish response to light glabellar tap; (6) no response to light glabellar tap.

The discharge criteria included normal cardiovascular function, patent and stable airway, intact protective reflexes, and ability to walk and sit up unaided.

STATISTICAL ANALYSIS

The Yates-corrected chi-square test and Fisher's exact test were performed after categorizing the independent variables based on sample data distribution. The goal was to determine the association between the independent variables and the final behavioral outcome (when expected cell frequencies were less than 5).

RESULTS

Ten patients (6 females and 4 males, average age=44.4 months) were selected and served as their own control. An attempt was made to select individuals with similar oral health conditions. A total of 60 sedation sessions were performed. The number of sessions for each child varied according to individual needs (minimum of 3 sessions and maximum of 9 sessions per child).

MIDAZOLAM EFFICACY (BEHAVIOR ASSESSMENT)

Regarding children's behavior at different phases of treatment, there was a statistically significant difference between the sedation and the placebo groups at the moment of "sitting in the chair" (P=.008) and during local anesthesia (P<.03). In the sedated group, children reacted with a positive or extremely positive behavior in both instances (Table 1).

Although not statistically significant (P>.05), a more positive behavior tended to prevail in between the sedation sessions, with a high number of children who received the placebo showing an extremely negative behavior. Similarly, no statistical difference was observed between the 2 groups at the end of the appointment (P>.05), but there was a tendency toward a higher rate of positive behaviors in the sedation sessions.

Table 2 shows the data for depth of sedation according to the Ramsay scale. The scores were collected every 15 minutes after drug administration. Statistically significant differences were observed between the groups (P<.05). Most children in the placebo group (69%) remained agitated (score 1), while 71% of the sedated children exhibited score 2 ("cooperative, orientated, and tranquil"). After 30 minutes, a higher number of children at deeper levels of sedation (scores 2 and 3 on the Ramsay scale) were observed. At 45 minutes, only 1 child received score 4.

Table 1. Behavioral evaluation (Frankl Scale) x intervention

		Behavior																			
		Sitting					Anesthesia					Procedure					Finish				
Frankl care score		1 N** (%)	2 N (%)	3 N (%)	4 N (%)	*P	1 N (%)	2 N (%)	3 N (%)	4 N (%)	*P	1 N (%)	2 N (%)	3 N (%)	4 N (%)	*P	1 N (%)	2 N (%)	3 N (%)	4 N (%)	*P
Interv	Plac	3 (10.3)	5 (17.2)	11 (37.9)	10 (34.5)	.008	12 (41.4)	8 (27.6)	4 (13.8)	5 (17.2)	.027	12 (41.4)	8 (27.6)	5 (17.2)	4 (13.8)	.345	5 (27.2)	8 (27.6)	6 (20.7)	10 (34.5)	.267
	Sed***	0	0	10 (32.3)	21 (67.7%)		3 (9.7)	10 (32.3)	11 (35.5)	7 (22.6)		7 (22.6)	8 (25.8)	10 (32.3)	6 (19.4)		3 (9.7)	4 (12.9)	12 (38.7)	12 (38.7)	

*Fisher's Exact test **Number of sessions ***Midazolam dose of 0.30 mg/kg

Table 2. Depth of sedation (Ramsay scale) x intervention

		Baseline			15 minutes			30 minutes				45 minutes					60 minutes				75 minutes		
Ramsay care score		1 N*** (%)	2 N (%)	*P	1 N (%)	2 N (%)	*P	1 N (%)	2 N (%)	3 N (%)	**P	1 N (%)	2 N (%)	3 N (%)	4 N (%)	**P	1 N (%)	2 N (%)	3 N (%)	**P	1 N (%)	2 N (%)	**P
Interv	Plac	14 (48.3)	15 (51.7)	.019	18 (62.1)	11 (37.9)	.071	20 (69.0)	9 (31.0)	0	.000	10 (52.6)	9 (47.4)	0	0	.581	4 (50)	4 (50)	0	.799	1 (100)	0	.261
	Sed****	24 (77.4)	7 (22.6)		12 (38.7)	19 (61.3)		5 (16.1)	22 (71.0)	4 (12,9)		15 (48.4)	13 (41.9)	2 (6.5)	1 (3.2)		13 (54.2)	10 (41.7)	1 (4.2)		5 (41.7)	7 (58.3)	

* Chi-square test ** Fisher's Exact test ***Number of sessions ****Midazolam dose of 0.30mg/kg

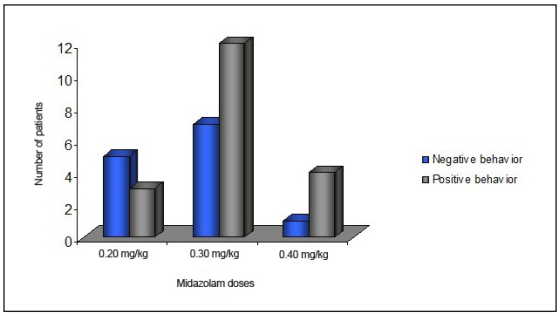

Figure 1. Behavior of children while receiving anesthesia x dosage.

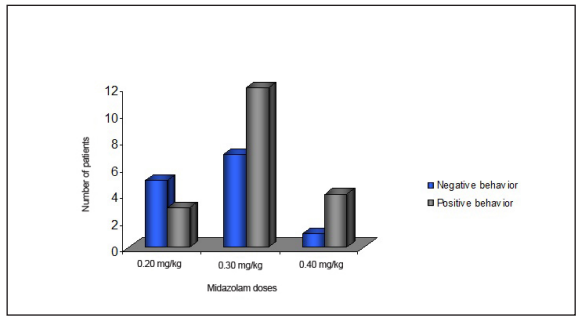

Figure 2. Behavior of children during the procedure x dosage.

MIDAZOLAM EFFICACY (BEHAVIOR ASSESSMENT) VS DOSAGE REGIMENS

Although a comparison between doses was not within the scope of this study, it was possible to observe, both during anesthesia administration and the procedure itself, that doses of at least 0.30 mg/kg produced the highest frequency of positive behavior compared to lower doses (Figures 1 and 2).

APPOINTMENT DURATION

To evaluate the impact of sedation on the duration of the appointment, the sessions were classified as either short (up to 60 minutes) or long (more than 60 minutes). This was based on the median duration of the appointment (60 minutes). Longer sessions were possible in the sedation group, which was statistically significant (Table 3).

MIDAZOLAM SAFETY

No significant changes to oxygen saturation (98.53 % ±0.57), heart rate (106 beats per minute ± 10.04), respiratory frequency (24 breaths per minute ± 4.58), systolic blood pressure (9.78 cm Hg ± 0.78), and diastolic blood pressure (7.15 cm Hg ± 0.83) were detected.

DISCUSSION

There are several ways to manage fear and anxiety in children undergoing dental procedures. However, it is well known that in many cases, psychological approaches are not sufficient to reduce aversion to dental treatment. This issue becomes more complex in situations involving multiple or urgent treatment needs. The utilization of effective and safe sedation techniques is necessary as an adjunct to promote cooperative behavior.

In the present study, the choice of midazolam for pediatric sedation was due to its proven efficacy and safety. The ability to administer midazolam by different routes is a great advantage but it makes it difficult to compare studies. Some have used it intranasally,[6,7,14,15] rectally,[16,18] orally,[4,21,22,25-28] or via other routes.[12,19,20] In addition to that, it must be pointed out that several studies used it combined with other sedative agents,[12,14,18,20-22,28] thereby confounding the outcome. This combined use has also contributed to an increased risk ofcomplications for the patient.[4]

In this study, midazolam was administered mixed in 3 ml of strawberry or grape yogurt, which may explain its high rate of acceptance by the children in contrast with what has been reported.[29] Patient noncompliance occurred in only 1 session but had no significant impact on the study results. This corroborates a study that showed good compliance in taking the agent, despite the bitter taste of the mixture.[30]

The most used method to evaluate the efficacy of a sedative agent in dentistry relies on its ability to change a negative behavior into a positive one. A case-control design may produce conflicting data, since inherent sample features can elicit different changes in behavior. In the present study, a crossover model was selected to minimize this type of bias.

When comparing the total number of sessions, a statistically significant difference was observed in the 2 initial phases of assessment [sitting in the chair (P<0.008) and local anesthesia (P<0.027)] when doses of at least 0.30mg/kg were used. No statistically significant difference was detected during the procedure itself and at the end of the appointment, although a tendency toward positive behavior was observed more frequently in the sedation group. Without sedation, most stimuli from dental treatment may hinder compliance, especially in children with aversive behavior.

A successful sedation appointment enables a greater number of procedures to be accomplished more quickly as seen in our study. The sessions for the placebo

Table 3. Appointment duration according to treatment group

Variable	Appointment duration		Odds ratio	*P*-value
	Short N* (%)	Long N (%)		
Intervention				
Placebo	22 (61)	7 (29)	3.816	<.02
Sedation	14 (39)	17 (71)		

**Number of sessions*

group were shorter than those for the sedation group. Persistence of uncooperative behavior prevented the accomplishment of many procedures, leading to appointment interruption before the conclusion of the treatment plan. Sedation duration of oral midazolam, despite its reduced working time compared to other sedative agents (triclofos and promethazine), is sufficient to allow the execution of most planned procedures.[4]

The Ramsay scale was used to assess the efficacy and safety of the drug. It can be suggested from our results that this tool should be included in the protocol of clinical studies using sedative agents. The 30-minute interval between the time of drug administration and the beginning of treatment produced the highest number of children at deeper levels of sedation (scores 2 and 3 on the Ramsay scale), what suggests that this wait time may be ideal for the initiation of invasive procedures when using a dose of 0.30mg/kg of midazolam.

More cooperative behavior was seen with a midazolam dose of at least between 0.30 mg/kg. This finding is in accordance with Gallardo et al.,[25] who achieved satisfactory results with a mean dosage of 0.32 mg/kg of oral midazolam. Other authors have shown that 0.2 mg/kg of midazolam intranasally produced more advantages than 0.3 mg/kg administration via the same route.[14] Such divergences can be explained by the different route of administration. Oral intake leads to a greater variability of effects, due to individual differences in pharmacokinetics. All monitored parameters (oxygen saturation, heart rate, respiratory frequency, and blood pressure) were maintained within normal levels.

According to the American Academy of Pediatric Dentistry (AAPD) guidelines for the elective use of moderate sedation, deep sedation, and general anesthesia in pediatric dental patients, the stability of a patient's vital signs is the most used safety parameter in studies about sedation.[31] However, it is extremely important to monitor the depth of sedation, since the intended level of sedation is not always reached by all patients. Some patients can progress to a deeper level of sedation, which can result in hypoventilation, obstruction, or cardiovascular compromise.

To be regarded as effective, anxiolytic drugs do not need to promote sedation to the point of making the child sleep throughout the entire session. What is important is that the drug makes the child more receptive to treatment with no need for physical restraint. In our study, children were effectively maintained under sedation (Ramsay scale scores between 2 and 3) without compromising safety. Only one child attained deep, undesirable sedation (score 4) 45 minutes after the administration of the drug. Despite the low occurrence of deep sedation, the practitioner should always be alert to the possibility of complications.

Notwithstanding the proven safety of sedation when the guidelines are followed, the existence of a great variability in children's physiology must always be considered. For this reason, the reaction to these drugs only has a predictive value. Moreover, regardless of which technique is utilized, knowledge of the pharmacokinetics and pharmacodynamics of the chosen drug is paramount. The same is true when it comes to monitoring and training of the staff because they need to be able to recognize an emergency as soon as it arises and provide life support if needed.

CONCLUSIONS

Based on the results of this study, the following conclusions can be made:

1. Oral midazolam (0.2-0.4 mg/kg) is safe and effective for dental procedures in 2- to 4-year-old children.
2. A 30-minute interval between the administration of the drug and the start of the dental procedures yielded the highest number of children at deeper levels of sedation.

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