Assessment of Intranasal Midazolam Administration with a Dose of 0.5 mg/ Kg in Behavior Management of Uncooperative Children

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Aim: *Intranasal midazolam has been used to induce conscious sedation in children with negative and aggressive behavior. The main goal of this study was to determine the effectiveness of intranasal administration of midazolam (with a dose of 0.5 mg/kg) in behavior management of uncooperative children. Materials and methods: Thirty healthy, difficult children of 3-5 years were evaluated. At the beginning of each session, ordinary techniques of behavior management to treat patients were applied. In cases of unsatisfactory responses, intranasal midazolam was immediately employed. To determine the efficacy of the drug, child behavior was evaluated before and after administration of midazolam using Houpt rating scale of general behavior. Results: A statistically significant difference was demonstrated in the patients' behavior before and after administration of intranasal midazolam. Conclusions: this drug is effective in sedation and reduction of the anxiety of children under treatment.*

Keywords: *Intranasal midazolam, Pediatric dentistry, Conscious sedation*
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INTRODUCTION

Despite advances in promotion of oral and dental health, tooth decay remains a major health challenge among children.[1] Most children consent to dental treatments straightforwardly. However, uncooperative children or those with negative behaviors require measures for behavior modification prior to dental procedures.[1,2] Some of these children can be suitably controlled using usual psychological methods, but many others may require the use of pharmacological methods for conscious sedation.[1,3]

Several types of drugs and routes of administration (e.g. oral, anal, intravenous, intramuscular, etc.) have been tested to this end. Among these, mention can be made of antihistaminic agents and benzodiazepines, each with their own advantages and drawbacks[1]. For instance, diazepam is a readily available drug the use of which has decreased significantly following the introduction of midazolam.[4] Midazolam enjoys several advantages compared to diazepam, e.g. its intravenous and intramuscular injections are associated with less vascular reaction owing to higher water solubility and are thus less painful.[5-7] Amnesic effects of midazolam are greater than diazepam[5,6,8] and it is 3-5 times as potent as diazepam.[5,9] Oral midazolam has a more rapid onset of action compared to oral diazepam.[4,5,10] Hepatic clearance of midazolam is ten times faster than diazepam,[11] hence it has a significantly shorter half-life of distribution and excretion.[5,6,11] These features make midazolam easier to use in dentistry, as patients are willing to be discharged immediately after the procedure.[5,6]

General anesthesia is another way of controlling behavior during dental procedures. Despite being frequently used, this method has certain disadvantages such as the risks normally associated with general anesthesia, high cost of treatment, and the need for a recovery period and sometimes hospitalization.[12]

Intranasal midazolam administration has been recognized as a conscious sedation technique. Studies have demonstrated the rapid effect of midazolam, as well as the short period of recovery after its administration. It is a simple, effective method requiring the least patient cooperation during administration.[2,13-16] Anesthesiologists have recently used this drug as a sedative prior to induction of general anesthe-

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sia.[5,17] However, few studies have addressed the applications of this drug in dentistry.[2]

In 1993, a study evaluated the sedative effect of intranasal midazolam administration (0.2 mg/kg) in 4 to 21 year-old uncooperative mentally challenged patients for the first time; it reported significant changes in behavioral patterns of the patient's studied.[13] Another study assessing the effect of intranasal midazolam administration with doses of 0.02 mg/kg and 0.03 mg/kg did not report any significant difference between the case and control groups in respect of success rate, sedative effect, side effects, and recovery period.[14] A 2001 study assessing the effect of three different doses of intranasal midazolam (0.3, 0.4, 0.5 mg/kg) reported significantly different behavioral patterns in these groups; administration of the 0.5 mg/kg dose produced greater sedation and easier acceptance of treatment compared to the other two doses.[2]

In view of the presumed benefits of intranasal midazolam administration and given the small number of studies on this drug, this study was conducted to assess the effectiveness of intranasal midazolam (0.5 mg/kg) in behavior control of uncooperative children. Administration of this dose was aimed at minimizing the need for additional medications (nitrous oxide and oxygen) within the allowable dose range of the drug.

MATERIALS AND METHODS

In this clinical study, 30 uncooperative children aged 3-5 years attending the pediatric clinic were selected (regardless of sex) using simple sampling method. Selection of these children was conducted based on Frankl's behavioral rating scale (grades I and II).[1] The selected age group was presumed to include the least cooperative children. All children were healthy and fell in groups ASA I and II. Midazolam was not contraindicated in any of the selected children. The children's parents were fully briefed about the procedure, as well as involved risks and benefits. All instructions were given to them both orally and in writing (e.g. the child should stop eating solid food or milk 6-8 hours and drinking liquids 2 hours before the visit). Written informed consent was taken from all parents for sedation with midazolam.

On the day of the visit, to obtain assurance of the children's health, they were taken along with one of their parents to the ward for patients with special conditions and thoroughly examined by an anesthesiologist. The children were weighed and their basic vital signs, i.e. heart rate and respiratory rate (determined visually) were recorded. Peripheral oxygen saturation was also determined using a pulse oximeter and recorded.

Initially, routine behavioral control methods were used (tell-show-do or voice control) to persuade the child to accept treatment. An anesthesiologist would immediately administer Midazolam if the child displayed negative behaviors (Frankl 1 and 2), such as resisting examination or treatment. To compare the children's general behavior during treatment, before and after midazolam administration, their behavioral pattern before midazolam administration was assessed and recorded according to Houpt rating scale of general behavior.[2,15]

With the child sitting reclined on the parent's lap, Midazolam (Roche - Sweden) (intravenous solution, 5 mg/ml ampoule) was alternately administered in a dose of 0.5mg/kg (at 5-10 second intervals) into both nostrils using an insulin injection syringe without a needle (SUPA-Iran). The child's acceptance of treatment during intranasal drug administration, as well as any possible complications including coughing, sneezing, etc. was carefully assessed and recorded. The patient was monitored for signs of onset of drug action (e.g. glazed looks, slurred speech, etc.) and after 10 to 15 minutes was separated from the parent and placed in a restraint device (Pedi rap) so that the patient's feet were visible. The same researcher performed the clinical acts, monitored the patient's vital signs, and recorded the events on each patient.

Meanwhile, the presence of anxiety symptoms following drug administration and separation from the parents was evaluated and recorded. The patient's state of consciousness was continuously assessed through verbal communication. The patient's vital signs from the time of drug administration to discharge were continuously monitored and recorded at 10-minute intervals. The presence of any possible side-effects or complications (e.g. vomiting, etc.) was also recorded. Furthermore, general behavioral assessment of the child during treatment (like before drug administration) was performed based on Houpt rating scale of general behavior.

Grades I, II, and III of Houpt general scale indicated unacceptable behavior and unsuccessful sedation and grades IV, V, and VI indicated acceptable behavior and successful sedation. Grading according to Houpt' scale was used to judge the success of sedation by intranasal midazolam administration. The child was finally transferred to the recovery room and discharged after being examined by anesthesiologists and obtaining assurance of the child's normal condition.

Comparison of general behavioral rating before and after drug administration was performed using Wilcoxon test. The degree of cooperativeness was assessed with McNemar test using SPSS software.

RESULTS

Coughing was seen in seven children and vomiting in one, following intranasal midazolam administration. No complications were seen in other instances. The onset of drug effects was seen within 4-5 minutes of administration. After onset of drug effect and upon separation from parents, 21 children (70%) were not anxious and the rest showed signs of anxiety.

Tables 1 and 2 represent the frequency distribution and percentage of children under study in respect of degree of crying and movement for the type of procedure after administration of drug.

Table 3 shows the frequency distribution of children under study in respect of behavior rating and cooperativeness, before and after drug administration based on Houpt scale. Wilcoxon test showed a significant statistical differ-

Table 1. Frequency distribution and percentage of children under study in respect of degree of crying for the type of procedure

		Type of crying				
		Hysterical crying	Continuous or strong crying	Intermittent or mild crying	No crying	Total
Treatment procedure	Local anesthesia	0	13 (48%)	9 (33.5%)	5 (18.5%)	27 (100%)
	Preparation	0	10 (45.5%)	2 (9%)	10 (45.5%)	22 (100%)
	Filling	0	2 (20%)	2 (20%)	6 (60%)	10 (100%)
	Pulpotomy	0	7 (50%)	0	7 (50%)	14 (100%)
	Extraction	1 (7.5%)	4 (31%)	1 (7.5%)	7 (54%)	13 (100%)

Table 2. Frequency distribution and percentage of children under study in respect of degree of movement for the type of procedure

		Type of movement				
		Violent, interruption of treatment	Continuous, making tratment difficult	Controllable, not interfering with treatment	No movement	Total
Treatment procedure	Local anesthesia	0	7 (26%)	10 (37%)	10 (37%)	27 (100%)
	Preparation	0	4 (18%)	8 (36.5%)	10 (45.5%)	22 (100%)
	Filling	0	0	4 (40%)	6 (60%)	10 (100%)
	Pulpotomy	0	4 (28%)	3 (21.5%)	7 (50%)	14 (100%)
	Extraction	0	4 (30.5%)	2 (15.5%)	7 (54%)	13 (100%)

ence between the children's general behavioral rating during treatment, before and after midazolam administration, indicating that the drug had increased behavioral ratings and cooperativeness in a significant percentage of children. Finally, McNemar test was used to determine the sedative effect of midazolam. The results of the test and the change in the percentage of individuals with acceptable (cooperative) behavior and unacceptable (uncooperative) behavior before and after drug administration show the effectiveness of midazolam in successful sedation of children ($P<0.0001$).

During the entire length of the study, all of the patients had stable and normal vital signs and their arterial oxygen saturation remained within normal limits (97-98%). No adverse effects (e.g. hypoxia, vomiting, etc.) were seen. All children were drowsy and only one fell asleep. Recovery period (period between drug administration and discharge) was short (50-60 minutes).

DISCUSSION

Intranasal midazolam administration resulted in successful sedation of a significant percentage of children under study, increasing their general behavioral rating based on the Houpt scale.

The features which make this drug superior to other seda-

Table 3. Frequency distribution and percentage of children under study in respect of behavioral rating and degree of cooperation before and after drug administration

Type of behavior and degree of cooperativeness	Before administration	After administration
Unacceptable		
1. No treatment (aborted)	0	0
2. Interruption of treatment, partial treatment (poor)	17 (57%)	4 (13.5%)
3. Treatment interrupted but eventually completed (fair)	8 (26.5%)	3 (10%)
Sum	25 (83.5%)	7 (23.5%)
Acceptable		
4. Difficult, but all treatment performed (good)	5 (16.5%)	10 (33.5%)
5. Some limited crying or movement e.g. during anesthesia or mouth prop insertion (very good)	0	8 (26.5%)
6. No crying or movement (excellent)	0	5 (16.5%)
Sum	5 (16.5%)	23 (76.5%)
Total	30 (100%)	30 (100%)

tive agents include its safety of use, high potency, rapid onset of action (when administered intranasally), stable sedative effects, relatively short duration of action, and anterograde amnesic action.

Like in other studies,[2,13-15] coughing during intranasal administration of the drug was the most common side-effect due to entrance of midazolam solution into nasal foramina. As reported by earlier studies,[2,13-16] midazolam had a rapid onset of action (4-5 minutes), which is due to the rich vascularity of the nasal mucosa and direct absorption of the drug into systemic circulation. In this study, midazolam was found to be effective in reducing the children's anxiety after separation from their parents. Anxiety symptoms resolved in 70% of children. This figure was 100% in another study.[2] This difference may have arisen from different qualitative interpretations of anxiety and its definition.

All children became drowsy following drug administration and one fell asleep. Drowsiness and reduction of anxiety both contribute to the effectiveness of midazolam in producing sedation, as they increase the child's threshold of response to painful stimulants. Moreover, some of the children became euphoric after the onset of drug action.

On the other hand, midazolam administration might lead to drowsiness combined with restlessness and unwanted behaviors in some children; this is known as a paradoxical response (drug-related anxiety as a side-effect). In this study, persistence of negative behaviors in some children could be attributed to the paradoxical response.

Houpt rating scale of general behavior was used in this study to assess the children's behavioral patterns (Table 3). Before administration of the drug, only 16.5% of the children displayed acceptable behavior of type IV, whereas after drug administration this figure increased to 76.5%. These findings indicate the effectiveness of midazolam and confirm views of other researchers also referring to this drug as being effective in improving children's behavioral patterns.[2,13-16,18,19]

Another aim of this study was to assess the adverse effects of stopping eating (8 hours) and drinking liquids two hours before administration of the drug. Based on American Dental Association (ADA) protocol, a 3-5-year-old child must be prohibited from drinking liquids nearly 6 hours before sedation. This is difficult to tolerate for a young child, hence the no-drinking period was decreased in this study to two hours and no side-effects (e.g. nausea and vomiting during the recovery period) were seen. Another study obtained a similar result, reporting no significant difference in children's behavioral patterns, time of onset of drug action, and duration of sedation in fasting and non-fasting states [2]. Hence, it may not be necessary to keep the child in fasting state for long hours before intranasal midazolam administration which is compatible with recent protocol of ASA regarding usage of clear liquids by the child about 2-3 hours prior to G.A.[1]

Although a statistically significant difference was observed between children's behavior before and after drug administration and the results were suggestive of the positive sedative effect of midazolam, behavioral ratings of I or II on Houpt rating scale of general behavior cannot be expected to increase to V or VI after drug administration. In fact, administration of the drug only tranquillizes the children compared to their previous state and decreases crying and movements so that the dentist can perform dental procedures with greater ease. The children can be expected to reach the desired conduct with a lower dose of the drug in the following sessions, owing to gradual behavioral change and anxiety reduction; this is consistent with other studies.[2,6,13-15,18,19] The drug produces more desirable effects in children with mild to moderate anxiety and higher potential for cooperating, turning them into fairly calm children (grades V and VI on Houpt's scale).

In general, intranasal midazolam administration is associated with two main problems, namely nasal irritation and inapplicability in a child with nasal discharge. However, in view of its multitude of advantages, intranasal midazolam administration can be used as an effective sedation technique.

The use of lower doses of midazolam in combined methods, administration of more concentrated solutions of the drug, and oral administration of midazolam are among the recommendations of this study.

CONCLUSIONS

Although the results indicate the positive effect of the drug in sedating patients, it cannot be concluded that a child with a behavioral score of 1 or 2 on Houpt scale will have scores of 5 or 6 after administration of the drug. In fact this drug makes children more controllable only compared to their previous state and reduces their range of movements and crying so that the dentist will be able to work with greater ease. Midazolam has greater effect in children who have a greater potential to cooperate and have a mild to moderate degree of anxiety.

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