Comparison of Drops Versus Spray Administration of Intranasal Midazolam in Two- and Three-year-old Children for Dental Sedation

Robert E. Primosch, DDS, MS, MEd[1] Marcio Guelmann, DDS[2]

Abstract

Purpose: The purpose of this retrospective record review of 2- and 3-year-old dental patients receiving intranasal midazolam (INM) was to compare drops vs spray administration to behavioral outcomes observed for agent acceptance during administration and for agent efficacy during parental separation, local anesthesia injection, and delivery of restorative dentistry.

Methods: Temperament and attachment scores based on adaptability and approachability determinants judged by the parent and interactive and Frankl behavior rating scores determined by the operator were used to compare preoperative behavioral characteristics between the 2 groups. The Ohio State Behavioral Rating Scale (OSBRS) and the Frankl behavior rating scale were used to determine intraoperative behavioral outcomes for agent acceptance and efficacy.

Results: Analysis of 64 sedation records revealed that the 2 groups had similar preoperative behavioral characteristics. Improvements in the Frankl behavioral rating scores were observed during the sedation, but no statistically significant difference between the drops and spray groups was measured using the OSBRS. For the procedural event of drug administration, however, the spray group demonstrated a statistically significant reduction (P=.025) in aversive behaviors when compared to drops administration as measured by the OSBRS. This finding was observed, even though the volume of spray was greater than used in the drops group.

Conclusions: Spray administration of INM produced significantly less aversive behavior than administering drops in 2- to 3-year-old dental patients of similar behavioral characteristics. The effectiveness of the conscious sedation technique was not influenced by the method of nasal administration. This study suggested that the use of a commercially available atomizer improved patient acceptance of INM administration but did not influence agent efficacy compared to drops administration for 2- to 3-year-old dental patients in an office setting. (Pediatr Dent 2005;27:401-408)

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The advantages and limitations of using different administration routes for midazolam, especially with respect to the ease of administration and patient acceptance, is controversial.[1-18] Although the oral route of administration is the most popular among pediatric dentists,[19,20] confrontation and frustration often arise when children refuse to accept the sedative medication.

Despite efforts to disguise the often bitter taste, children occasionally spit or regurgitate the medication when administered orally.[1,7,10-12,16,21] Similar controversy existed in the literature regarding patient acceptance of intranasal midazolam (INM). Some authors have reported that the nasal route required less patient cooperation and was a simple, convenient, noninvasive, painless, and reliable alternative to oral drug administration.[2,12] In contrast, other authors reported INM to be noxious, painful, and poorly tolerated.[3,5,7,10,13,16] Low patient tolerance was a result of the injectable solution, stabilized by storage in 3.3 pH solution, irritating the nasal mucosa with a burning sensation. Early approaches to the INM sedation used drops,[2,7,10,12,13,15,22,23] but more recently use of an atomizer for intranasal administration has become more popular.[13,24-27] Griffith et al reported improved patient tolerance to spray administration using

[1]*Dr. Primosch is professor and* [2]*Dr. Guelmann is associate professor, Department of Pediatric Dentistry, University of Florida, Gainesville, Fla.*
Correspond with Dr. Primosch at rprimosch@dental.ufl.edu

Table 1. Behavioral Scores Determined by Parental Questionnaire

Temperament determinants (T score)	Never	Rarely	Sometimes	Often	Very often	Always
My child enjoys new places and people.	1	2	3	4	5	6
My child enjoys a visit to the doctor (MD).	1	2	3	4	5	6
My child plays well with other children.	1	2	3	4	5	6
Attachment determinants (A score)	**Always**	**Very often**	**Often**	**Sometimes**	**Rarely**	**Never**
When an adult, unknown to my child, comes to our house, my child tends to cling to or come near me.	1	2	3	4	5	6
When exposed to a new situation, my child tends to be shy and timid.	1	2	3	4	5	6
When I take away a favorite drink or toy, my child tends to cry or gets angry.	1	2	3	4	5	6

an atomizer over using drops, but the effectiveness of sedation between these 2 methods of administration was reported as equal.[13] The intranasal route provided the advantage of rapid absorption into the systemic circulation without first-pass metabolism effecting the agent's bioavailability.

In summary, clinical trails using INM in children were sparse and inconclusive in regards to patient acceptance during administration. Therefore, the purposes of this retrospective review of conscious sedation records of 2- and 3-year-olds receiving INM for pediatric dental care were to compare drops vs spray administration to behavioral outcomes observed for agent acceptance during administration and for agent efficacy during parental separation, local anesthesia injection, and delivery of restorative dentistry.

Methods

Conscious sedation records for 72 dental patients, 24 to 47 months of age and sedated with INM for treatment at the Pediatric Dental Clinic at the University of Florida College of Dentistry, Gainesville, Fla, were randomly selected for review following approval by the University's Institutional Review Board. A similar protocol was followed for each sedation procedure using the guidelines established by the American Academy of Pediatric Dentistry (AAPD).[28] Written parental informed consent was obtained for each patient prior to the sedation.

Preoperatively, the treating dentist reviewed the health history with the parent or guardian and performed a physical assessment of the patient's airway and vital signs. Only healthy patients receiving an American Society of Anesthesiologists (ASA) rating of I or II were selected for sedation. All patients were weighed on a standard hospital scale, and the weight was recorded in kilograms. Preoperative behavior displayed by the child was rated using a Frankl behavior rating scale[29] as either definitely negative (--), negative (-), positive (+), or definitely positive (++).

Temperament (T) and attachment (A) scores based on adaptability and approachability determinants judged by the parent (Table 1) and an interactive (I) behavior score determined by the operator (Table 2) were calculated and recorded. Each of the 3 behavioral scores (T, A, and I) were calculated as a simple summation of the values recorded for the 3 conditions listed in Table 2. The lower the score, the poorer the behavioral characteristic. Temperament and attachment questions found in Table 1 were a slightly modified version of the abridged and modified behavioral style questionnaire[30] described by Fraone and coworkers.[31] The interactive score scale found in Table 2 was likewise described by Fraone and coworkers[31] in their study of oral midazolam use for pediatric dental sedation.

The Ohio State Behavioral Rating Scale (OSBRS), as described by Lochary and coworkers[32] and used in other pediatric dental sedation studies,[31,33] was employed at the

Table 2. Interactive (I) Score Determined by Operator Observation

Patient interaction
1 – Unable to talk (age or foreign language)
2 – Refuses to talk
3 – Talks only when prompted
4 – Talks most of the time
5 – Talks freely without prompting
Behavioral interaction
1 – Cries when initially seen and actively seeks parent to hold/protect patient
2 – Frowns most of the time; intermittently makes eye contact
3 – Shows little expression initially, but is approachable after initial prompting
4 – Smiles when addressed and is easily approached
Level of cooperation
1 – Never follows any request; cries and is combative
2 – Rarely follows any request; appears angry but does not cry
3 – Follows most requests, but with hesitation following prompting
4 – Follows all requests without hesitation

following procedural events: (1) subject weighing; (2) physical assessment (airway and vital signs); (3) drug administration; (4) parental separation; (5) local anesthesia injection; and (6) delivery of operative dentistry. The OSBRS uses a hierarchical scale labeled for observed behavior as: (1) quiet; (2) crying; (3) struggling; and (4) crying/struggling. For each event procedural event, the lowest OSBRS score (most aversive behavior displayed) was recorded.

A generic injection solution of midazolam, 5 mg/mL (Novaplus, Irving, Tex) was administered intranasally by the operator with the patient in a supine position stabilized and supported by the parent-operator pair in a knee-to-knee position. Nasal administration was accomplished using either a drop or spray technique, as preferred by the operator. Drop administration employed a needless 1-cc tuberculin syringe slowly depositing equal volume of solution in each naris. Spray administration employed a commercially available atomizer (MAD 300 Mucosal Atomizer, Wolfe Tory Medical, Inc, Salt Lake City, Utah) attached to a 1-cc tuberculin syringe (Figure 1) and sprayed by short, quick puffs equally distributed between the nares.

Figure 1. MAD 300 Mucosal Atomizer (Wolfe Tory Medical, Salt Lake City, Utah) attached to a 1-mL tuberculin syringe.

Onset of sedative effect and separation of the child from parent was approximately 10 minutes. When separated from the parent, the child was placed on a papoose board (Olympic Medical, Seattle, Wash) but not immobilized initially unless movement warranted such action. In certain cases, 30% to 50% nitrous oxide was administered via nasal hood intraoperatively at the discretion of the operator based on patient cooperation and responsiveness levels. Pulse rate and hemoglobin oxygen saturation were continuously monitored using a pulse oximeter (Vital Signs Monitor, 506DXN2, Criticare Systems Inc, Waukesha, Wis) placed on the patient's great toe. The operator recorded intraoperative vital signs and OSBRS scores at intervals based on the level of patient responsiveness in accordance with AAPD guidelines.[28] In addition, at the end of dental treatment, the operator recorded an assessment of the child's overall behavior using the Frankl scale,[29] as well as making specific comments regarding the quality of the sedation. The duration of the procedure, measured from parent separation to completion of dental treatment, was recorded in minutes. Following the sedation session, written postcare instructions were reviewed with parents and the child was discharged when the appropriate discharge criteria were met. The collected data were analyzed with chi-square analyses using Statview software (SAS Institute, Inc, Cary, NC). Comparisons were deemed statistically significant at $P<.05$.

Results

Sixty-four sedation records were selected for final data analysis from the initial 72 charts. Eight sedation records were eliminated from the review, as they lacked completeness or legibility for all the variables selected for analysis. An equal number of subjects (N=32) received either drops or spray administration; gender distribution was 31% females and 69% males. Mean data comparison for subject variables (age, weight, dose, dosage, volume, and duration of procedure) between the 2 methods of administration is found in Table 3.

An analysis of behavioral characteristics of the subjects, as determined by the temperament (T), attachment (A), and interactive (I) scores, were not statistically different between the drops and spray administration groups (Table 4). This suggests that the 2 groups exhibited remarkably similar characteristics in their temperament, attachment, and interactive behavior. Also, comparison of preoperative

Table 3. Subject and Dose Characteristics (Mean±SD) by Administration Vehicle

Subject/dose characteristics	Administration vehicle				
	Drops	Spray	Total	Range	*P* value*
Age (mos)	38.6±7.4	38.2±7.1	38.3±7.2	24-47	.823
Weight (kg)	14.7±2.0	15.4±3.2	15.1±2.6	10-20	.110
Dose (mg)	3.2±0.7	3.6±1.0	3.4±0.8	2.5-5.0	.053
Dosage (mg/kg)	0.22±0.03	0.23±0.04	0.22±0.03	0.18-0.30	.241
Volume (mL)	0.64±0.08	0.72±0.10	0.69±0.09	0.5-1.0	.053
Duration (min)	23.3±8.1	26.3±12.5	24.7±10.3	10-40	.264

*ANOVA analysis.

Table 4. Subject Preoperative Behavioral Characteristics (Mean±SD) by Administration Vehicle

Behavioral characteristics	Administration vehicle		
	Drops	Spray	*P* value*
Temperament score (T)	12.2±2.8	11.6±2.5	.995
Attachment score (A)	10.1±2.8	10.2±2.3	.848
Interactive score (I)	8.8±2.4	8.9±2.4	.958

*Chi-square analysis.

Table 5. Comparison of Pre- and Intraoperative Frankl Behavior Rating Scores by Administration Vehicle

	Preoperative N (%)		Intraoperative N (%)	
Frankl score	Drops	Spray	Drops	Spray
++	0	0	9 (28)	7 (22)
+	2 (6)	2 (6)	9 (28)	7 (22)
-	19 (59)	18 (56)	6 (19)	10 (31)
--	11 (35)	12 (38)	8 (25)	8 (25)
P value*	.965		.682	

*Chi-square analysis.

Frankl behavior rating scores (Table 5) and the OSBRS for subject weighing and physical assessment (Table 6) demonstrated no significant differences between drops and spray administration groups for INM. These findings further supported the speculation that the 2 study groups were similar in their behavioral characteristics.

Improvements in the Frankl behavioral rating scores were seen following the administration of INM (Table 5). Regarding the effectiveness of the resultant sedation, no statistically significant difference between the drops and spray groups was measured by intraoperative Frankl behavior rating scores (Table 5) and for the OSBRS measured during parental separation, local anesthesia administration, and placement of dental restorations (Table 6). Only 9 cases received supplemental nitrous oxide-oxygen inhalation intraoperatively to augment the sedation. These cases were fairly distributed between the spray (N=5) and drops (N=4) groups.

For the procedural event of drug administration, however, the spray administration group demonstrated a statistically significant reduction (P=.025) in aversive behaviors compared to drops administration when measured by the OSBRS (Table 6). This finding was observed, even though the volume of spray was greater than used in the drops group (0.72 vs 0.64 mL, P=.053, Table 3). A comparison of the mean dose of INM by the OSBRS displayed during drug administration did not demonstrate (P=.095 by analysis of variance [ANOVA]) a dose (or volume) effect on the behavior displayed. The mean dose for each OSBRS recorded during drug administration was as follows: (1) quiet (3.1 mg); (2) crying (3.6 mg); (3) struggling (3.0 mg); and (4) crying and struggling (3.6 mg).

Discussion

Midazolam is a benzodiazepine possessing hypnotic, anticonvulsant, muscle relaxant, anterograde amnestic, and anxiolytic activity that has been used extensively in medicine and dentistry.[1-3] Midazolam is administered by intravenous (IV), intramuscular (IM), submucosal, intranasal, oral, and rectal routes. Each of these routes has its own particular advantages and limitations. The literature regarding these advantages and limitations, however, especially regarding the ease of administration and patient acceptance by various routes, was conflicting.[1-18]

Since variables related with drug absorption did not play an important role when using the intravenous (IV) route

Table 6. Comparison of Behavioral Rating* at Various Procedural Events by Administration Vehicle

Procedural event	Drops				Spray				*P* value†
	Q	C	S	CS	Q	C	S	CS	
Subject weighing	29	2	1	0	28	3	1	0	.877
Physical assessment	25	5	2	0	24	3	2	3	.318
Drug administration	11	3	3	15	13	9	3	7	.025‡
Parental separation	22	5	0	5	17	7	1	7	.511
Local anesthesia	12	7	5	8	10	11	2	9	.108
Operative dentistry	12	8	4	8	12	12	1	7	.446

*Q=quiet; C=crying; S=struggling; CS=crying and struggling.
†Chi-square analysis.
‡Statistically significant difference.

of administration, reliable results were easily obtained. The intravenous use of sedative drugs was not routinely performed in pediatric dental practice, however, since it required training often unavailable to practitioners and required excellent behavior management and technique skills.[14,34] In addition, IM and IV routes were reported to be painful, did not alleviate a child's fear of an injection, and sensitized the patient to injections prior to beginning the proposed dental treatment.[1,5,12,14] Similarly, the submucosal route of midazolam administration was not recommended because of prolonged pain produced at the injection site.[35]

Despite difficulties and limitations associated with the oral administration of midazolam, many pediatric dentists—when sedating an uncooperative dental patient—considered it the route of choice. Although the oral route of administration was the most popular among pediatric dentists,[19,20] confrontation and frustration often arose when children refused to accept the sedative medication. Despite efforts to disguise the often bitter taste, children occasionally spit or regurgitated the medication when administered orally.[1,7,10-12,16,21] Nasal administration has been compared to oral administration of midazolam in several clinical trials.[2,15-17] Results of these trials demonstrated an insignificant difference in sedation outcome in children. Nasal route provided a faster onset, shorter working time, and faster recovery due to its higher bioavailability than by oral route and mimicked plasma levels of IV route. These factors contributed to the classification of nasal administration as a parenteral, not enteral, route.[27,36]

A recent survey of US advanced education programs in pediatric dentistry reported a rise in the use of midazolam and the intranasal route of administration.[19] Clinical trials of INM are well documented in medicine[7,10,13,15,18,22-24,26,37-48] and dentistry.[2,12,16,17,25,49-53] These studies have reported on INM's effectiveness, despite its negative acceptance by some patients.[2,3,7,10-13,16,24] Besides its sedative potency, midazolam has the ability to produce anterograde amnesia.[54-56] Use of INM rarely resulted in adverse outcomes, but respiratory depression,[57,58] allergic reaction,[59] and disinhibition[60] were reported. INM was rapidly absorbed through the nasal mucosa,[61] and resultant rapid plasma uptake was well documented.[62-71] Nasal mucosa was the only location in the body where there existed a direct link to the central nervous system (CNS). An animal study by Henry et al demonstrated that INM spray produced a greater CNS and plasma uptake than drops.[72] The nasal atomizer used in this study (Figure 1) produced a fine 30-μ particle spray and was designed with a semipermeable soft plug to cushion the naris and catch solution leak-back.[73] It is impossible to speculate how much of the spray was directly absorbed by the nasal mucosa compared to that spray amount reconstituted back into droplet form in the nasopharynx and swallowed by the patient.

Early approaches to the INM sedation used drops,[2,7,10,12,13,15,22,23] but more recently use of an atomizer for intranasal administration has become more popular.[13,24-27] Improved patient tolerance to spray administration using an atomizer was reported over using drops, but the effectiveness of sedation between these 2 methods of administration was reported as equal.[13] The present study's findings, using a new commercially available atomizer (MAD 300 Mucosal Atomizer, Wolfe Tory Medical, Inc, Salt Lake City, Utah), confirmed what was reported earlier by Griffith et al concerning agent acceptance and efficacy using a customized atomizer.[13] Their study used a custom-made device composed of a pump spray attached to a midazolam ampule contained within a modified plastic bottle and is, therefore, not commercially available to make a test comparison.

Results of this retrospective study should be interpreted with caution. Limitations included multiple operators who performed and recorded the sedation results and who were not blinded to the method of nasal administration and the child's preoperative behavior displayed. In addition, the influence of the confounding variable of nitrous oxide-oxygen inhalation used in a selected number of cases upon the level of sedation recorded is unknown. The sedation protocol used in this study dictated that nitrous oxide-oxygen inhalation be applied to augment cases where the desired level of sedation was not achieved. Often, the decision to use nitrous oxide was not applied uniformly in all cases qualified by the protocol. More prospective studies are needed to determine the predictive value of the various parameters affecting pediatric sedation behavior during dental treatment, thereby optimizing the success rates of different sedation regimens.

Conclusions

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

1. The use of a commercially available atomizer for intranasal spray produced significantly less aversive behavior than administering drops in 2- to 3-year-old subjects of similar behavioral characteristics receiving midazolam conscious sedation for dental procedures.
2. The effectiveness of the conscious sedation technique was not influenced by the method (drops vs spray) of nasal administration.
3. More research is needed to determine the predictive value of various parameters affecting pediatric sedation behavior during dental treatment.

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Abstract of the Scientific Literature

The Ability of Promotional Events to Encourage Tobacco Use Among College Students

Smoking rates among young adults who do not attend college are higher than smoking rates among college students. This study assessed young adults' exposure to the tobacco industry's marketing strategy of sponsoring social events at bars, nightclubs, and college campuses. Data was analyzed from the 2001 Harvard College Alcohol Study, a random sample of 10,904 students enrolled in 119 nationally representative 4-year colleges and universities. During the 2000-01 school year, 9% of respondents attended a bar, nightclub, or campus social event where free cigarettes were distributed. Events were reported by students attending 118 of the 119 schools (99%). Attendance was associated with a higher student smoking prevalence after adjusting for demographic factors, alcohol use, and recent bar/nightclub attendance. This association remained for students who did not smoke regularly before 19 years of age, but not for students who smoked regularly by 19 years of age. Attendance at a tobacco industry-sponsored event at a bar, nightclub, or campus party was associated with a higher smoking prevalence among college students. It was concluded that promotional events may encourage the initiation or progression of tobacco use among college students who don't smoke regularly when they enter college.

Comments: This study's findings call attention to a tobacco marketing strategy that is reaching students across the United States and may be encouraging them to use tobacco. These results may have implications for universities and community colleges, which should be alert to tobacco industry sponsorship of events on their campuses. The potential is great for these tobacco promotions to spread more widely and to target more college populations. **FSS**

Address correspondence to Dr. Nancy A. Rigotti, Tobacco Research and Treatment Center, Massachusetts General Hospital, 50 Staniford St., 9th Floor, Boston, MA 02114.

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