# Nasal Versus Oral Midazolam Sedation for Pediatric Dental Patients

*Su Jun Lee-Kim, DDS, MS Shahrbanoo Fadavi, DDS, MS*
*Indru Punwani, DDS, MSD Anne Koerber, DDS, PhD*

## ABSTRACT

**Purpose:** The purpose of this study was to evaluate and compare intranasal (IN) and oral (PO) midazolam for effect on behavior, time of onset, maximum working time, efficacy, and safety for patients requiring dental care.
**Methods:** Forty anxious subjects (20 IN, 20 PO, Frankl Scale 3 and 4, ages 2-6 years, ASA I and II) were sedated randomly with either IN (0.3 mg/kg) or PO (0.7 mg/kg) midazolam. The dental procedure under sedation was videotaped and rated by a blinded and calibrated evaluator using Houpt's behavior rating scale.
**Results:** There was no statistical difference for overall behavior ($F_{3,27}$=0.407; *P*=.749). The planned contrasts showed significant interactions between time and route (IN vs PO) between 25 and 30 minutes after starting sedation. The time of onset (*P*=.000) and the working time (*P*=.007) were significantly different between IN and PO midazolam. There were no statistically significant differences in vital signs ($O_2$ sat, HR, RR, BP) between PO and IN (*P*=.595). IN subjects showed more movement and less sleep toward the end of the dental procedures, and faster onset time but shorter working time than PO. Vital signs were stable throughout the procedures with no significant differences.
**Conclusions:** Mean onset time was approximately 3 times faster with IN administration compared to PO administration. Mean working time was approximately 10 minutes longer with PO administration than it was with IN administration. Overall behavior under PO and IN was similar. However, more movement and less sleep were shown in subjects under IN than those under PO toward the end of the dental session. All vital signs were stable throughout the procedures and showed no significant differences between PO and IN administration. (*J Dent Child*. 2004;71:126-130)

KEYWORDS: ANXIOUS PEDIATRIC PATIENTS, MIDAZOLAM, NASAL SEDATION, ORAL SEDATION

Delivering dental care to very young pediatric dental patients can be very challenging. These children benefit from conscious sedation, using medications which can be administered effectively, safely, and painlessly, which are beneficial for both the patients and their health care providers.[1]

Midazolam is a popular medication in pediatric dentistry, safety and efficacy of oral and nasal midazolam in infants and children has been reported. Midazolam is a water-soluble benzodiazepine, which is more potent than diazepam,[2] and can be administered through intramuscular, intravenous, rectal, and oral routes.[3] The intranasal route has the potential advantage of rapid absorption, bypassing the first portal pass metabolism.[4] The oral route is the most favorable way to administer this medication in pediatric dentistry, due to the discomfort associated with other routes. The onset of drugs given orally or rectally, however, is slower than if administered nasally.[5,6] Some children still spit out the medication, even with careful administration according to Houpt's recommendation.[7]

The purpose of this study was to:

1. compare the efficacy and safety of midazolam through a single dose of 0.7 mg/kg via oral route (PO) vs 0.3 mg/kg by nasal route (IN);
2. compare the onset time and maximum working times of the 2 regimens (PO and IN midazolam);
3. evaluate and compare the pediatric patients' behavior under the 2 regimens.

*Dr. Lee-Kim is a pediatric dentist in private practice, Seoul, South Korea and a former resident; Dr. Fadavi is professor and residency program director, Dr. Punwani is professor and head, and Dr. Koerber is assistant professor and director of behavioral science, Department of Pediatric Dentistry, University of Illinois at Chicago, Ill.*
*Correspond with Dr. Fadavi at sfadavi@uic.edu*

The hypotheses tested were:

1. The onset time will be faster with nasal administration, since midazolam given nasally bypasses the first hepatic portal system.
2. Behavior during sedation should be similar under the 2 regimens, since these regimens should metabolize through the same mechanism.

## METHODS

### SAMPLES

A total of 40 (19 female, 21 male) subjects were recruited for this IRB-approved study from the patient population of the Department of Pediatric Dentistry at the University of Illinois at Chicago.

The following inclusion criteria were met:

1. children ages 24 to 72 months old who demonstrated Early Childhood Caries (ECC);
2. medically healthy subjects (ASA I) or subjects with well-controlled systemic disease such as asthma, uncomplicated diabetes, etc. (ASA II);
3. subjects in need of 1 or more dental visits for comprehensive dental care, including amalgam and/or composite restorations, pulpotomy procedures, stainless steel crowns, and extractions;
4. subjects with a definitely or slightly negative behavior rating, based on the Frankl Behavior Rating Scale.

The parents or legal guardians were informed about the purpose of this study, and potential risks and benefits associated with it.

### METHOD

Five dental providers (residents and fellows), who had demonstrated similar clinical skills and proficiencies, performed all treatments. Providers were fully aware of the inclusion and exclusion criteria, the use of recording monitors, and dental procedures used for this study. The principal investigator conducted subject selection and random assignment of PO or IN midazolam administration.

### PROCEDURE

All selected subjects received preoperative instructions before the sedation appointment. Subjects were not allowed to eat or drink for at least 4 to 6 hours prior to the sedation appointment and had no signs or symptoms such as fever, runny nose, or cough in the preceding days and immediately prior to sedation. At the sedation appointment, the dental provider evaluated respiration, heart rate, blood pressure, and oxygen saturation prior to administering the sedative medication. Subjects randomly received 0.7 mg/kg PO midazolam HCL (cherry-flavored Versed syrup: 2 mg/1 cc, Roche Laboratories, Inc) or 0.3 mg/kg IN midazolam HCL (Versed vial: 10 mg/2 cc, Roche Laboratories, Inc) based on random assignment to a regimen. The drug was administered PO by either the dental provider or parents using a cup or syringe. The dental provider administered the IN drug with a 1 or 2 cc syringe.

The subject was brought into the sedation room 15 to 20 minutes after PO administration or approximately 5 minutes after IN administration. A pulse oximeter and a precordial stethoscope were used to record respiratory rate (RR), heart rate (HR), oxygen saturation ($O_2$ sat), and blood pressure (BP). All patients received 45% nitrous oxide and 0.9 to 3.6 cc of 2% lidocaine with 1:100,000 epinephrine during the sedation and were restrained in a papoose board without a head holder. The papoose board was used in the pediatric dentistry clinic as a standard of care restraint device for all subjects under sedation. The entire dental procedure was videotaped and vital signs (RR, HR, $O_2$ sat, BP) were recorded every 15 minutes by a trained dental assistant who also recorded the time of the onset and working time after dental procedure completion.

### DATA COLLECTION AND ANALYSIS

Gender, age, race, sex, weight, working time, onset time, and completed treatment were recorded. The videotapes were evaluated and scored independently by blinded and calibrated evaluator using a modified Houpt's behavior rating scale. Intraexaminer reliability was determined after the evaluator watched 3 pilot studies at 3 different times separated by a 1-week interval, with 100% concordance. These 3 pilot studies were not included in the main study. Data were entered into Microsoft Excel Spreadsheet and transferred to SPSS 10.0 (Statistical Package for the Social Sciences, SPSS, Chicago, Ill) software for statistical analysis. Chi-square was used for gender and race, and *t* test was used for evaluating age, weight, onset, and working time. Multivariate analysis of variance (ANOVA) was used to evaluate behavior (BX) and vital signs between PO and IN.

## RESULTS

Forty subjects met inclusion criteria and participated in this study. Demographic and weight distribution of PO and IN are displayed in Table 1. There were no statistical differences in gender, age, and weight between PO and IN administrations ($P \leq .05$). Mean onset time of PO and IN routes was 15.5 (SD±5) minutes and 5.55 (±2.2) minutes, respectively. These differences were statistically significant (T=8.068, df=38,

***Table 1. Demographics of Subjects Based on Gender, Ethnicity, Age, and Weight****

| Route of administration | Gender† | Ethnicity‡ | Age (mos) | Weight (kg) |
|---|---|---|---|---|
| PO | 9 (F)<br>11(M) | 8 (AA)<br>3 (C)<br>9 (H) | 40.8 (±11) | 17.1 (±3.6) |
| IN | 10 (F)<br>10 (M) | 7 (AA)<br>4 (C)<br>9 (H) | 38.5 (±9.8) | 16.2 (±4) |
| *P* Value | NS | NS | NS | NS |

***NS=not significantly at P=.05.**
**†F=female; M=male.**
**‡AA=African American; C=Caucasian; H=Hispanic.**

*P*=.000). Mean working times of PO and IN were 38.1 (±7.58) minutes and 29.3 (±11.6) minutes, respectively. These values showed statistically significant differences (T=2.868, df=38, *P*=.007).

Behavior under sedation was rated every 5 minutes by using Houpt's behavior rating scale for sleep, movement, crying, and overall behavior. Houpt's scale is an ordinal measure and allows the operator to evaluate the behavior during sedation at different time points. Five-minute means of rating scale for sleep in PO and IN are depicted in Figure 1. Five-minute means for (1) movement in PO and IN and (2) crying in PO and IN are depicted in Figures 2 and 3, respectively.

The effect of IN vs PO on behavioral variables was analyzed using a multivariate ANOVA with repeated measures of sleep, movement, and crying and revealed no significant differences between PO and IN administration ($F_{3,27}$=0.407; *P*=.749). However, planned contrasts showed significant differences in behavioral variables at certain times (Table 2). Between 25 and 30 minutes after the sedation began, subjects with IN showed more movement and less sleep than those with PO. Subjects in both groups showed significant changes toward waking between 30 and 35 minutes after administration of sedation.

MANOVA with repeated measures showed no significant differences in vital signs ($O_2$ sat, HR, RR, BR) between PO and IN, recorded every 15 minutes ($F_{15,18}$=0.879; *P*=.595).

## DISCUSSION

Although hypoventilation and hypoxemia are major risks associated with high doses of midazolam, there are few reports of respiratory depression in children.[8] Unlike diazepam, midazolam metabolites are inactive: therefore, patients can be discharged immediately after the dental procedure with midazolam sedation.[9] PO is the most common method of

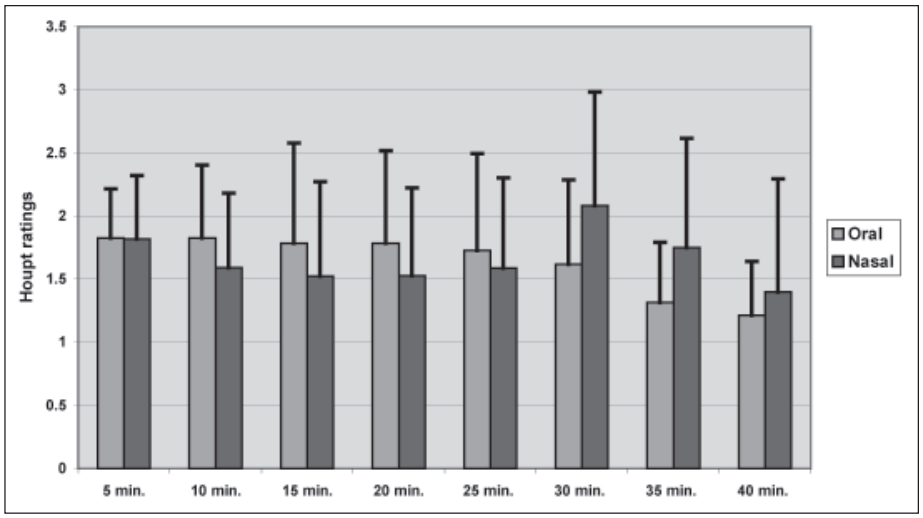


***Figure 1. Comparison of Houpt's BX–sleep scale for intranasal and oral administration (error bars are 1 standard deviation).***

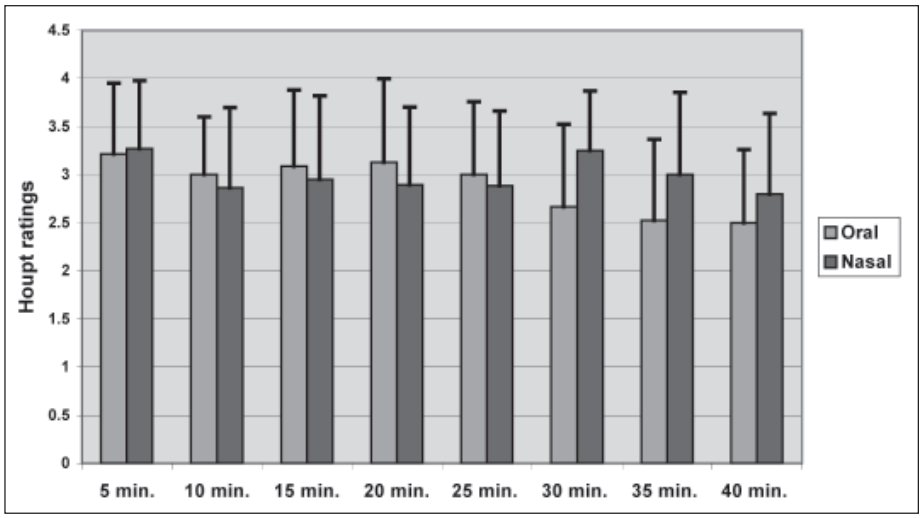


***Figure 2. Comparison of Houpt's BX–movement scale for intranasal and oral administration (error bars are 1 standard deviation).***

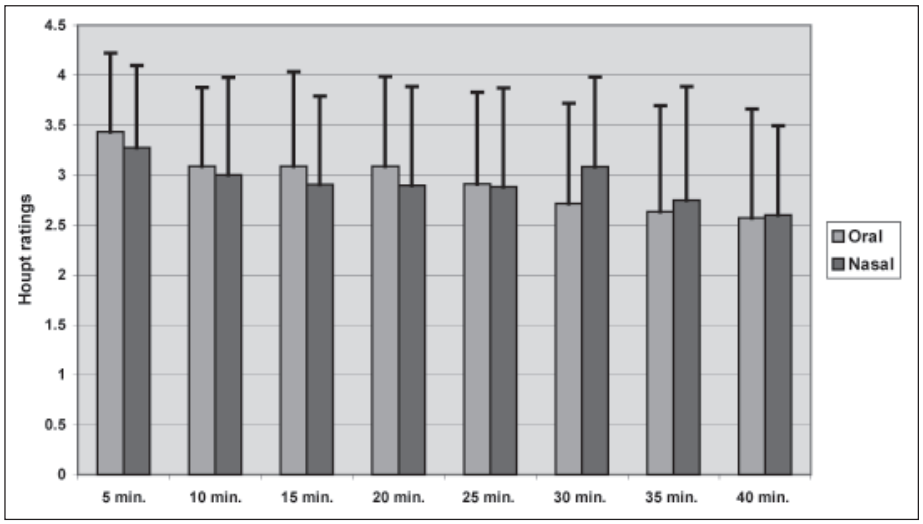


***Figure 3. Comparison of Houpt's BX–crying scale for intranasal and oral administration (error bars are 1 standard deviation).***

**Table 2. Tests of Within-subject Contrasts of Effects of Route of Administration on Behavioral Variables Over Time**

| Source | Variable | Time contrast | F | df | Significance |
|---|---|---|---|---|---|
| Time | Sleep | 30 vs 35 min | 14.8 | 1,29 | .001 |
| | Movement | 30 vs 35 min | 5.5 | 1,29 | .026 |
| | Crying | 30 vs 35 min | 5.29 | 1,29 | .029 |
| Time route | Sleep | 25 vs 30 min | 6.15 | 1,29 | .019 |
| | Movement | 25 vs 30 min | 4.71 | 1,29 | .038 |
| | Crying | 25 vs 30 min | 1.02 | 1,29 | .321 |

administration in pediatric dentistry—more common than intravenous (IV), rectal, or intranasal administration due to:

1. fear of injection (IV);
2. poor and irregular absorption via rectal administration[10];
3. IN administration, which gives a nasal burning sensation.

Fuks et al[11] with random assignment to 0.2 mg/kg or 0.3 mg/kg of IN midazolam in 30 children (age range=20-42 months), documented that IN midazolam had a rapid onset and short duration. Walbergh et al[12] reported the rapid onset of IN midazolam with relatively high plasma concentration. Kupietzky and Houpt[9] discussed the possibility that the IN route led to the drug being absorbed in the brain and cerebrospinal fluid through the cribriform plate; however, the exact mechanism of IN medication absorption is not fully understood. This study's data demonstrates that IN drug administration leads to faster onset time, and somewhat shorter working time. This suggests that both absorption and metabolism of midazolam is faster with IN administration.

Connors et al[13] found that there were no significant differences in behaviors and alteration of vital signs of patients undergoing laceration repair under nasal and oral midazolam administration. This study showed similar results: there were no statistically significant differences in overall behavior and alterations of vital signs ($O_2$ sat, HR, RR, BP) between PO and IN midazolam regimens for pediatric dental patients undergoing dental procedures. Subjects under IN, however, showed more movement and less sleep between 25 and 30 minutes after sedation began, indicating that subjects with IN administration were waking up from sedation about 5 to 10 minutes before the PO subjects.

Forty-five percent $N_2O$ was used in this study for all the cases and may have prolonged the working time and given analgesic effects. Use of a papoose board did not have any noticeable effects on behavior scale assessment. Any irrational or subtle effects were common for both experimental groups. If the child moved, feet, head, and hand movements were very easily identifiable and recorded according to the behavior scale. It is possible that some of the IN midazolam was swallowed, but the authors were not able to quantify the amount. The swallowed amount was not therefore measured or included in the results. In addition, a cross-over design that tested the same subject for both PO and IN routes would have been preferable, since the same subject would be his/her own control. Midazolam sedation with or without $N_2O$ can be an objective for a future study.

This study's possible limitations are:

1. The operator and assistant were not blind to the administration route, which could have compromised the onset time accuracy since these were subjective ratings of the operator and assistant.
2. Multiple operators were used, whose experiences and ratings of onset and working time may have varied slightly.

Future studies should consider blinding the operator and assistant to the route of administration.

## CONCLUSIONS

The following conclusions were made based on this study:

1. Mean onset time was approximately 3 times faster with IN administration compared to PO administration.
2. Mean working time was approximately 10 minutes longer with PO administration than it was with IN administration.
3. Overall behavior under PO and IN was similar. However, more movement and less sleep were shown in subjects under IN than those under PO toward the end of the dental session.
4. All vital signs were stable throughout the procedures and showed no significant differences between PO and IN administration.

## REFERENCES


1. Baraff LJ. Conscious sedation of children. *Ann Emerg Med*. 1994;24:1170-1172.
2. Holroyd SV, Wynn RJ, Requa-Clark B. Clinical Pharmacology in Dental Practice. 4th ed. St. Louis, Mo. Mosby Saunders. 1988:81-103.
3. Malinovsky JM, Populaire C, Lepage JY, Lejus C, Pinaud M. Premedication with midazolam in children: Effect of intranasal, rectal and oral routes on plasma midazolam concentration. *Anesthesia*. 1995;50:351-354.
4. Hussain AA. Mechanism of nasal absorption of drugs. *Prog Clin Biol Res.* 1989;292:261-272.
5. Lejus C, Renaudin C, Testa S, Malinorsk JM, Vigier T, Souron R. Midazolam for premedication in children: Nasal versus rectal administration. *Eur J Anaesthesiol.* 1997;14:244-249.
6. Wilton NCT, Leigh J, Pandit UA. Preanesthetic sedation of preschool children using intranasal midazolam. *Anesthesiology*. 1988;69:972-975.
7. Houpt MI, Weiss NJ, Koenigsberg SR, Desjardin PJ. Comparison of chloral hydrate with and without promethazine in the sedation of young children. *Pediatr Dent.* 1985;7:41-46.
8. Sievers TD, Yee JD, Foley ME, Blanding PJ, Berde CB. Midazolam for conscious sedation during pediatric oncology procedures: Safety and recovery parameters. *Pediatrics*. 1991;88:1172-1179.

9. Kupietzky A, Houpt M. Midazolam: A review of its use for conscious sedation in children. *Pediatr Dent.* 1993;15:237-241.
10. Payne K, Mattheyse FJ, Liebenberg D, Dawes T. Pharmacokinetics of midazolam in pediatric patients, *Eur J Clin Pharmacol*. 1989;37:267-272.
11. Fuks A, Kaufman E, Ram D, Hovav S, Shapira J. Assessment of two doses of intranasal midazolam for sedation of young pediatric dental patients. *Pediatr Dent*. 1994;16:301.
12. Walbergh EJ, Wills RJ, Eckhert J. Plasma concentration of midazolam in children following intranasal administration. *Anesthesia*. 1991;74:233-235.
13. Connors K, Terndrup TE. Nasal versus oral midazolam for sedation of anxious children undergoing laceration repair. *Ann Emerg Med*. 1994;24:1074-1079.