Scientific Article

Comparing the safety, efficacy and recovery of intranasal midazolam vs. oral chloral hydrate and promethazine

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Abstract

Purpose: *The purpose of this study was to compare the safety, efficacy and recovery time of intranasal midazolam spray administered using an atomizer to orally administered chloral hydrate and promethazine for the sedation of pediatric dental patients.*

Methods: *A randomized double-blind crossover study design was utilized in which 31 patients (mean age 41.8 months, range 26-58 months) underwent two restorative dental appointments. At one appointment, subjects received 0.2 mg/kg intranasal midazolam; at the other appointment subjects received 62.5 mg/kg chloral hydrate with 12.5 mg promethazine. Administered at each appointment was 25% – 50% $N_20/0_2$. Physiologic parameters (heart rate, blood pressure, respiratory rate, oxygen saturation) and behavior assessments (crying, movement, sleep) using the Houpt Sedation Rating Scale were recorded at baseline and every five minutes during treatment. Overall behavior was assessed at baseline and at the end of treatment. Following treatment, a modified Vancouver Recovery Scale was used to determine the length of time it took each subject to meet established discharge criteria.*

Results: *There were no clinically significant differences in physiologic parameters, however a statistically significant decrease in systolic and diastolic blood pressure was observed in patients sedated with chloral hydrate/promethazine. There were no significant differences in behavior between groups. Patients sedated with intranasal midazolam slept less and recovered quicker than patients sedated with oral chloral hydrate/promethazine.*

Conclusions: *Intranasal midazolam administered using an atomizer is as safe (as assessed by physiologic parameters) and effective (as assessed by behavior ratings) as oral chloral hydrate/promethazine for conscious sedation of pediatric dental patients. (Pediatr Dent 23: 424-430,2001)*

According to the American Academy of Pediatric Dentistry (AAPD), the goals of conscious sedation in pediatric dentistry are to: facilitate quality care, promote a positive response to treatment, minimize obstructive behavior, maintain safety and return the patient to a physiologic state where safe discharge is possible.[1] The profession of pediatric dentistry has long searched for the ideal agent or regimen that will allow all of these goals to be met. Despite the fact that dozens of drugs have been used for conscious sedation both alone and in combination and in varying routes of administration, the drug regimen that consistently and effectively meets the AAPD goals for conscious sedation has yet to be found.

Chloral hydrate (Noctec®, Geneva Pharmaceuticals, Broomfield CO) is a sedative-hypnotic agent that was first synthesized in 1832 and is widely used in both pediatric medicine and dentistry.[2,3] Used alone or with a co-medication such as hydroxyzine or promethazine, chloral hydrate is the most frequently used oral agent for conscious sedation in pediatric dentistry.[4,5] Despite its popularity, the use of chloral hydrate for conscious sedation in pediatric dentistry is less than ideal. Oral chloral hydrate has variable absorption, causes gastric irritation and has a bitter taste.[6,7] Chloral hydrate may cause respiratory depression and has a wide range of effectiveness.[6,8,10] Trichloroethanol, the active metabolite of chloral hydrate, has a half-life of eight to 40 hours which may prolong patient recovery.[2,11] There is no known reversal agent for chloral hydrate.

Midazolam HCL (Versed®, Roche Laboratories, Nutley NJ), first synthesized in 1976, is a benzodiazepine that possesses anxiolytic, sedative, anticonvulsant, skeletal muscle relaxant and anterograde amnesic properties.[12] Midazolam has high lipid solubility, which provides rapid onset of action, and a half-life of one to four hours, which provides for a rapid rate of elimination and recovery.[13] Midazolam is also advantageous because it has no active metabolites and because it is able to be reversed with an antagonist, flumazenil (Romazicon®, Roche Laboratories, Nutley NJ).[14] Midazolam has multiple routes of administration including: oral, rectal, intravenous, sublingual and intranasal (drops or spray), which have become popular in both pediatric medicine and dentistry.[15-19]

Hartgraves and Primosch[16] compared the effectiveness of 0.2 mg/kg intranasal midazolam, administered as drops, to 0.5 mg/kg oral midazolam/25 mgs hydroxyzine for conscious sedation of 100 children ages 1.5-6 years. All patients received 40% $N_20/0_2$ and the following treatment was rendered: "extractions, restorations and pulpotomies." Two-thirds of the sedation appointments in both groups were rated satisfactory by non-blinded evaluators. Intranasal administration involved dripping half the volume of midazolam into each nostril with a 1cc needleless syringe, but this appeared to be noxious for many

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Fig 1. Midazolam spray eing expelled from the atomizer

subjects. Hartgraves and Primosch speculated that administration of midazolam with an atomizer would be less irritating.

Fuks et al[17] compared 0.2 mg/kg to 0.3 mg/kg intranasal midazolam, administered as drops, for conscious sedation of pediatric dental patients in a double-blind crossover study. All patients received 50% N_2O/O_2 and required "two restorative visits." Successful sedation, described as "minimal crying and/or movement that interrupted treatment," was observed in all subjects. Fuks et al concluded that 0.2 mg/kg was the preferred dose.

Henry et al[18] utilized beagle dogs to investigate the pharmacokinetics of midazolam following intranasal drop, intranasal atomizer and intravenous administrations. Both intranasal routes resulted in significantly higher levels of midazolam in the cerebrospinal fluid than in plasma. Intranasal administration of midazolam using the atomizer resulted in significantly higher cerebrospinal fluid levels than did intranasal administration of drops. No published studies have investigated the administration of midazolam via nasal atomizer in humans.

The purpose of this study was to evaluate the safety, efficacy and recovery time of midazolam administered by nasal atomizer compared to chloral hydrate and promethazine administered orally to pediatric dental patients.

Methods

Subjects

This study was approved by the University of Michigan and the Mott Children's Health Center Human Subjects Committees. The procedures, possible discomforts or risks as well as possible benefits were explained fully to the parents of the subjects involved, and informed consent was obtained prior to the investigation. Preoperative instructions including dietary precautions consistent with AAPD guidelines[1] were provided. Subjects were between the ages of 24 and 54 months and were healthy (ASA I). Thirty-one subjects were included in the study following uncooperative, obstructive or otherwise negative behavior at initial examination. Each child needed at least two quadrants of restorative dentistry and had no previous sedation experience. Subjects were excluded from the study if they failed to keep both sedation appointments.

Study design

A double-blind, crossover design was used for this study. Patients randomly received either 0.2 mg/kg midazolam HCL (Versed®, Roche Laboratories, Nutley, NJ) via nasal atomizer or 62.5 mg/kg chloral hydrate (Noctec®, Geneva Pharmaceuticals, Broomfield CO) and 12.5 mg promethazine HCL (Phenergan®, Steris Laboratories, Phoenix, AZ) orally. Subjects who received intranasal midazolam at their first operative appointment were given oral chloral hydrate and promethazine at their second appointment and vice versa. All patients received N_2O/O_2 in a range of 25-50% during treatment.

The midazolam was administered by a metered-dose atomizer which originally held Nasalcrom® (Cromolyn sodium nasal solution, Fisons Pharmaceuticals Corp. Rochester, NY). These bottles were emptied, sterilized and calibrated to determine the volume of midazolam delivered per spray (Figure 1). The concentration of midazolam placed in the atomizer was 5mg/ml. A table based on patient weight was devised to determine number of sprays necessary for the 0.2 mg/kg dose of midazolam (Table 1).

Table 1. Number of midazolam sprays for 0.2 mg/kg dose

Patient weight	Patient weight	midazolam dose	mgmean	# of sprays
lbs	kgs	0.2 mg/kg		
14 – 19	6.4 - 8.6	1.3 - 1.7	1.5	3
20 - 24	9.1 - 10.9	1.8 - 2.2	2.0	4
25 – 30	11.4 - 13.6	2.3 - 2.7	2.5	5
31 – 35	14.1 - 15.9	2.8 - 3.2	3.0	6
36 – 40	16.4 - 18.2	3.3 - 3.6	3.5	7

At the beginning of each appointment, medical history and NPO status were reviewed with the parent. Physiologic parameters were obtained using a Criticare Systems Model 507S Series Patient Monitor (Criticare Systems, Inc., Waukesha, WI) for respiration rate (RR), pulse (HR), blood pressure (BP) and oxygen saturation (O_2 Sat). After baseline measurements were obtained, patients were escorted to a separate room for drug administration. Patients either received intranasal midazolam spray 10 minutes prior to the start of treatment or received oral chloral hydrate and promethazine 30 minutes prior to the start of treatment. The operating dentist, assistant and independent observer who recorded vital signs and assessed behavior and recovery time were blinded to the drug regimen used.

Patients were brought into a treatment room, leads were placed for the Criticare monitor and vital signs and behavior assessment were recorded. Patients were then placed in a Papoose Board (Olympic Medical Group, Seattle, WA). Safety was assessed by vital signs and efficacy was assessed by behavioral parameters that were recorded by an independent observer at specified pre-treatment events and every five minutes during treatment.

Behavioral assessment

The Houpt Sedation Rating Scale was utilized for behavior assessment (Table 2). Three training sessions were held to familiarize 10 observers in the use of this rating scale. Videotapes of pediatric dental patients undergoing conscious sedation were shown during these training sessions; these videotapes demonstrated all behavior ranges for sleep, movement, crying and overall behavior employed by the Houpt Scale. Differences in ratings for each behavior were made clear to the observers by stopping the videotape and highlighting specific behavior corresponding to each score in the Houpt Scale.

The observers were calibrated for agreement at the end of each training session. At the conclusion of the third training session, the observers were shown a new videotape of a patient undergoing conscious sedation. This videotape was stopped six times and ratings were made for sleep, movement, crying and overall behavior. The observers demonstrated an 88% agreement for all behaviors. One of these observers recorded behavior using the Houpt Scale for each sedation appointment.

Recovery assessment

The Vancouver Sedative Recovery Scale[20] was modified to better reflect the dental setting and was used to assess recovery at two-minute intervals following the termination of dental treatment (Table 3). This scale utilized six-point non-parametric scoring to assess the level of patient alertness. The range for the modified Vancouver Recovery Scale is from patient fully awake and oriented (score of 1) through patient with eyes closed not arousable upon mild stimulation (score of 6). Successful recovery was accorded to those subjects who had met established discharge criteria. The criteria were reflected in a modified Vancouver Sedative Recovery Scale score of 1 (patient fully awake and oriented) or 2 (eyes open, responds to verbal questions). Parents were contacted by phone one day after the second operative visit to determine which drug regimen they preferred for the sedation of their child.

Results

The study population consisted of 23 males and 8 females who ranged in age from 26 to 58 months (mean 41.8 ±11.4). The weights of the patients ranged from 13.2 to 21.4 kg (mean 16.4 ±2.3). The mean dose of midazolam administered was 3.26 mg or seven sprays, while the mean dose of chloral hydrate was 1019 mg. All subjects who received chloral hydrate also received 12.5 mg promethazine. Mean treatment time for patients receiving midazolam was 42.1 minutes (±19.4) and the mean treatment time for patients receiving chloral hydrate/promethazine was 48.9 minutes (±22.8).

Physiologic measure

A two-tailed paired t-test was employed to determine significance in mean physiologic parameters between the two drug groups across five-minute time periods. The only physiologic variables showing a statistically significant difference ($P < 0.05$) between the two groups were mean systolic and diastolic BP. Subjects receiving chloral hydrate/promethazine had significantly lower systolic BP at rubber dam placement and minutes 5, 10, 15, 20, 40, 45, 50 and 55 (Figure 2). Diastolic BP was significantly lower in the same subject group at treatment start and minutes 5, 10, 15, 20, 35 and 40 (Figure 3). There were no statistically significant differences between groups for mean heart rate (Figure 4), respiratory rate (Figure 5) or O_2 saturation (Figure 6). There was one incident of vomiting for a patient sedated with chloral hydrate and promethazine and none for patients sedated with midazolam.

Table 2. Houpt Sedation Rating Scale

Sleep	Score
Fully awake, alert	1
Drowsy, disoriented	2
Asleep	3
Movement	
Violent movement interrupting treatment	1
Continuous movement making treatment difficult	2
Controllable movement that does not interfere with treatment	3
No movement	4
Crying	
Hysterical crying that demands attention	1
Continuous, persistent crying that makes treatment difficult	2
Intermittent, mild crying that does not interfere with treatment	3
No crying	4
Overall Behavior	
Aborted	1
Poor - treatment interrupted, only partially completed	2
Fair - treatment interrupted, but eventually all completed	3
Good - difficult, but all treatment performed	4
Very Good -some limited crying or movement	5
Excellent - no crying or movement	6

Table 3. Modified Vancouver Sedative Recovery Scale

	Score
Fully awake and oriented	1
Eyes open, patient responds to verbal questions	2
Eyes open, does not respond to verbal questions	3
Eyes closed, patient does not respond to verbal questions	4
Eyes closed, patient arousable on mild stimulation	5
Eyes closed, patient not arousable on mild stimulation	6

Behavior

The four categories of the Houpt Sedation Rating Scale (crying, movement, sleep and overall behavior) were used to compare the efficacy of midazolam vs. chloral hydrate/promethazine. For the purpose of this study, a Houpt Scale score of 1

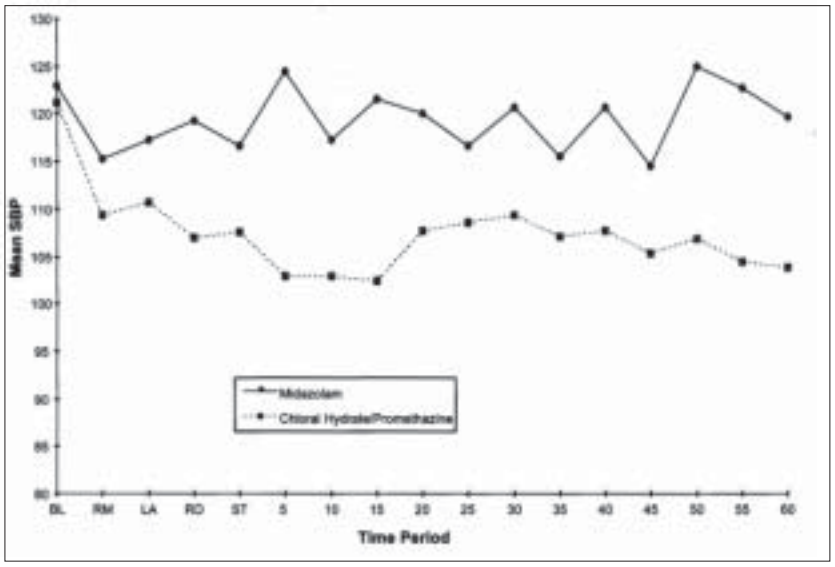

Fig 2. Mean systolic blood pressure

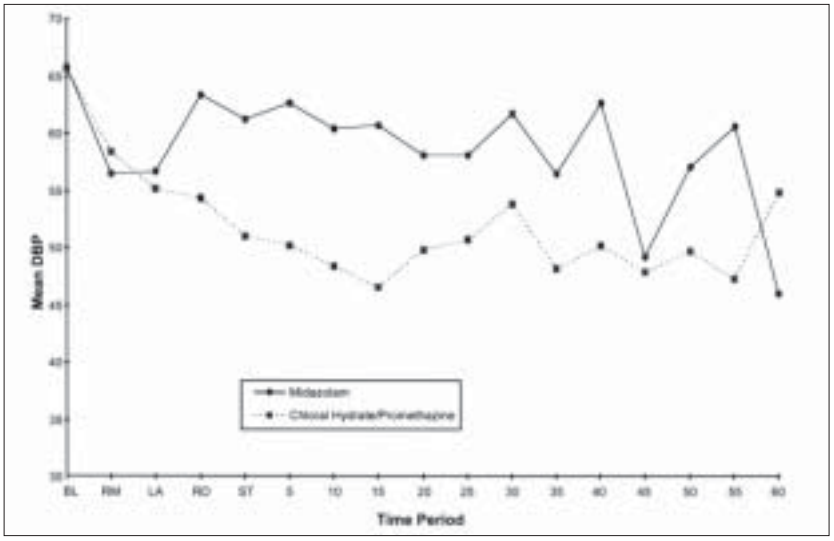

Fig 3. Mean diastolic blood pressure

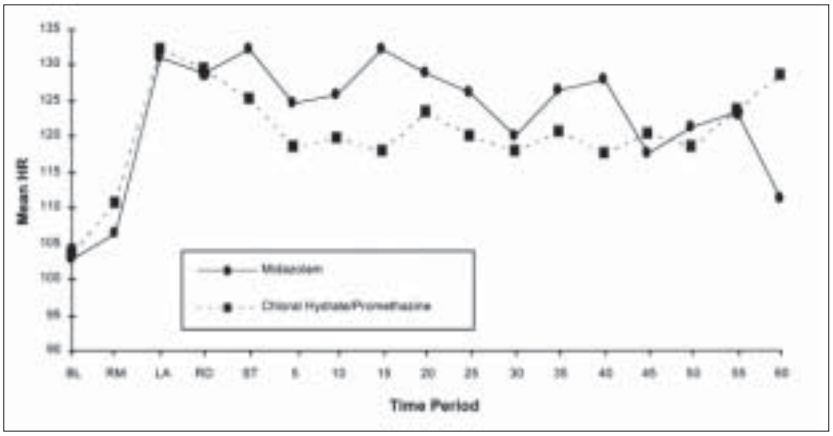

Fig 4. Mean heart rate

for crying (hysterical crying that demands attention) or 2 (continuous, persistent crying that makes treatment difficult) was considered disruptive. A two-tailed Fischer's Exact Test ($p<0.05$) was utilized to compare percentage of subjects with disruptive crying at baseline and during treatment. No significant differences were found in the percentage of patients with disruptive crying between midazolam and chloral hydrate/promethazine groups (Figure 7).

A Houpt Scale score of 1 for movement (violent movement that interrupts treatment) or 2 (continuous movement that makes treatment difficult) was deemed disruptive. No significant differences ($p< 0.05$) were found in the percentage of patients with disruptive movement between midazolam and chloral hydrate/promethazine groups (Figure 8).

The McNemar test of symmetry for two related outcomes showed a significantly higher percentage of patients sedated with chloral hydrate/promethazine who slept during treatment than patients sedated with midazolam (Figure 9).

There were no significant differences between midazolam and chloral hydrate/promethazine groups for overall behavior ($p<0.05$). At baseline, 26 of 31 subjects who received midazolam and 25 of 31 subjects who received chloral hydrate/promethazine had Houpt Scale Overall Behavior scores of 5 (very good) or 6 (excellent). At the end of treatment, 21 of 31 subjects who received midazolam and 22 of 31 subjects who received chloral hydrate/promethazine had Houpt Scale Overall Behavior scores of 5 (very good) or 6 (excellent) (Table 4).

Recovery

The modified Vancouver Recovery Scale was used to assess recovery during the 20-minute post-operative period. Patients sedated with intranasal midazolam met established discharge criteria more quickly than patients sedated with chloral hydrate/promethazine. Thirty of 31 patients in the midazolam group and 24 of 31 patients in the chloral hydrate/promethazine group achieved a score of 1 (fully awake and oriented) or 2 (eyes open, patient responds to verbal questions) on the modified Vancouver Sedative Recovery Scale (Figure 10). This difference was considered significant using the Log-Rank statistic in a survival analysis ($p=0.0153$). Parents were asked after the second appointment which regimen they preferred; there was no significant difference in the parent's preference for a particular regimen. Sixteen parents stated they

preferred intranasal midazolam, 12 preferred oral chloral hydrate/promethazine and three were undecided.

Discussion

This is the first study to examine the use of an atomizer to administer intranasal midazolam for conscious sedation of pediatric dental patients. This study demonstrated that midazolam spray delivered by an atomizer provided conscious sedation that was as safe and effective as orally administered chloral hydrate/promethazine. Safety, as assessed by the physiologic parameters of blood pressure, heart rate, respiratory rate and oxygen saturation, was similar between drug regimens. All of the physiologic parameters fell within normal ranges for healthy pediatric patients. The lower blood pressure for patients sedated with chloral hydrate/promethazine was not clinically significant and was consistent with chloral hydrate acting as a central nervous system depressant.

The Houpt Sedation Rating Scale was used to assess efficacy because of its demonstrated reliability and frequent use in other studies.[21] The similar crying, movement, and overall behavior scores indicate that intranasal midazolam was as effective as oral chloral hydrate/promethazine for conscious sedation. Significantly more patients treated with chloral hydrate/promethazine slept during treatment than those treated with midazolam. This result is consistent with previous studies that reported patients sedated with chloral hydrate frequently fall asleep during treatment.[6,9] The finding of increased sleep in patients sedated with chloral hydrate/promethazine compared to midazolam will provide guidance to the pediatric dentist when choosing a sedation regimen. Pediatric dentists who prefer a sedated, but awake patient, may choose midazolam over chloral hydrate/promethazine.

Nitrous oxide was utilized in this study in a range of 25-50%. This range is consistent with most practicing members of the AAPD.[22] Other studies have demonstrated that 50% nitrous oxide will modify behavioral responses for pediatric dental patients during conscious sedation and may attenuate physiological responses.[23-25] The disruptive crying and movement observed in this study may have been modified by the varying amount of nitrous oxide.

One purpose of this study was to assess the time and quality of patient recovery. Prolonged recovery time during conscious sedation of pediatric dental patients is a definite clinical complication. No other published study has examined recovery quality and time when intranasal midazolam was used for the conscious sedation of pediatric dental patients. Patients sedated with intranasal midazolam achieved successful recovery more quickly than patients sedated with chloral hydrate/promethazine. Intranasal midazolam offers a distinct clinical advantage over orally administered chloral hydrate/promethazine for the conscious sedation of pediatric dental patients because of its faster recovery time.

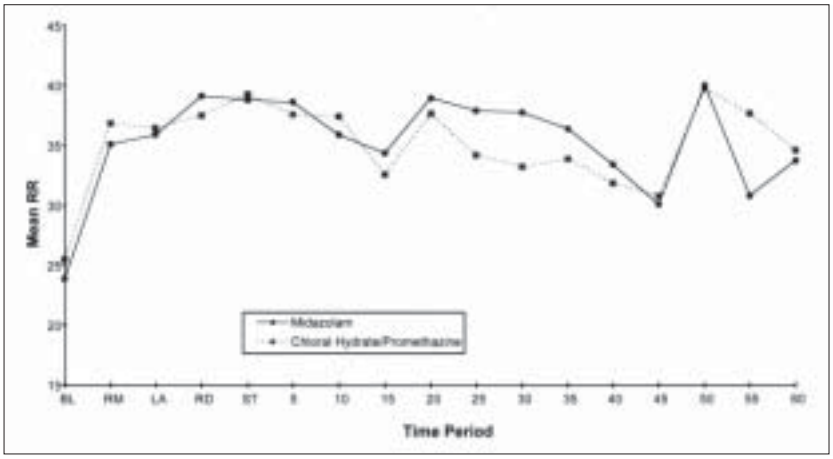

Fig 5. Mean respiratory rate

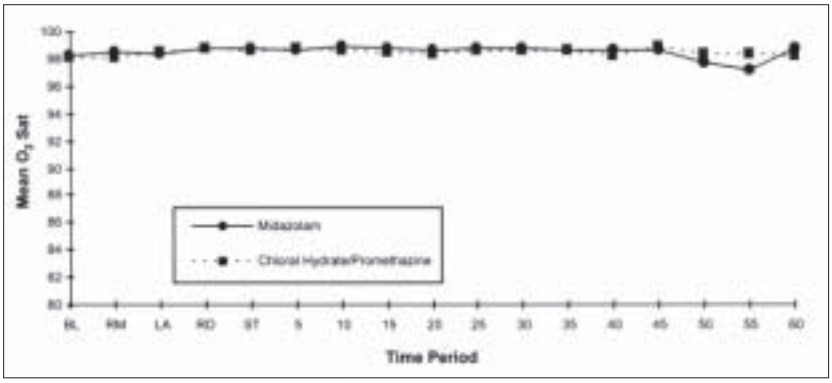

Fig 6. Mean oxygen saturation

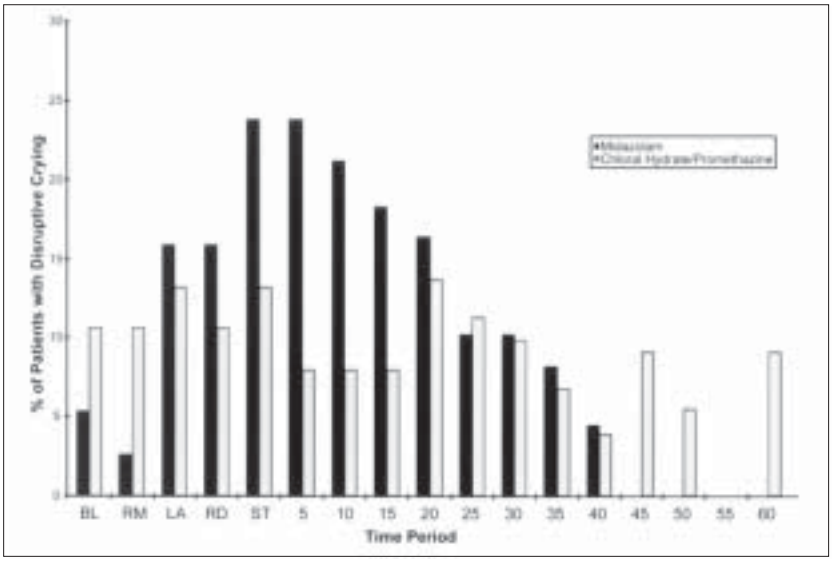

Fig 7. Percentage of subjects with disruptive crying

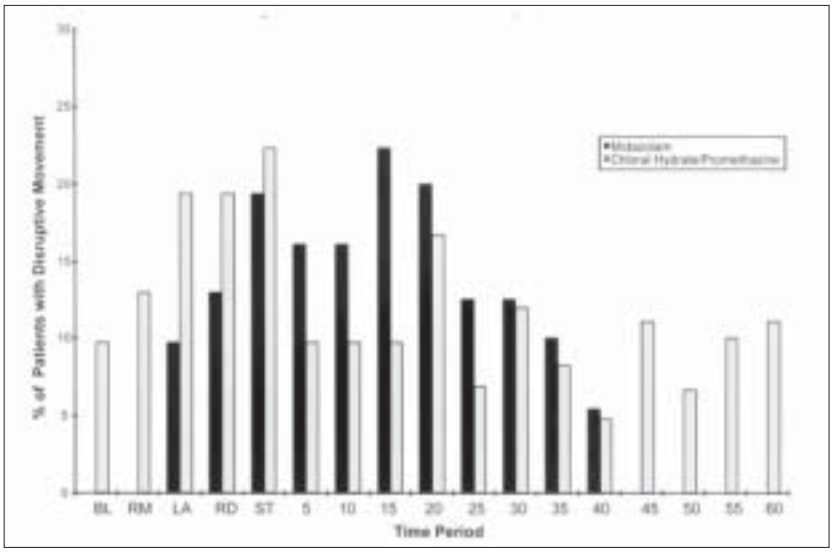

Fig 8. Percentage of subjects with disruptive movement

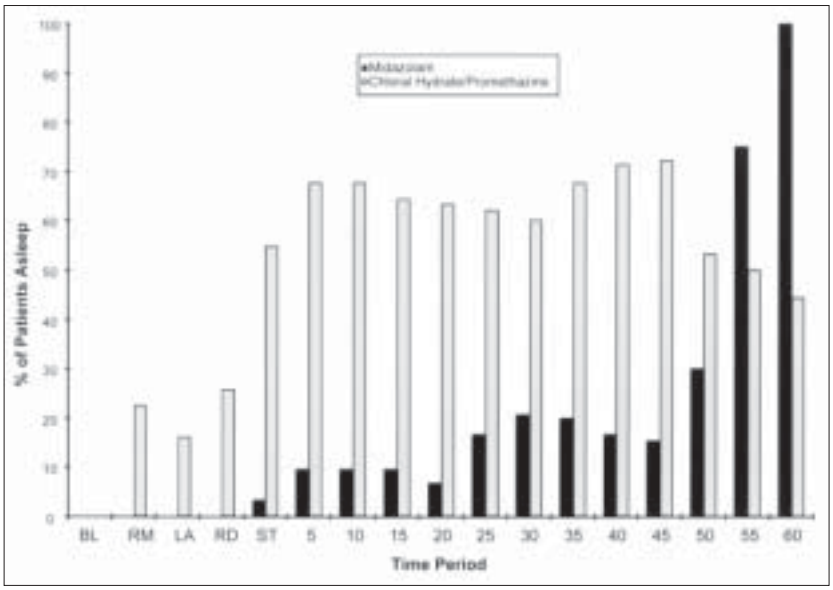

Fig 9. Percentage of subjects asleep

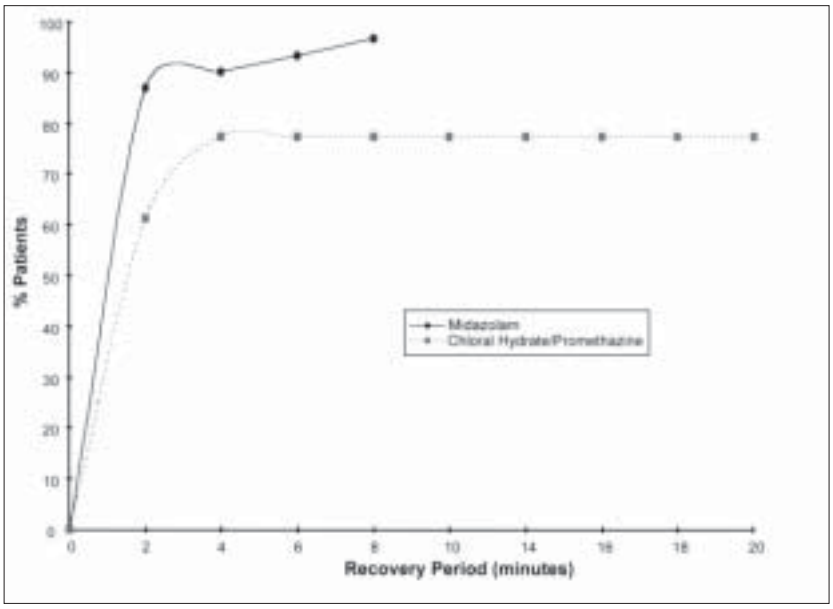

Fig 10. Survival analysis of recovery effectiveness as assessed by percentage of subjects with recovery ratings of 1 or 2 (Modified Vancouver Recovery Scale)

Table 4. Number of Patients with Very Good or Excellent Overall Behavior Ratings (n=31)

	Midazolam	Chloral hydrate/ promethazine	Significance
Baseline	26	25	N.S.
End of Treatment	21	22	N.S.

The adverse event of vomiting for the one patient in the chloral hydrate group is not unusual. Chloral hydrate is a known gastric irritant and emesis is a frequent side effect.[6,9,26] The use of an antihistamine such as hydroxyzine or promethazine has been shown to reduce this untoward effect.[26] The combination of chloral hydrate and promethazine in this study was designed to minimize vomiting. An untoward effect for patients receiving intranasal midazolam was nasal burning and crying reported anecdotally after administration. This effect has been noted by other investigators.[27,28] This burning was likely the result of the alcohol content and low pH of the intravenous midazolam solution used in this study. The clinical effect of nasal burning may be lessened with the use of a topical lidocaine spray as suggested by Lugo *et al*.[29]

A practical concern for the clinician considering conscious sedation may be the cost of medicaments.[30] The cost of midazolam for this study was $18 per 2 ml vial. Because considerable dead space exists at the bottom of the atomizer, two vials of midazolam were required for each child undergoing sedation. The total realized cost of midazolam per sedation therefore was $36, compared to approximately $2 for the chloral hydrate and promethazine. A delivery vehicle that did not have dead space and a formulation of midazolam that did not cause nasal burning would address the two main problems with this regimen.

Conclusions

1. Intranasal midazolam spray administered using an atomizer is as safe and effective as oral chloral hydrate and promethazine for conscious sedation of pediatric dental patients.
2. Subjects sedated with chloral hydrate and promethazine slept significantly longer than those sedated with intranasal midazolam.
3. Subjects sedated with intranasal midazolam recovered more quickly than those sedated with chloral hydrate and promethazine.

Acknowledgements

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