Comparison of Chloral Hydrate, Meperidine, and Hydroxyzine to Midazolam Regimens for Oral Sedation of Pediatric Dental Patients

Jyoti Chowdhury, BDS, MPH[1] Kaaren G. Vargas, DDS, PhD[2]

Abstract

Purpose: The purpose of this retrospective study was to compare the effects of oral administration of a combination of chloral hydrate (CH) 25 mg/kg, hydroxyzine (H) 1 mg/kg, and meperidine (M) 1 mg/kg to midazolam 0.65 mg/kg using 50% nitrous oxide (N_2O) on behavioral and physiological parameters of young children sedated for dental procedures. Factors associated with sedation effectiveness were identified, including age, preoperative behavior, and type of procedure.

Methods: Records of 116 sedation sessions of 66 healthy, uncooperative children ages 24 to 60 months at The University of Iowa Centers for Disabilities and Development were reviewed. Patients received 1 of the 2 regimens. Intraoperative behavior was rated using a dichotomous scale. Physiological variables including heart rate and oxygen saturation were recorded at baseline and at 10-minute intervals of the session. Data were analyzed using SPSS Version 9.

Results: Overall, 81% of sessions were rated successful. Sedation sessions using CH+H+M combination had significantly higher success rate ($P<.01$, odds ratio=3.38, 95% confidence interval=1.06 to 7.15) compared to sessions with midazolam. Sedation success was not associated with age, preoperative behavior, or type of dental procedure performed. Physiological variables were within the normal range for both regimens, although midazolam regimen recorded higher heart rates.

Conclusions: CH+H+M combination using 25 mg/kg CH resulted in significantly more effective sedation sessions compared to midazolam. Both regimens used 50% N_2O and were found to be safe. (Pediatr Dent 2005;27:191-197)

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A 1983 survey of Diplomates of the American Academy of Pediatric Dentistry (AAPD)[1] revealed that chloral hydrate (CH) was used either alone or in combination in 62% of all sedations. Later surveys of AAPD members[2-4] confirmed that oral CH and hydroxyzine (H) with nitrous oxide (N_2O) was the most frequently used sedative drug regimen. Results with CH and H were reported to be unpredictable and unsatisfactory.[5] Other agents and combinations continue to be investigated. Midazolam is routinely used in pediatric dentistry for short procedures because of its faster onset of action, quick recovery time, and reported amnesic effects.[6-8] Recent studies have investigated regimens using midazolam with H[9] and CH[10] with varying results. Meperidine (M) is a narcotic analgesic that has been used with CH and H previously[12-14] and, more recently, with midazolam,[15] with the expectation that it will reduce arousal from painful stimuli.

Due to the risk of cardiovascular and respiratory depression from drug interaction,[11] considerable concern and confusion exists because there is no consensus about dosages of agents used in combination sedation regimens for pediatric dental procedures. For example, Nathan and West[12] reported significantly more successful sedation sessions with the addition of 1.5 mg/kg M to a combination of 50 to 70 mg/kg CH and 25 mg H with 60% N_2O/O_2 in a retrospective study of 135 pediatric dental patients 18 to 60 months in age. Similarly, Poorman et al[13] reported

[1]*Dr. Chowdhury was a resident, Pediatric Dentistry Program, and Dr. Vargas is associate professor, Department of Pediatric Dentistry and Dow's Institute of Dental Research, both at The University of Iowa, College of Dentistry, Iowa City, Iowa.*
Correspond with Dr. Vargas at kaaren-g-vargas@uiowa.edu

higher success rates, but no statistical difference by the addition of 0.5 mg/kg M to 40 mg/kg CH and 25 mg H with 50% N_2O/O_2 in a double blind study with 40 children.

This study's purpose was to evaluate the effectiveness and safety of sedation using 25 mg/kg of CH in combination with H and M and to compare it to midazolam, with both regimens using a fixed level of N_2O. The safety and influence of the 2 regimens on physiological variables were also examined. In addition, the study investigated the influence of factors such as age and preoperative behavior on the outcome of sedation.

Methods

Selection of subjects

After Institutional Review Board approval was obtained, 627 records were reviewed of sedation sessions performed at the Center for Disabilities and Development (CDD) at The University of Iowa, Iowa City, Iowa between January 1998 and June 2002. Of these, 116 records of sedation sessions of 66 children were selected based on the following criteria. All subjects:

1. were between 24 to 60 months of age;
2. were in good health without special physical/psychological needs, including mental retardation;
3. were not allergic to drugs used for sedation;
4. exhibited fearful or refractory behavior at previous dental appointments, as documented by Frankl's behavior rating scale[17];
5. had complete standardized documentation pertaining to age, weight, treatment requirements, drug regimen with dosage, latent period, monitors used, physiological variables, type(s) of procedure(s) performed, assessment of intraoperative behavior, recovery, and discharge.

Drug regimen

The following drug regimens were used:

1. 25 mg/kg CH (Morton Grove Pharmaeuticals, Morton Grove, Ill)+1 mg/kg H (Ivax Pharmaeuticals, Miami, Fla)+1 mg/kg M (Abbott Laboratories, Chicago, Ill)+50% N_2O inhalation;
2. 0.65 mg/kg midazolam HC l (Bedford Labs, Bedford, Ohio)+50% N_2O inhalation.

Procedure

After an initial examination that included radiographs whenever possible, treatment needs and behavioral ratings were recorded and preoperative written instructions—including dietary restrictions, escort policy, and explanation of the sedation procedure including risks, and benefits, and recovery—were given to the parent or legal guardian. A comprehensive physician evaluation form for sedation with oral agents in combination with N_2O inhalation was also included.

After discussing the risks and benefits of the procedure with sedation, each parent or guardian gave informed consent for the sedation either in person or through standard University of Iowa Hospitals and Clinics (UIHC)-monitored telephonic consent. The health history was reviewed with the caregiver, usually a parent, on the day of sedation. Children were weighed using a standard hospital scale (calibrated annually) at the CDD if they had:

1. their most recent history and physical conducted within 30 days of the sedation appointment;
2. nothing by mouth for at least 6 hours prior;
3. no medical condition that contraindicated sedation.

The standard protocol included oral administration of either midazolam (0.65 mg/kg) or a "cocktail" consisting of CH 25 mg/kg, H 1mg/kg, and M 1mg/kg. The drugs were drawn and flavored with grape syrup by the operator and administered by cup to the child by the parent. If the child refused to take the medication, the operator used a needleless 10 ml disposable syringe to deposit the drug in the buccal vestibule. No additional drug was administered if the child spat out the drug or vomited. The number of children who spat out the drug was not recorded. The patient, accompanied by the caregiver(s), remained in a "quiet" family lounge after ingesting the sedative. A latent period of 45 minutes was given for children receiving CH+H+M regimen and 25 minutes for those receiving midazolam.

After the latent period, the patient was separated from the caregiver, brought to the operatory, and laid on a size-appropriate Papoose Board (Olympic Medical Corp, Seattle, Wash) for use in case of disruptive behavior. Records did not indicate what criteria were used to determine whether children were adequately sedated after the latent period. Respiratory sounds and rates were monitored with a precordial stethoscope. Heart rate and transcutaneous oxygen saturation were recorded using a Minitorr pulse oximeter (BCI International, Waukesha, Wis) attached to the patient's toe and a NIBP monitor (BCI International) was used to evaluate blood pressure. Oxygen saturation levels were recorded at 60-second intervals and blood pressure was recorded every 10 minutes.

A nitrous oxide nasal hood was placed over the patient's nose, and N_2O/O_2 was administered at 50% at 3 to 5 (L/min), depending on the patient's size. Physiological parameters, recorded as soon as the patient was brought to the operatory, were used as preoperative physiological variables. Children who moved their heads, hands, or torso in a manner that interfered with their treatment were immobilized using the Papoose Board.

The operating dentist was a first- or second-year pediatric dental resident, while the supervising dentist was a faculty member. The operating and supervising dentists evaluated the overall level of sedation for each session based on criteria mentioned in Table 1.

Following the sedation session, the child was awakened and taken to the parents. The child remained in the operatory until established discharge criteria mentioned in the American Academy of Pediatric Dentistry guidelines[18]

Table 1. Intraoperative Assessment of Sedation

Excellent	Lack of movement or crying. Patient is often asleep. No restraints are required. Treatment objectives are easily accomplished.
Adequate	Patient is mostly cooperative, with occasional crying or movement interfering with treatment. May need some, little, or no restraint. Treatment objectives met with little or some difficulty.
Inadequate	Patient is uncooperative, with uncontrollable movement and crying requiring continuous physical restraint to complete treatment or partial treatment; or treatment abandoned/no treatment rendered.

for conscious and deep sedation were met. This was usually accomplished 15 to 75 minutes (median=47) postoperatively. Appropriate postoperative instructions were given to caretaker(s).

Results

Sample and overall effectiveness

Of the 66 children sedated, 45% (30) were girls and 55% (36) were boys. Thirty-eight percent of the subjects were 24 to 36 months of age, 40% were between 37 to 48 months old, and 22% were 49 to 60 months old at the time of sedation. Half the patients (50%) had one sedation session. The remaining children had 2 (30%), 3 (14%), or 4 (6%) sedation sessions, respectively. The gender (chi-square=.90, *P*=.89), age (chi-square=4.28, *P*=.64), and preoperative behavior rating (chi-square=9.53, *P*=.39) distribution of children with one or more sessions was identical.

Treatment needs and behavior assessment using Frankl's behavior rating scale are described in Table 2. Younger children tended to display significantly more negative preoperative behavior (chi-square=30.45, *P*<.001). There was no statistical difference in treatment needs between age groups (chi-square=8.72, *P*=.18).

Regression analysis (data not shown) was conducted to determine factors influencing the choice of sedation regimens employed. While age and preoperative behavior were not statistically significant, treatment need was the only statistically significant predictor for selecting one regimen over the other (*P*=.003, odds ratio [OR]=2.41, 95% confidence interval [CI]=1.35 to 4.31). For example, the authors found that patients requiring treatment of 5 to 8 teeth were more than 2 times as likely to receive CH+H+M as patients requiring treatment of 3 to 4 teeth. No statistical difference between regimens and procedures by type and location were observed.

The authors wanted to examine the role of treatment needs further and found that duration of treatment was significantly associated with the choice of regimen used (chi-square=28.40, *P*<.001). While midazolam was associated with shorter duration of treatment, with 30% sessions lasting 15 to 29 minutes and 32% lasting 30 to 39 minutes, the corresponding figures for CH+H+M were 3% and 13%, respectively. Conversely 84% of sedation sessions using CH+H+M lasted 40 to 49 minutes, compared to 38% of sessions using midazolam. Treatment duration was not associated with either the type or the location of dental procedure.

Physiological variables

Since increase in heart rate is a physiologic indicator of stress and fluctuation in oxygen saturation is indicative of the overall safety of the drugs used, the authors evaluated these in association with age, preoperative behavior, and sedation regimen using Pearson's chi-square test. At the preoperative stage, 10, 20, 30, and 40 minutes into the operative procedure, children were assessed based on heart rate more or less than 130 beats/min (bpm).[24] At the same time points, oxygen saturation levels were evaluated as more or less than 96%.

Heart rate and age

There was a significant association between age and heart rate of 130 bpm or more at 10 -minute (chi-square=18.06, *P*=.02), 20 minutes (chi-square=25.43, *P*=.001), and 30 minutes (chi-square=19.37, *P*=.03) into the procedure. Younger children (24 to 36 months) exhibited significantly more episodes of heart rates >130 bpm (*P*<.001).

Heart rate and preoperative behavior

To categorize preoperative behavior, the authors used the Frankl behavior rating scale. Due to sparseness of data in some categories, "somewhat negative" and "negative" categories were combined, while "somewhat positive" and "positive" ratings were merged to form the other category. No statistically significant difference was found at any preoperative recording points: 10 minutes, 20 minutes, 30 minutes, and 40 to 50 minutes.

Heart rate and drug regimen

While there were no statistically significant differences in heart rate elevation beyond 130 bpm at the preoperative recording (chi-square=6.80, *P*=.15), significantly fewer children sedated with CH+H+M experienced elevations of heart rate beyond 130 bpm at 10 minutes (chi-square=27.40, *P*<.001), 20 minutes (chi-square=19.02, *P*=.001), 30 minutes (chi-square=29.40, *P*<.001), and 40 minutes (chi-square=40.80, *P*<.001).

Oxygen saturation and drug regimen

There was no statistically significant difference in oxygen saturation below 96% between regimens at preoperative (midazolam=6/47, CH+H+M=6/69, *P*=.26) and at the 20-minute recording (midazolam=8/47, CH+H+M=8/69, *P*=.82). At 10 minutes (midazolam=7/47, CH+H+M=2/69, *P*=.02), 30 minutes (midazolam=5/33, CH+H+M=5/68,

Table 2. Assessment of Successful Outcome of Sedation Sessions: Results of Multivariate Analyses

	Sessions	%	*P*	OR (95% CI)
Regimen			.03	3.38 (1.06-7.15)
CH+H+M	69	60		
Midazolam	47	41		
Age (mos)			39	0.37 (0.28-1.64)
24-36	44	38		
37-48	47	41		
49-60	25	22		
Preoperative behavior (Frankl behavior rating scale)			.42	0.63 (0.20-1.98)
Definitely positive	3	3		
Somewhat positive	4	3		
Somewhat negative	53	46		
Definitely negative	56	48		
Treatment requirements			.72	0.48 (0.12-13.96)
1-2 teeth (1 sextant)	14	12		
3-4 teeth (2-3 sextants)	53	46		
5-8 teeth (4 sextants)	44	38		
9/+ teeth (5-6 sextants)	5	4		

P<.001), and 40 minutes (midazolam=2/19, CH+H+M=7/59, *P*=.01), however, significantly more children sedated with midazolam had oxygen saturation levels below 96%. One episode of oxygen desaturation of 90% to 93% was observed with both regimens at each point of recording. All episodes of oxygen saturation less than 96% were transient and corrected immediately by repositioning the head.

Oxygen saturation and age/preoperative behavior

There was no statistical association between oxygen saturation and age or with preoperative behavior.

Factors associated with intraoperative behavior

Intraoperative assessment of sedation was based on criteria mentioned in Table 1. "Adequate" (47%) and "excellent" (34%) categories were merged as effective sedation sessions for purposes of data analyses. Only 19% of the sedation sessions were categorized as "inadequate." Although 84% of sedation sessions involving girls were effective compared to 75% with boys, the difference was not statistically significant (chi-square=2.78, *P*=.09). Sedation effectiveness was similar for children with one sedation session and those with more than one session (chi-square=1.46, *P*=.69). Regardless of regimen, the authors found 81% of the sedations to be effective. When analyzed by regimen, however, 89% of sedation sessions with CH+H+M were effective, as compared to 70% of midazolam sedation sessions (chi-square=6.02, *P*=.01).

Age, preoperative Frankl behavior rating, treatment needs, and drug regimen were significantly associated with successful outcome of sedation in bivariate analyses using binary logistic regression (data not shown). These factors were entered as covariates into multiple logistic regression analysis to assess the sedation outcome (Table 2). Only drug regimen was found to be significantly associated with sedation effectiveness (*P*<.01, OR=3.38, 95% CI=1.06-7.15).

Children sedated with CH+H+M regimen were more than 3 times as likely to have a successful outcome compared to those sedated with midazolam. Dental procedures by location (anterior or posterior), total number, and type of procedure such as extraction, stainless steel crown, amalgam restoration, pulpotomy, and composite restoration were not entered into multivariate analyses because these were not significantly associated with the outcome of sedation in bivariate analyses.

Discussion

Overall, the authors found 81% of sedation sessions were effective, regardless of the regimen used. Nevertheless, children receiving CH+H+M in combination with N_2O were more than 3 times as likely to have a successful outcome as those receiving midazolam with N_2O. This study's success rate of 90% using CH+H+M with N_2O compares well with studies using CH+H+M combination[13,14] and is better than that reported by Nathan and West.[12] This study's success rate of 70% using midazolam was also comparable to one study[14] that reported a 67% success rate but higher than another study (42% to 49%).[6] The significantly higher success rate using CH+H+M, as compared to midazolam in this study, is similar to the only other study of its kind.[14]

It is difficult to compare outcomes between these studies, however, because of different methodologies and criteria of success used.

Contrary to reports in the medical literature,[16] sedation effectiveness was not influenced by age in this study. This finding, however, is similar to other studies involving pediatric dental patients.[6,20] Children in the youngest age group (24-36 months) were as likely to have a successful outcome as older children. It should be noted that 87% of the children in this group were between 32 and 36 months of age. Unlike previous studies,[14,20] preoperative behavior was not associated with intraoperative behavior in multivariate analyses. This study's tertiary care facility provides treatment to patients referred from private and public clinics, including The University of Iowa College of Dentistry. Treatment needs of children in the youngest age group were similar to older age groups. Treatment needs influenced the drug regimen, which was the only variable in multivariate analyses to significantly affect the outcome.

Although dental procedures by location, type, or total numbers were not associated with the outcome, the duration of treatment (indicating treatment needs) was found to be significantly associated with the regimen, which in turn significantly influenced the outcome. It is very likely that treatment duration is acting as a dummy variable for dental procedures in this study's analyses. Treatment need was the only factor associated with selection of the regimen.

Gender was not a factor in sedation success in this study. While 2 studies reported sedations of males as more successful than females,[20,21] 1[6] reported female sedations as more successful. There were no significant differences in sedation effectiveness among children with 1 sedation session compared to others with more than 1 session across age, preoperative behavior, and sedation regimens.

Two cases of vomiting immediately after ingestion of CH+H+M were reported. This is similar to the incidence of vomiting reported by Nathan and West.[12] On the other hand, Wilson et al[14] did not report incidents of vomiting. It is unclear whether poor cooperation of patients was related to the vomiting episodes in this study. Needleman et al[20] reported a higher incidence of vomiting (8%) in their investigation using chloral hydrate with hydroxyzine and nitrous oxide. Recovery was uneventful, and none of the children experienced nausea or vomiting during or after the procedure. Some children were unsteady on their feet. No case of paradoxical agitation following treatment with midazolam was observed. A post-treatment "angry" response using midazolam has been noted in the literature.[19]

No significantly adverse reactions occurred in any of the sessions. A significantly higher percentage of children receiving midazolam experienced oxygen saturation of 95% or less, compared to those sedated with a CH combination at 10, 30, and 40 minutes into the procedure, respectively. These episodes were very short, however, and may be false readings related to movement or children holding their breath while crying. While no episode of oxygen saturation less than 90% was observed, the episodes of oxygen saturation between 90% and 93% were transient and corrected immediately by repositioning the head. Nathan and West[12] and Wilson et al[14] reported no respiratory depression or oxygen desaturation incidents.

Needleman et al[20] reported that 21% of their patients experienced at least one episode of oxygen saturation of less than 95% occurring mainly among moderately and heavily sedated subjects. It is unclear whether transient desaturation episodes in this study were caused by pharmacologic actions of sedative agents alone, obstruction hypoxemia, or crying or a combination of these factors. This study, however, confirms the overall safety of both regimens.

Statistically significant differences in heart rate were found between age groups, preoperative behaviors, and sedation regimens, although these were within normal range. Younger children were expected to have higher heart rates—not only because of physiological reasons but also for cognitive reasons.[22] Fraone et al,[6] however, found no differences in their study comparing effectiveness of 2 midazolam regimens. Contrary to other studies,[14,20] there was no association between preoperative behavior and heart rate in the present study. Fewer children sedated with a CH combination had higher heart rates compared to children sedated with midazolam. This agrees with Wilson et al,[14] who reported that children receiving a CH combination were less likely to exhibit increased heart rates during local anesthetic injection and rubber dam placement.

Because of its retrospective nature, this study has some inherent limitations. Neither operating dentists nor supervising dentist were blinded to the regimens. Selection of regimens may have been influenced by the operator's previous experience and the child's previous sedation experience to a particular regimen. For example, the operator may have chosen a regimen that was successful previously. Likewise, the previous experience and "comfort level" of operators in treating children in general and using sedation in particular was not examined as a factor influencing the outcome. In addition, the authors did not investigate the use of other management techniques such as voice control during the sedation procedure. Use of such additional behavior techniques are known to affect the outcome. Additional factors were not examined, such as children spitting out the drug after administration, criteria used to determine whether patient was adequately sedated after the latent period, and distribution of patients needing more treatment to more experienced second-year residents.

Standardization of measurements and calibration of more than 20 dentists involved with performing and monitoring the procedures using sedation were not possible in this retrospective study.

This may have introduced errors in the assessment of preoperative and intraoperative patient behavior and may have influenced the results of this study. While lack of standardization and calibration is a drawback in this study, the

large number of operatives with varied levels of experience in sedation strengthens the results' general validity. Only one other study[12] used 10 different operators employing a similar sedation regimen.

As mentioned earlier, this study did not record behavioral and physiological responses during specific events of the procedure such as during local anesthetic injection, rubber dam placement, etc. It would be interesting to examine how behavior and stimulation at various stages in the procedure affected the session's outcome.

N_2O possesses sedative properties, and it is known to potentiate the action of other sedative agents.[22,23] In addition, N_2O tends to ameliorate stress in apprehensive children.[23] Wide variation in patient response to different N_2O concentrations has been reported. This study used the same N_2O concentration with both regimens to statistically control variance in the results. The role of N_2O as a confounding variable in examining the behavioral and physiological effects of each regimen is, therefore, limited.

To increase our understanding of the efficacy of sedation regimens, randomized clinical trials will be needed that control for:

1. age;
2. preoperative behavior;
3. treatment procedure types, including assessment at different stages of treatment;
4. physiological variables.

Conclusions

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

1. Chloral hydrate 25 mg/kg combined with 1mg/kg hydroxyzine and 1mg/kg meperidine with N_2O/O_2 inhalation produced more effective sedation sessions compared to midazolam 0.65 mg/kg with N_2O/O_2 inhalation.
2. Although midazolam produced increased heart rates compared to the chloral hydrate combination, heart rate was consistent with the children's age. No prolonged periods of oxygen desaturation were observed. Both regimens appear to be safe for oral conscious sedation.

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Abstract of the Scientific Literature

Emdogain Does Not Prevent or Cure Ankylosis: A Clinical Study

Emdogain has been shown in clinical and experimental studies to promote regeneration of all periodontal tissues in connection with treatment of marginal periodontitis. The purpose of this study was to analyze whether this regenerative capacity upon the periodontal ligament (PDL) also worked in a trauma situation where a significant number of PDL cells have been eliminated because of unphysiologic storage or actual damage during avulsion or replantation. Furthermore, if ankylosis sites—already established because of earlier replantation after avulsion—could be surgically removed, then applying Emdogain could revert the ankylosis stage to a normal PDL situation. The first treatment situation was tested in 7 patients with a total of 16 avulsed teeth with varying times of extraoral storage. The teeth were endodontically treated extraorally, and the root and socket were covered with Emdogain before replantation. All teeth demonstrated subsequent ankylosis, primarily diagnosed by a percussion test. The second treatment situation, where an ankylosis was already established, constituted 7 patients with a total of 11 teeth due to previous replantation after avulsion. These teeth were all extracted, the ankylosis sites were removed, and the root and socket were treated with Emdogain. After 6 months, all teeth showed recurrence of ankylosis. It is concluded that Emdogain was not able to prevent or cure ankylosis.

Comments: The present study concluded that applying Emdogain to prevent or cure ankylosis was not successful in any case of avulsed and replanted teeth. It is, therefore, questionable whether Emdogain has any particular role in treating avulsion injuries. The question of whether Emdogain delays the progress of replacement resorption (ankylosis) or not, however, has not yet been answered. FSS

Address correspondence to Dr. J.O. Andreasen, Department of Oral and Maxillofacial Surgery, University of Copenhagen (Rigshospitalet), Blegdamsvej 9, Copenhagen-2100, Denmark.

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