Efficacy of Midazolam/Meperidine vs Midazolam/Hydromorphone for Enteral Moderate Sedation in the Pediatric Dental Patient

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Objective: The goal of this study was to compare the efficacy of midazolam/meperidine (M/M) vs midazolam/hydromorphone (M/H) for enteral moderate sedation along with inhalational sedation in pediatric dental patients.

Methods: This retrospective chart review analyzed the charts of pediatric patients who received dental treatment under enteral moderate sedation with either M/M or M/H in combination with inhalational sedation (nitrous oxide/oxygen) at El Rio Community Health Centers (affiliated with NYU Langone) in Tucson, Arizona, from July 2014 to December 2020. Included subjects were between 2 and 5 years of age, less than 20 kg, and otherwise healthy. In addition to demographic and drug-dosing data, treatment completion, sedation level, behavioral score, overall effectiveness, and sedation duration data were collected and analyzed from each patient's chart.

Results: No statistically significant differences were observed when comparing the 2 drug regimens in treatment completion ($P = .89$), sedation level ($P = .74$), and overall effectiveness ($P = .70$). There was a statistically significant difference in behavior scoring, with the M/H group demonstrating higher scores ($P = .04$) than the M/M group.

Conclusion: The combination of midazolam and hydromorphone may provide an effective alternative to midazolam and meperidine when used with inhalational sedation (nitrous oxide/oxygen) for the moderate sedation of pediatric dental patients.

Key Words: Midazolam; Meperidine; Hydromorphone; Enteral sedation; Pediatric dentistry.

Dental caries is the most prevalent chronic disease in the pediatric population, and approximately 40% of children are affected by dental caries by the time they reach kindergarten.[1] Thus, the need to treat dental caries and improve a child's overall health at a young age is imperative. High levels of fear and anxiety in young children toward dental treatment may require pharmacologic interventions to permit safe and effective care.[2]

Oral administration of anxiolytics, opioids, and/or sedative-hypnotics, often in combination with inhalational sedation (nitrous oxide/oxygen), is used to achieve moderate levels of sedation during dental procedures.[3] Midazolam is one of the most used medications for enteral sedation in the pediatric dental field. However, its working time is limited, and it notably lacks any analgesic properties.[4] The addition of opioids such as meperidine has been used to overcome these deficiencies.[5]

Recently, the use of meperidine has diminished due to its active metabolite, normeperidine, and negative side effects such as altered mental status, nervousness, myoclonus, seizures, delirium, and psychosis.[6] Hydromorphone is an effective alternative that should be assessed. However, a PubMed search of "hydromorphone pediatric dental sedation" produced no results. There was no established research comparing oral midazolam and meperidine vs oral midazolam and hydromorphone in any sedation realm.

The purpose of this investigation was to retrospectively compare the sedation and treatment success of enteral midazolam and meperidine with that of enteral midazolam and hydromorphone in a pediatric dental setting. The primary

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goal was to provide practitioners with an effective alternative to meperidine without compromising patient behavior or treatment outcomes.

METHODS

NYU Langone Dental Medicine Institutional Review Board and El Rio Community Health Center Institutional Review Board approved this retrospective chart review. This study was conducted using electronic dental records from El Rio Community Health Center in Tucson, Arizona. Patient charts were identified with a search for the CDT code D9248 (nonintravenous conscious sedation) between July 1, 2014, and December 1, 2020, via NextGen Electronic Dental Record software.

Inclusion criteria consisted of patients between 2 and 5 years of age at the date of the sedation appointment, American Society of Anesthesiologists Physical Status (ASA-PS) classes of I or II, and weights less than 20 kg. In addition, all dental treatment was completed under enteral moderate sedation using either midazolam/meperidine or midazolam/hydromorphone along with inhalational sedation with nitrous oxide. Exclusion criteria consisted of patients younger than 2 years or older than 5 years of age, ASA-PS classes of III or greater, weights greater than 20 kg, or charts with incomplete sedation records.

Each patient was treated by pediatric dental residents under the direct supervision of an attending pediatric dentist. Two residents were present for each sedation appointment, with one providing dental treatment and one monitoring the patient's vital signs, behavior, and sedation level. During the sedation, nitrous oxide/oxygen (a minimum of 50%/50%) was also administered in combination with appropriate local anesthesia. Multiple sedation experiences for a single patient did not exclude the subject from the study.

Subjects received 1 of 2 medication regimens: midazolam/meperidine (M/M) or midazolam/hydromorphone (M/H). Midazolam dosing was 0.5 to 1.0 mg/kg (maximum: 20 mg). Meperidine dosing was 1.0 to 2.0 mg/kg (maximum: 50 mg). Hydromorphone dosing was 0.025 to .040 mg/kg (maximum 0.80 mg).

Recordkeeping during each moderate sedation included the sedation level obtained, patient behavior, duration of sedation, and treatment completion per the American Academy of Pediatric Dentistry Sedation Record.[7] Possible sedation levels included general anesthesia (5), deep sedation (4), moderate sedation (3), minimal sedation (2), and no sedation (1). Behavior scores were defined as prohibitive (1), poor (2) fair (3), good (4), or excellent (5). Prohibitive patients showed active resistance and did not allow for the planned treatment to be completed. Poor behavior was defined as struggling that interfered with the dental procedure. A fair behavior rating involved a crying patient with minimal disruption to the treatment rendered. Good behavior was displayed as mild objections and/or whimpering but no treatment interruptions. Excellent behavior was recorded when the patient was quiet and cooperative.[7] The duration of sedation was determined from the time the medication was administered to the time discharge vitals were recorded and sedation monitoring ceased. Treatment completion was noted if the original treatment plan was finished. If treatment had to be modified to a less definitive treatment modality (eg, placement of a temporary filling or silver diamine fluoride application) because of prohibitive behavior or ineffective sedation, it was deemed incomplete.

The principal researcher reviewed all the sedation and dental records, and data were stored securely through REDcap. All statistical analyses were completed by NYU Langone Health statisticians. Mean and standard deviation were calculated for continuous variables. Count and proportion were calculated for categorical variables. Comparisons of various clinical and demographic factors for the 2 sedation groups (M/M vs M/H) were assessed with an independent-sample t test for continuous variables and chi-square analysis and/or Fisher exact test, as needed, for categorical variables. A P value of less than .05 was considered statistically significant. All tests were 2 tailed. RStudio 2.4 for Windows was used for all analyses.

RESULTS

A total of 1036 cases of enteral moderate sedation were initially identified for the study period, 879 cases failed to meet the inclusion criteria, and a total of 157 cases were ultimately included for analysis. Of those 157 cases, 65 subjects received the M/M regimen, and 92 subjects received the M/H regimen.

Comparisons of the demographic and dosing data for the patients within the M/M and M/H groups are presented in Table 1. There were no significant differences in age ($P = .94$), gender ($P = .62$), or weight ($P = .72$) between the groups. However, there were significant differences in midazolam dosing, with the M/H group receiving higher total (mg) and weight-based (mg/kg) mean midazolam doses than the M/M group (16.7 mg vs 15.5 mg; $P = .002$; 0.98 mg/kg vs 0.91 mg/kg; $P < .001$).

Table 2 displays the correlation of each drug regimen to the outcome variables. There were no statistically significant differences for treatment completion ($P = .89$), sedation level ($P = .74$), overall effectiveness ($P = .70$), or duration of sedation ($P = .45$). Regardless of regimen, most treatments were successfully completed, provided a moderate level of sedation, were considered effective or very effective, and had an average duration of 63 to 65 minutes. There was a statistically significant difference regarding behavior scoring, with the M/H group achieving higher scores than the M/M group ($P = .04$).

Table 1. Demographic and Drug Dosing Characteristics

	Midazolam/hydromorphone (n = 92)	*Midazolam/meperidine (n = 65)*	*P value*[a]
Age, mean (SD), y	4.02 (0.8)	4.03 (0.7)	.94
Gender, n (%)			.62
Male	39 (42.4)	31 (47.7)	
Female	53 (57.6)	34 (52.3)	
Weight, mean (SD), kg	17.1 (1.7)	17.0 (1.8)	.72
Midazolam dosing			
Total dose, mean (SD), mg	16.7 (2.1)	15.5 (2.6)	.002[b]
Weight-based dose, mean (SD), mg/kg	0.98 (0.07)	0.91 (0.11)	<.001[b]
Hydromorphone dosing			
Total dose, mean (SD), mg	0.5 (0.1)	—	n/a
Weight-based dose, mean (SD), mg/kg	0.03 (0.004)	—	n/a
Meperidine dosing			
Total dose, mean (SD), mg	—	23.8 (6.2)	n/a
Weight-based dose, mean (SD), mg/kg	—	1.4 (0.3)	n/a

[a] Chi-square or Fisher exact test, unless otherwise indicated.
[b] $P < .05$.

DISCUSSION

This study showed that the outcomes of enteral moderate sedation with M/H are similar to M/M when used in combination with inhalational sedation (nitrous oxide/oxygen). The data demonstrated no statistically significant differences in the efficacy of the 2 drug regimens, with both showing similar sedation levels and treatment completion success rates. However, there was a statistically significant difference in 1 covariate, behavior score, with higher ratings noted in the M/H group. This regimen produced a higher percentage of "excellent" behavior scores when compared with the M/M group. The noted causes of no treatment involved in this study were diminished behavior due to multiple appointments with enteral moderate sedation as well as patients not ingesting full medication dosages.

Only 157 of the 1036 moderate enteral sedation cases completed during the study period met the inclusion criteria. Some were excluded due to not meeting the defined age range and weight criteria, but most of the excluded cases were due to the use of a nonopioid drug regimen. This likely reflects the general trend of decreased opioid use in the pediatric population.[8]

In considering the safety of the 2 drug regimens, no adverse events were reported, and no patients entered a level of deep sedation or general anesthesia. A study published in 2012 by Somri et al[9] studied the efficacy of oral midazolam at different dosing levels and found that the 1.0 mg/kg group had a significant increase in treatment completion rates.[9] These results aided in developing the dosing ranges used for this study, as both regimens used a midazolam dose close to 1.0 mg/kg.

Table 2. Comparison of the Outcome Variables

	Midazolam/hydromorphone (n = 92)	*Midazolam/meperidine (n = 65)*	*P value*[a]
Treatment complete, n (%)			.89
Yes	77 (83.7)	53 (81.5)	
No	15 (16.3)	12 (18.5)	
Sedation level, n (%)			.74
Moderate	65 (70.7)	42 (64.6)	
Mild	26 (28.3)	22 (33.8)	
None	1 (1.1)	1 (1.5)	
Behavior score, n (%)			.04[b]
Excellent	22 (23.9)	5 (7.7)	
Good	30 (32.6)	26 (40.0)	
Fair	13 (14.1)	17 (26.2)	
Poor	22 (23.9)	13 (20.0)	
Prohibitive	5 (5.4)	4 (6.2)	
Overall effectiveness, n (%)			.70
Ineffective	22 (23.9)	12 (18.5)	
Effective	45 (48.9)	33 (50.8)	
Very effective	25 (27.2)	20 (30.8)	
Duration of sedation, mean, min	65.2	63.8	.45, *t* test

[a] Chi-square or Fisher exact test, unless otherwise indicated.
[b] $P < .05$.

With respect to sedation duration and the use of meperidine, a study published by Nathan found that midazolam (0.7-1.0 mg/kg) with meperidine (1.0-1.5 mg/kg) provided the most effective sedation for improving behavior and limiting the use of restraints.[5] That study revealed working time was significantly increased with the addition of meperidine to midazolam, and their results were consistent with our study's findings regarding sedation duration.

Unanticipated significant differences in midazolam dosing were discovered in our study as the M/H group received higher mean total and weight-based midazolam doses compared with the M/M group (Table 1). As our study was a retrospective chart review, these identified differences were attributed to uncalibrated midazolam prescribing by the attending pediatric dentists. Individual attending pediatric dentists may have varying regimen and dosing preferences, and that variability was likely reflected in the midazolam dosing. While both groups received a therapeutic dose, the effect of midazolam dosing could be an opportunity for future research.

Limitations of this study included but were not limited to subject bias, type of procedure, local anesthetic administration, and details of the nitrous oxide delivery. Regarding subject bias, multiple pediatric dental residents completed the sedation cases over several years without any formal standardization. Behavior scores and sedation levels may have been influenced based on dental resident knowledge and experience during the procedure.

Furthermore, the type of dental procedure was not included in the sedation record, which may have affected the sedation level and treatment outcome, as more complex and stimulating procedures could have adversely affected the sedation result. Similarly, the type, delivery, and profoundness of local anesthetic was not included in data collection. The delivery and adequacy of local anesthesia could have affected the sedation success. Nitrous oxide was administered in each sedation, but specific details regarding concentrations >50% and changes in concentrations were not included in the data collection. Future research targeting these factors could provide additional insight into the differences between each medication regimen.

CONCLUSION

The combination of midazolam and hydromorphone appears to provide a viable, if not advantageous, alternative to midazolam and meperidine when used for enteral moderate sedation along with inhalational sedation for pediatric dental patients. Further study is suggested, as the literature regarding hydromorphone use in pediatric dental enteral sedation is very limited.

REFERENCES

1. American Academy of Pediatric Dentistry. Policy on oral health care programs for Infants, children, adolescents, and individuals with special health care needs. In: *The Reference Manual of Pediatric Dentistry*. American Academy of Pediatric Dentistry; 2021:39-42.

2. American Academy of Pediatric Dentistry. Behavior guidance for the pediatric dental patient. In*: The Reference Manual of Pediatric Dentistry*. American Academy of Pediatric Dentistry; 2021:306.

3. Femeini EM, Bennett JD. oral surgery for the pediatric patient. In: Dean JA, ed. *McDonald and Avery's Dentistry for the Child and Adolescent*. 10th ed. Elsevier: 2016;627-644.

4. Gentz R, Casamassimo P, Amini H, Claman D, Smiley M. Safety and efficacy of 3 pediatric midazolam moderate sedation regimens. *Anesth Prog*. 2017;64(2):66-72. https://doi.org/10.2344/anpr-64-02-04

5. Nathan JE. Retrospective comparisons of the efficacy and safety of variable dosing of midazolam with and without meperidine for management of varying levels of anxiety of pediatric dental patients: 35 years of sedation experience. *J Clin Pediatr Dent*. 2022;46(2):152-159. https://doi.org/10.17796/1053-4625-46.2.11

6. Dobbins EH. Where has all the meperidine gone? *Nursing*. 2010;40(1):65-66. doi:10.1097/01.NURSE.0000365924.16631.a4

7. American Academy of Pediatric Dentistry. Resources: sedation record. In: *The Reference Manual of Pediatric Dentistry*. American Academy of Pediatric Dentistry; 2021:606-607.

8. Sutherland TN, Wunsch H, Newcomb C, Hadland S, Gaskins L, Neuman MD. Trends in routine opioid dispensing after common pediatric surgeries in the United States: 2014–2019. *Pediatrics*. 2022;149(5):e2021054729. doi:10.1542/peds.2021-054729

9. Somri M, Parisinos CA, Kharouba J, et al. Optimising the dose of oral midazolam sedation for dental procedures in children: a prospective, randomised, and controlled study. *Int J Paediatr Dent*. 2012;22(4):271-279. doi:10.1111/j.1365-263X.2011.01192.x