A Retrospective Study of 248 Pediatric Oral Sedations Utilizing the Combination of Meperidine and Hydroxyzine for Dental Treatment

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Oral sedation for pre-cooperative and anxious pediatric patients is an important tool for the pediatric dentist. Few studies have examined the sedation regimen of meperidine and hydroxyzine. ***Objectives****: The primary goal of this study was to evaluate the overall safety and effectiveness of the meperidine/hydroxyzine drug combination. Secondary goals included detecting potential factors that alter sedation effectiveness.* ***Study Design****: Two hundred and forty eight electronic health records of pediatric patients (131 females, 117 males) who received meperidine/hydroxyzine sedations in a university setting were evaluated. Pediatric dental residents rated each case according to the Frankl behavioral scale and for effectiveness. Numerous factors were analyzed to evaluate their significance on overall effectiveness. Factors examined included age at time of treatment, gender, ASA status, Frankl score at various points during treatment, sextant of treatment, operator experience, dosage, use of nitrous oxide, and any complications encountered during treatment, both major and minor.* ***Results:*** *Over 81% of sedations were considered effective or very effective. Statistically significant findings included age of patient, pre-sedation behavior, and willingness to take the medication. Less than 5% of sedations were aborted due to behavior. Only one major complication was found, which was not related to the sedation.* ***Conclusions:*** *Meperidine combined with hydroxyzine is a safe and effective sedation regimen for uncooperative or pre-cooperative children during dental treatment.*

Key Words*: Conscious sedation, meperidine, hydroxyzine, pediatric dentistry*

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INTRODUCTION

Providing safe and effective dental care to uncooperative pediatric dental patients is not only a priority for dentists, but is also one of the most challenging situations in pediatric dentistry. Several factors have perpetuated the trend to treat children under oral sedation in the dental office. Limited access to hospital operating rooms for general anesthesia (GA), as well as a shift in parental and provider attitudes regarding behavior management, have increased the need for moderate level sedation in the dental office.[1] A survey regarding trends in parenting styles and the effect on dental practices taken by diplomates of the American Board of Pediatric Dentistry revealed that children's behaviors have worsened over the past few decades and that the use of sedation in dental practices has risen as a result .[2] Some of the longest used techniques have come under criticism by mainstream media, as well as medical professionals, making their use passé .[1] Pediatric dentists may be more likely to use pharmacological management because of the negative perception of hand-over-mouth, immobilization (both active and passive), and voice control. However, despite the common use of GA for simple medical procedures justified by patient fear, anxiety, and potentially painful procedures (*eg*. placement of tympostamy tubes), coverage of full mouth dental rehabilitation by insurance providers is not as common.[1]

Sedation of a pediatric patient has inherent risks. These risks increase for very young children and unhealthy patients.[3] Only

children classified as category I or II by the American Society of Anesthesiologists (ASA) should be considered for in-office sedation. All patients should be carefully examined and evaluated for sedation risk prior to consideration of this route of treatment, and the proper guidelines, monitoring, and post-recovery care must be followed.[4]

The combination of chloral hydrate with hydroxyzine is one of the most popular and time-tested regimens, but it has several disadvantages.[5-7] Chloral hydrate has a lengthy half-life, no reversal agent, and has become increasingly difficult to acquire since Pharmaceutical Associates discontinued manufacturing the oral solution in 2012.[8] Dentists must rely on different drug regimens. One combination commonly used involves the two drugs meperidine and hydroxyzine (M-H).[6, 7, 9] Meperidine is a synthetic opioid used to induce analgesia, sedation, and euphoria.[6, 7] Oral administration of meperidine is convenient and widely accepted, although the bioavailability of the drug is greatly diminished.[9-11] Major contraindications to meperidine include increased intracranial pressure, hepatic disorders, renal disorders, and those with pulmonary disorders such as severe asthma.[12] Meperidine, especially at higher doses, has been known to induce nausea and vomiting.[6, 13] The addition of hydroxyzine potentiates meperidine's effects and serves as an antiemetic.[7] A distinct advantage of the combination is the ability of naloxone to reverse meperidine.[6] Meperidine and hydroxyzine have been studied in combination with other drugs;[6, 7, 9, 14-17] However, there is limited literature on the combination of the two used together. The objectives of this study are to examine the safety and effectiveness of the M-H regimen as well as to identify potential factors which may influence the success of this drug combination.

MATERIALS AND METHOD

A case review (IRB 11-01644-XM) evaluated 251 electronic health records (EHR) of patients who received an oral sedation using the M-H combination performed by the residents of the University of Tennessee Graduate Pediatric Dentistry Clinic, Memphis, TN, USA. Numerous factors were examined and recorded for statistical analysis. Inclusion criteria for the study included any patient sedated with the drug combination of M-H, with or without nitrous, from April 2008 through June of 2012. Two patients were excluded because information in the EHR was insufficient for evaluation. In some instances, in which the patient expectorated the majority of medication, the clinician and parent elected to defer dental treatment and to monitor the patient until he or she could be properly discharged, electing to reappoint for future treatment. These cases were excluded from the study due to the fact that conclusions about patient behavior during treatment could not be properly evaluated. Hence, the data from 248 EHRs was recorded for analysis.

All children included in the study were deemed healthy enough for moderate sedation (ASA I or II) with no contraindications to the drug combination. Each patient visited the clinic for a treatment planning appointment, in which sedation was treatment planned based on behavioral considerations and clinical and radiographic evaluation. The risks and benefits of treatment were explained; written consent was obtained; and any medical consults indicated were obtained prior to treatment. Patients returned for restorative care, in which NPO status was verified and the medical status was assessed. Blood pressure, height, weight, pulse, tonsillar status, general health, and chest auscultation were all evaluated prior to dosing. The drug combination of M-H was administered orally to each child. Dosage was determined based on several factors, including the amount of work, the level of sedation desired, and previous behavior. All dosages were within the recommended guidelines for both drugs. The maximum dosage of meperidine administered was 2.2 mg/kg (1mg/lb) with a maximum dose of 50 mg (ranging from 1 mg/kg to 2.2mg/kg). Hydroxyzine was typically administered in 12.5 mg increments, ranging from 0.5 mg/kg to 2.2 mg/kg with a maximum dose of 50 mg. The majority of patients (n=210) received a standard 25 mg dose of hydroxyzine regardless of weight. Each patient was brought into the operatory after a latency time of 45 minutes to 1 hour. A pulse oximeter (506N3 Series—Criticare Systems Inc., Waukesha , WI) was placed on the patient's finger or toe and an automatic blood pressure cuff was applied (Comfort Cuff, Criticare Systems Inc., Waukesha, WA). Vitals including blood pressure, pulse, and oxygen saturation were recorded every 5 minutes on a strip recorder during the course of sedation. Precordial stethoscopes were available for use and applied when the patient slept through procedures. Most cases (n=238) were used with nitrous, up to a 50% concentration at 3-6 liters/minute. Of the 10 cases not using nitrous, 9 were due to a lack of patient cooperation for use of a nasal hood, and one was electively conducted without nitrous due to ideal cooperation. Topical anesthetic was applied, and 2% lidocaine with 1:100,000 epinephrine was injected as needed, not to exceed 4.4 mg/kg. Treatment was administered, and patients were discharged after meeting recommended American Academy of Pediatric Dentistry discharge criteria[18] with both written and verbal post-operative instructions. Each operator completed the EHR for the patient visit. In order to homogenize ratings and documentation in the EHR, all residents received formal training in their curriculum on how to 1) rate behavior according to the Frankl behavioral rating scale[19], 2) evaluate the interaction and approachability of the patient (Table 1)[20], and 3) rate the effectiveness of sedation (Table 2).

One evaluator (ML) reviewed patient EHRs and recorded factors to be examined into a Microsoft Excel Spreadsheet (Microsoft, Inc, Redmond, WA). These factors included patient's age at time of sedation, gender, Frankl score at the treatment planning appointment, the year of residency of the clinician administering treatment, the number of previous sedations, ASA status, sextant of treatment, number of teeth treated, dosage of each drug, behavior of child prior to dosage, willingness to take medication by cup without expectorating or if a syringe was needed for dosage, any major or minor complications, the use of nitrous, the length of the procedure, and the overall effectiveness of the sedation.

Overall effectiveness was scored by each clinician. Sedations were categorized as Very Effective, Effective, Ineffective, or Extremely Ineffective/Aborted (see Table 2). Recorded factors were analyzed statistically in SPSS (IBM, Inc, Armonk, NY), using Pearson Chi Squared and paired sample t-tests with significance set for $p<0.05$.

Table 1: Behavior Rating

Score	Behavior	Interactive Score*
1	Completely uncooperative, crying, very difficult to make progress, movement interrupted treatment	Refuses to talk or unable to talk (age/language), crying, avoids eye contact, never follows any request
2	Uncooperative, very reluctant to listen, some progress possible; strong movement making treatment difficult	Talks only when prompted, withdrawn, reluctant to engage, frowns most of the time, intermittently makes eye contact, rarely follows any request
3	Cooperative with some reluctance, mild movement or verbal protest with limited treatment interference	Talks most of the time after prompting, shows no expression initially but is approachable, follows most requests but with hesitation
4	Completely cooperative, even enjoys visit; no interference with treatment	Talkative, smiles and is easily approachable, follows requests without hesistation

*The interactive score was a modified and abridged version of the scale described by Fraone and coworkers[20]

Table 2: Sedation effectiveness

Score		Description
1	Very ineffective or aborted	No treatment delivered or extremely limited treatment rendered (i.e. treatment temporized)
2	Ineffective	Treatment rendered with difficulty, less treatment delivered than desired
3	Effective	Desired amount of treatment delivered, limited interference of treatment
4	Very Effective	Desired amount of treatment delivered, no interference of treatment or movement, full cooperation of patient

RESULTS

The sample population is described in Table 3. Working time for each case varied between 12 minutes (aborted) and 125 minutes. The average working time was 45 minutes. Only one instance was classified as a major complication, in which the patient potentially aspirated a crown. The patient was referred for a chest radiograph, and no complications ensued. This event was not related to sedative medications. Approximately 5% (n=14) of patients experienced minor complications which included nausea, vomiting, rash, or minor desaturation (>90% Sp02) reversed with repositioning or minor stimulation. Physiological parameters and oxygen saturation remained within clinically acceptable ranges for all sedations.

The general effectiveness is listed in Table 3. Approximately 81% of cases were considered successful sedations (effective or very effective). To examine factors that might correlate with effective sedations, sedations were dichotomously grouped into effective (very effective and effective sedations grouped together, n=202) and ineffective sedations (ineffective and aborted grouped together, n= 45). For one sedation case, the effectiveness was not recorded leaving a total of 247 sedations for analysis. The effective sedations were crosstabulated against other variables in SPSS. Several factors relating to the effectiveness of the sedation were found to be statistically significant: age (p=0.043), behavior during treatment planning (p=0.001), behavior prior to dosage (p=0.010), and the patient's willingness to take medication without expectorating or the use of a syringe (p=0.013) (Table 4). The effectiveness of the sedation increased as the age of the child increased. Children who were very cooperative (Frankl score of 4) during the treatment planning appointment and the pre-operative assessment prior to dosing had more effective sedations (90.9% and 86.7%, respectively) than those children who were not cooperative (Frankl score of 1) in the treatment planning session (59.5%) and pre-operative assessment (53.8%). Children who were willing to take the medication by cup were more likely to have an effective sedation (84.7%) than children who took the medication via syringe (59.1%).

Other factors that may have related to the effectiveness of the sedation were not found to be statistically significant (Table 4). Though male children trended toward more effective sedations (84.7%) compared to female children (78.4%), this was not statistically significant (p=0.20). Similarly, when the providers were second year pediatric dental residents, the sedations trended towards improved effectiveness (83.6%) versus first year residents (78.9%); however, this was also not statistically significant (p=0.36).

Finally, the dosage of medication was examined for an effect on the success of the sedation. Given that meperidine is the narcotic and main "sedative" in the combination, meperidine was the medication chosen for analysis of variation in dosage. The correlation of the dosage of meperidine and effectiveness of sedation was not statistically significant (p=0.23). The dosing of meperidine was divided into lower dose and higher dose categories. Meperidine dosed at 1.5mg/kg (+0.1mg/kg) or lower was classified as a low dose. Thirteen children were dosed at 1.6mg/kg and these were considered in the low dose category for a total of 49 children in the low dose category. Meperidine dosed at 1.7 mg/kg or higher was classified as a high dose with a total of 198 children in the high dose category. A higher dosage of medication did not correlate with increased effectiveness (Table 4).

A multivariate analysis looking at the combination of several factors on the effectiveness of the sedation regimen was conducted (not shown). The results did not deviate from the bivariate analysis presented in Table 4 and described above.

Table 3: Characteristics of the Sample

Descriptor	% Cases (n)
Gender	
Male	47.2 (117)
Female	52.8 (131)
Age	
3 years and younger	18.2 (45)
4 years	25.0 (62)
5 years	18.5 (46)
6 years	17.7 (44)
7 years and older	20.6 (51)
ASA Status	
I	91.9 (228)
II	8.1 (20)
Year of Resident	
First year	38.5 (95)
Second year	61.5 (153)
Repeated Sedation	
First sedation	71.3 (177)
Second sedation	21.8 (54)
> 2 previous sedations	6.9 (17)
Dose of Meperidine	
Low ≤1.5 (+0.1) mg/kg	19.8 (49)
High ≥1.7 mg/kg	80.2 (199)
Area of Treatment	
Posterior treatment only	74.9 (186)
Maxillary anterior treated	25.1(62)
Treatment Planning Behavior	
F1	15.3 (38)
F2	26.0 (64)
F3	26.9 (67)
F4	31.8 (79)
Effectiveness of Sedation	
Very Effective	61.3 (152)
Effective	20.2 (50)
Ineffective	13.7 (34)
Extremely Ineffective/Aborted	4.4 (11)
Not Recorded	0.4 (1)

Table 4: Factors examined for effectiveness of sedation

Factor (n total)	% Effective or Very Effective (n)	P value
Gender		p>0.20
Male	84.7 (111)	
Female	78.4 (91)	
Age		p<0.043*
3 years and younger	73.3 (33)	
4 years	73.8 (45)	
5 years	82.6 (38)	
6 years	88.6 (39)	
7 years and older	92.2 (47)	
Behavior during Treatment Planning		p<0.001*
1	59.4 (22)	
2	77.8 (96)	
3	87.5 (56)	
4	90.9 (70)	
Behavior Prior to Dosing		p<0.010*
1	53.8 (7)	
2	72.0 (18)	
3	88.0 (73)	
4	86.7 (42)	
Willingness to take Medication		p<0.013*
Willing by Cup	84.7 (150)	
Taken via Syringe	59.1 (13)	
Year of Resident		p>0.36
First year	78.9 (75)	
Second year	83.6 (127)	
Repeated Sedation		p>0.48
First sedation	81.7 (144)	
Second sedation	85.2 (46)	
> 2 previous sedations	70.6 (12)	
Dose of Meperidine		p>0.23
Low ≤1.5 (+0.1) mg/kg	75.5 (40)	
High ≥1.7 mg/kg	82.9 (162)	
Area of Treatment		p>0.38
Posterior treatment only	80.5 (149)	
Maxillary anterior treated	85.5 (53)	

*denotes statistical significance

DISCUSSION

More than a decade ago, the American Academy of Pediatrics and the American Pain Society published a joint recommendation that meperidine not be used as an opioid of choice in managing post-operative or trauma-related pain in infants and children.[21] Many pediatric institutions have significantly reduced their use of meperidine due to lack of proven efficacy, adverse events, and drug interactions, and some institutions have removed it entirely from their formularies.[22] With large or repeated doses of meperidine, or in individuals with renal dysfunction, meperidine's active metabolite, normeperidine, can accumulate and has been associated with neurotoxic effects such as agitation, tremors, and even seizures.[23] National pain management clinical practice guidelines recommend that meperidine use be restricted to short-term, procedure-related pain, to be administered for no more than 48 hours, and that the dosage be limited to 600 mg/24 hours.[24] In dentistry, utilizing no more than a single dose of meperidine, up to 50 mg, for a sedation appointment would fall within the limits of the clinical recommendations. The Physician's Desk Reference lists the pediatric dosage of meperidine as 1.1-1.8mg/kg, up to the adult dose (50-150mg).[25] Similar to this study, other studies of pediatric sedation have safely utilized doses ranging from 1-2.2mg/kg.[13, 26-28]

Hydroxyzine is an anti-histamine (H_1 blocker) which also has sedative, antiemetic, antispasmodic, and anticholinergic properties. It is available as hydroxyzine hydrochloride or hydroxyzine pamoate, has a wide safety margin, and is a popular drug in pediatric conscious sedation.[26] It may be used a sole agent or in combination with other medications like meperidine or midazolam. When used in combination with other central nervous system depressants, hydroxyzine can potentiate the depressant effects.[26] The Physician's Desk Reference lists the sedation dosage for children to be 0.6mg/kg[29]; however, numerous studies of pediatric sedation have utilized doses ranging from 1-2mg/kg when in combination with other sedative medications.[13, 26, 30-32] The incidence of side effects is low with hydroxyzine, and several studies have reported its safety in combination with other medications.[26, 28]

Safety

In this retrospective sedation records review, the M-H regimen was safe in the dosing range examined. No major adverse events were observed, and physiological parameters remained within acceptable limits. Of the three patients that experienced desaturations (>90% Sp02), all were reversed with repositioning or stimulation. One patient experienced an extraoral rash during treatment which could not be definitively linked to the sedation medication. The patient did not experience any breathing difficulties and denied an itching sensation. However, treatment was discontinued, the patient was monitored and evaluated by emergency responders within the university, and oral diphenhydramine was recommended. Other studies have also found this regimen to be safe[7] and for patients to maintain normal cardiopulmonary parameters.[28]

Effectiveness

M-H alone and M-H with nitrous oxide appear to be effective sedative regimens. Intrinsic factors relating to patient temperament and disposition were statistically significant to overall sedation effectiveness. These included age of the patient, cooperation during treatment planning appointment, behavior prior to dosing, and the patient's willingness to take the medication by cup without expectorating. This study finds that younger children (ages 3-4 years) had statistically poorer sedation success than older children (>4 years). This has been observed by previous studies.[6, 33] Wilson, *et al*. hypothesized that children under 36 months may be poor candidates for light or moderate sedation due to their cognitive developmental stage.[16]

As expected, a child with an F1 rating during treatment planning or prior to dosing had the least amount of success, at 59.5% and 53.8% respectively. Pre-operative behaviors may provide important indicators for the clinician in deciding treatment.[16] It has been shown that the approachability and withdrawal tendency of a child can have a significant effect on the behavior and ultimately the success of a sedation.[17, 34] It is important for the clinician to note that even children who displayed definitely negative behaviors were still able to have an effective sedation in over 50% of cases, indicating that sedation is a valuable tool for the pediatric dentist, especially for practitioners with limited access to operating room settings.

Finally, the patient's willingness to take the medication was significantly correlated with the success of the sedation. The majority of the patients were willing to take the medication by cup (88.9%). For these cases, a tablet of hydroxyzine was crushed and mixed with the meperidine, and a small amount of flavoring agent was added. The high acceptance rate is most likely due to the small volume that must be ingested. If the patient expectorated any medication or the medicine had to be administered with a syringe, the effectiveness of the sedation was only 59.1%. Other studies have found that compliance with oral administration was not predictive of behavior during dental treatment.[33, 34] In this study, a patient's willingness to take the medication orally did not necessarily indicate that the sedation would be effective; however, the refusal of medication was significantly related to lower success. The clinician could use this information to educate the parent and to temper the parent's expectations of the effectiveness of the sedation. The clinician could also use the latency period as an opportunity to calmly discuss acceptable alternative treatments with the parent if the sedation proved to be ineffective and treatment were to be aborted.

The extrinsic factors, or factors external to the individual patient, did not show statistical significance. These included but are not limited to any specific dosage used inside the evaluated range, operator experience in residency, number of sedations, or sextant of treatment. Interestingly, no statistical correlation could be found for variation of the dose of meperidine (Table 4). This finding supports previous research that finds that a higher dose of a narcotic does not necessarily provide more effective sedations.[6, 35] However, of the 49 children in the low dose category, 33 were aged 6 years or older. As discussed earlier, older children trended towards improved sedations and may have more coping skills than younger children. This study supports that older children may not need a maximum dosage of medication to achieve adequate sedation. Furthermore, repeated sedations were no less effective, and this has been found for oral dental sedations in a previous study.[5]

The authors hypothesized that the area of mouth treated may influence the effectiveness of the sedation as the maxillary anterior area is highly sensitive. However, the area of mouth treated did not influence the effectiveness of the sedation in this study. In this similar vein of thought, another study examined the complexity of treatment and behavior during sedation.[34] Procedures such as

sealants and class I restorations were classified as "simple," and procedures such as extractions and pulpal therapy as "complex." This study found no difference in the behavior of the child during a sedation based on the complexity of the treatment. We infer that, given appropriate local anesthetic, a child who is experiencing an effective sedation will allow for most any dental procedure.

Limitations of this study are primarily due to the retrospective nature of the design. There is no way to compare overall effectiveness of treatment with this regimen to non-sedated children or to patients sedated with only nitrous oxide. Multiple operators (21 residents over the course of 5 years) performed the dental treatment and recorded the sedation results. However, the EHRs evaluated included a lengthy pre- and post-operatory sedation log which closely documented the details evaluated in this study and each operator was formally trained in their curriculum on rating scales. This greatly improved the homogeneity of the details evaluated. Another limitation of this study is the inability to evaluate the additive effect of hydroxyzine. Though hydroxyzine has been given as a standard 25mg dose regardless of weight in previous studies of sedation,[26, 36, 37] current recommendations for all pediatric medications are to administer medications based on the child's current weight. A prospective design could evaluate weight-based dosing of hydroxyzine and its impact on potentiating meperidine's desired sedative effects. Despite the limitations of the retrospective design, to the authors' knowledge, this is the largest cohort of M-H sedations to be examined.

CONCLUSION

The results of this study indicate that the M-H regimen is a safe and effective way to help children cope with the experience of dental treatment. The most important determinants of success of sedation appear to be the patient disposition or factors relating most intrinsically to the patient. Pre-operative and pre-sedation behavior is strongly associated with sedation success. Older children are significantly more likely to experience successful sedations, and a higher dose of medication does not statistically provide more effective sedations. Further prospective studies are recommended to support M-H as effective sedative agents for pediatric dental treatment.

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